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Impact of COVID-19 and non-COVID-19 hospitalised pneumonia on longer term cardiovascular mortality in people with type 2 diabetes: A nationwide prospective cohort study from Scotland

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Tweet: Pneumonia hospitalisation significantly raises long-term CVD death risk in people with diabetes, irrespective of COVID-19 or other causes.

Running Title: Pneumonia, COVID-19 & CVD Mortality in Diabetes

Keywords: Type 2 Diabetes, COVID-19, Pneumonia, Cardiovascular Mortality

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Abstract

Objective: This study examines if hospitalised COVID-19 pneumonia increases long-term cardiovascular mortality more than other hospitalised pneumonias in people with type 2 diabetes and aims to quantify the relative cardiovascular disease (CVD) mortality risks associated with COVID-19 versus non-COVID-19 pneumonia.

Research Design and Methods: Using the SCI-Diabetes register, two cohorts were identified: people with type 2 diabetes in 2016 and at the 2020 pandemic onset. Hospital and death records were linked to determine pneumonia exposure and CVD deaths. Poisson regression estimated hazard ratios (HR) for CVD death associated with both pneumonia types, adjusted for confounders. The median follow-up was 1461 days (2016 cohort) and 700 days (2020 cohort).

Results and Conclusions: The adjusted HR for CVD death following non-COVID-19 pneumonia was 5.51 (95% CI 5.31-5.71) pre-pandemic and 7.3 (95% CI 6.86-7.76) during the pandemic. For COVID-19 pneumonia, the HR was 9.13 (95% CI 8.55-9.75). Beyond 30 days post-pneumonia, the HRs converged to 4.24 (95% CI 3.90-4.60), for non-COVID-19 and 3.35 (95% CI 3.00-3.74) for COVID-19 pneumonia, consistent even when excluding prior CVD cases. Hospitalised pneumonia, irrespective of causal agent, marks an increased risk for CVD death immediately and over the long term. COVID-19 pneumonia poses a higher CVD death risk than other pneumonias in the short term, but this distinction diminishes over time. These insights underscore the need for including pneumonia in CVD risk assessments, with particular attention to the acute impact of COVID-19 pneumonia.

Research in Context

What is already known about this subject?

- Individuals at higher risk for CVD face increased pneumonia risk, with both COVID-19 and non-COVID pneumonia linked to heightened CVD risk, though precise comparisons remain unquantified.

What is the key question?

- Does COVID-19 pneumonia raise CVD death risk more than other pneumonias, and does this persist long-term?

What are the new findings?

- Both COVID and non-COVID pneumonia significantly increase CVD death risk; COVID-19 risk is initially increased but both lead to around a 4.2 fold increase post-30 days.

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

- A history of pneumonia, from any cause, is a key risk indicator for CVD death in diabetes, emphasising its importance in prioritising CVD prevention efforts for people with diabetes.

Introduction

There are concerns that the COVID-19 pandemic will lead to an explosion in the incidence of cardiovascular morbidity and mortality well beyond the pandemic, particularly in those with diabetes. The factors that could lead to such an explosion in CVD are complex including reduced diabetes and cardiovascular care during and beyond the pandemic[1], reduced operative interventions[2], potential effects of vaccines on myocarditis (though this seems very modest) but also long term effects of SARS-CoV-2 infection itself on the cardiovascular system[3]. In the UK excess all-cause mortality has continued well into 2023 partly due to an excess in CVD mortality and deaths mentioning diabetes[4].

Regarding the long term direct effects of severe SARS-Co-V-2 infection, as evidenced by COVID-19 pneumonia, on the cardiovascular system an important question is the extent to which prior COVID-19 pneumonia is associated with cardiovascular mortality in the immediate aftermath of pneumonia as well as subsequently. This question is complicated by the fact that risk of developing COVID-19 pneumonia is increased by prior frailty including prior CVD and diabetes. In the overall population increased risks associated with COVID-19 compared to historical controls have been found in some studies after 30 days[5] but not in all[6]. Systematic reviews of the literature on CVD incidence after COVID-19 pneumonia suggest that there is strong evidence of short term increased risk but there is insufficient data on whether this elevation in risk is sustained as most studies are of very short duration[7]. These studies differed in how COVID-19 was captured with some examining outcomes after testing positive for COVID-19 and some focusing on those hospitalised. A recent report from the U.S Centers for Disease Control[8] using insurance claims data found an increased risk of CVD associated with prior COVID-19 diagnosis codes compared to those without COVID-19 over a mean follow-up time of 8.5 months that was slightly greater in those without than with diabetes[8]. The aim of this study is therefore to examine the longer term relative risk of CVD death associated with COVID-19 pneumonia in the population with diabetes in Scotland since the start of the pandemic up to November 2021. To understand the extent to which any increased risk of CVD death is specific to COVID-19 as a cause of pneumonia, the relative risk of CVD death was compared to the relative risk for CVD death associated with non-COVID-19 pneumonia prior to and since the start of the COVID-19 pandemic. We focused on hospitalised COVID-19 because it has been estimated that up to a third of COVID-19 infections were asymptomatic so that accurate classification of infection status is not possible outside of a surveillance setting[9]. Furthermore, this allowed a more comparable inclusion for non-COVID-19 pneumonias since self referral community testing systems akin to that provided nationally for SARS-CoV-2 do not exist. Whilst both relative risks for CVD mortality for COVID-19 and other pneumonias will be subject to confounding by frailty, we reasoned that if we found a much higher relative risk for CVD mortality for COVID-19 pneumonias than other pneumonias this would be consistent with an especially detrimental effect of SARS-CoV-2 on the cardiovascular system that could have implications for milder infections.

Methods

Data Sources

The Scottish Care Information-Diabetes (SCI-Diabetes) serves as a comprehensive register and database encompassing the vast majority (> 99%) of individuals in Scotland who have been diagnosed with diabetes. It has been described in detail previously[10]. The database collects data from various sources, including clinical episodes, laboratory data from primary care, diabetes clinics in the National Health Service (NHS) hospitals, community care, and the national retinopathy screening program. By utilising a unique health service identifier, it has been linked to hospital admissions data (Scottish Morbidity Record 01) and mortality data from the National Records of Scotland.

Participants

We defined two cohorts including all people alive and observable with a clinical diagnosis of Type 2 diabetes in pre-COVID-19 and intra COVID-19 pandemic time windows January 1st, 2016 to December 31st, 2019 (N=263922, follow-up 946547 years) and January 1st, 2020 to November 30th, 2021 (N=284801, follow-up 515226 years) respectively. To define a cohort free of recent pneumonia at baseline, for each time window, we excluded individuals who were admitted to hospital with any bacterial or viral pneumonia infection in the preceding 3 years.

Exposure to pneumonia

Exposure was defined as a hospital admission with bacterial or viral pneumonia. We selected Scottish Morbidity Records inpatient and day case procedure records (SMR01) which use the World Health Organisation (WHO) International Classification of Disease version 10 (ICD-10). In the study, pneumonia was subset as ICD-10 coding in any position of the SMR01 hospital episode. ICD-10 codes used for Non-COVID-19 and COVID-19 pneumonia are provided in ESM Table 6.

Where a discharge included only a non-COVID ICD-10 pneumonia code but where there was a positive rt-PCR test for COVID-19 during the admission, we assigned that into the COVID-19 pneumonia category. Where both non-COVID and COVID-19 codes were present on the discharge summary we assigned that as COVID-19 pneumonia

Cardiovascular disease during the study and prior lookback windows was determined using hospital discharge ICD10 codes. The codes used are provided in ESM Table 9.

The outcome of cardiovascular mortality in the study window was ascertained from the Medical Certificate of Cause of Death (MCCD) data provided by the National Records of Scotland (NRS). Cause-specific information for the cause of death was defined by ICD-10 coding present at any position on an MCCD. The codes used are provided in ESM Table 10.

Other covariate and risk factor data were obtained from SCI-Diabetes on HbA1c, body weight, BMI, blood pressure, estimated GFR (eGFR), plasma total cholesterol, albuminuria, retinopathy, smoking status, treated for hypertension or dyslipidaemia, ever having atrial fibrillation and the number of ATC level 3 drug classes. The value for these routine measurement variables at the nearest time prior to each cohort entry point was used, with a maximum look-back period of 3 years. Other ever/never risk factors such as prior CVD, immune disease, chronic kidney disease, asthma, liver disease and neurological diseases had a greater lookback period of 10 years.

Observability

The observability status of individuals was defined using a proxy of routine observations and receipt of any prescriptions during the study period. If individuals became unobservable during the study period, they were censored on the date at which they first became unobservable.

Statistical methods

The analyses consisted of multivariable Poisson regression, with each cohort organised in longitudinal survival table format consisting of 28 day intervals. Individuals entered the study at the study entry date, or when they were diagnosed with type 2 diabetes, whichever was sooner. Individuals were right-censored when there was either a loss of observability or death. The exposure variable was constructed as a time updated exposure variable denoting any prior exposure to COVID-19 pneumonia, since the start of follow-up, any prior non COVID-19 pneumonia since start of follow-up or exposure to neither, the pneumonia exposure index date being that of hospital admission. There were a small number of individuals who during the COVID-19 era had first one type of pneumonia and then in a later separate admission had another type but for simplicity, these were excluded from the analysis as numbers were low (N=271). The regression coefficient in each model was used to estimate the association between pneumonia and cardiovascular death, considering all time and 30 days post infection.

Adjustment was carried out in two stages. Firstly, a simple model was used, which included age, sex, and diabetes duration as covariates. Secondly, a more complex model was employed, incorporating several additional covariates expected to confound the association between pneumonia exposure and cardiovascular death. The adjustment covariates were entered into the model at baseline and not time updated. The adjustment covariates were derived from previously developed cardiovascular[11,12] and COVID-19[13] risk prediction models (see Table 3 for list of covariates).

Missing covariate data as detailed in ESM Table 1 were imputed using a multiple imputation approach. The imputation process involved utilising an expectation-maximization with bootstrapping (EMB) algorithm, assuming that the missing data were random conditional on the covariates and independent of the cardiovascular death outcome. The imputation was performed using the Amelia II package in R[14,15]. Multiple imputation was used, where five imputed datasets were generated, and for continuous variables, the mean of the imputed values was utilised in the regression model. Categorical variables were converted into probabilities for each category, representing the frequency of occurrence across the five imputations.

Results

Table 1 shows the baseline characteristics by pneumonia status for the 2020-2021 (COVID-19 era) cohort. A similar table for the 2016-2019 (pre-COVID-19 era) is contained in ESM Table 2. The data demonstrate the importance of adjusting for confounders when assessing the association of pneumonias with CVD death since those who developed pneumonia were older, had more deprived socioeconomic status and more prior comorbid conditions including CVD, were on more drugs and were more likely to have smoked. Those developing non-COVID pneumonia were older than COVID-pneumonia and the interquartile range of their Charlson index was 4 to 7 versus 1-6 for the COVID-19 group.

Table 2 illustrates the large numbers of people in the cohorts and large number of events in this study. The minimally adjusted (age, sex and diabetes duration adjusted) risk ratios for CVD death associated with pneumonia type in the Scottish population with type 2 diabetes for 2016-2019 and 2020-2021 cohorts are given as a baseline risk ratio prior to adjustment for additional potential confounders. As shown both non-COVID-19 and COVID-19 pneumonia were associated with a more than 10 fold elevation in risk of CVD death adjusted for age sex and diabetes duration.

Table 3 illustrates the effect of adjusting for potential confounders on the risk ratio for CVD death associated with pneumonias. Even with this adjustment pneumonias are associated with a large elevation in risk that was somewhat greater for COVID-19 (9.13) than non-COVID-19 (7.3) pneumonia. A broadly similar degree of reduction in the risk ratio with adjustment for potential confounders was seen regardless of pneumonia type. The multivariate adjusted risks ratio for pneumonia in the pre-COVID-19 era is given in ESM Table 3; the RR for non-COVID-19-pneumona was lower than for non-COVID-19 during the pandemic years even after adjusting for the difference in frailty in the two eras as evidenced by the increase in the Charlson index interquartile range from the pre-pandemic to pandemic period in those with non-COVID-19 pneumonia. A similar reduction in the relative risk with covariate adjustment was found (5.51). As shown in ESM Table 4 a similar pattern was found when the analyses were restricted to those without prior CVD at baseline- exposure to any pneumonia being associated with an increased risk of CVD.

ESM Table 5 and Figure 1 show the risk ratios for CVD death when the analysis is restricted to the period beyond 30 days post pneumonia, or in other words conditional upon surviving the first 30 days post-pneumonia. The relative risk of CVD death remains high but is much less than that for the total period including the immediate post pneumonia period. Furthermore, as shown, conditional on surviving the first 30 days post exposure, the subsequent relative risk of CVD death associated with prior exposure to COVID-19 pneumonia alone are somewhat lower than for non-COVID-19 pneumonia RR (3.35 and 4.24 respectively).

We also examined the relationship of non-COVID-19 and COVID-19 pneumonia to all cause mortality during follow up (ESM Tables 6 and 7). The magnitude of RR for all cause mortality was similar to that for CVD mortality. A very similar pattern was also found i.e. a slightly higher RR for COVID-19 than non-COVID-19 pneumonia overall but slightly lower after the first 30 days.

Discussion

Statement of principal findings

The key findings of this study are that in those with diabetes, prior to the pandemic era non-COVID-19-pneumonias were associated with a 5.5-fold elevation in risks of CVD death adjusted for CVD risks factors. This elevation in risk worsened during the pandemic period. The increased risk associated with COVID-19 pneumonia (9.1 fold) was somewhat higher than that associated with other pneumonias (7.3 fold) during the pandemic period. However, most of this greater elevation in risk of CVD death with COVID-19 than non-COVID-19 pneumonia reflected a greater impact of COVID-19 in the short term after pneumonia. From the first 30 days after pneumonia, COVID-19 was not associated with a greater elevation in CVD death than non-COVID-19 pneumonia over an average follow-up of 21 months.

Thus, regardless of the cause of pneumonia, having had a prior hospitalisation for pneumonia remains an important risk marker for CVD death in people with diabetes. Therefore, when developing risk scores for incident CVD events in future, researchers should consider the potential for pneumonia history to improve prediction. However, the concern that COVID-19 has a much greater long term risk on the cardiovascular system than other causes of pneumonia is not supported by these data.

Strengths and weaknesses of the study

The strengths of this study are the comprehensive capture of data from everyone with type 2 diabetes in Scotland and the comprehensive capture of all deaths. Other strengths are the extensive covariate data from the clinical records. Strengths in the design is the comparison of the relative risks with those seen for other pneumonias and that we have shown that using pre-pandemic data for other pneumonias could exaggerate apparent COVID-19 effects since the relative risks for other pneumonias themselves increased during the

pandemic period.

A further strength is that we noted very similar pattern was noted for all cause mortality such that competing risks do not account for our observations.

Limitations of this study include that for both causes of pneumonia one cannot rule out residual confounding by prior risk of CVD or subclinical CVD being a risk factor for COVID-19 from a direct effect of pneumonia on subsequent CVD. However, that the relative risks were only moderately reduced by adjustment for a large set of known confounders makes it unlikely that residual confounding alone could account for the observed effects. Furthermore, regardless of whether elevated risks partly reflect confounding the data clearly show that a prior history of hospitalised pneumonia is at the least an important risk marker for future CVD. Another limitation is that with respect to comparing the impact of different pneumonia causes the analysis assumes that COVID-19 codes were correctly assigned, and non-assigned, to pneumonias during the pandemic and we cannot externally validate this coding. If random misclassification of cause occurred, this would tend to make the relative risks associated with the different types of pneumonia more similar.

Another important limitation is the potential for collider bias[16]. A collider is a factor that is caused by both the exposure and the outcome under consideration. Conditioning on such a collider can cause a biased estimate of the association. An issue for our analysis is whether hospitalisation is a collider in the analysis. We chose CVD mortality (regardless of the death being hospitalised or not) as the outcome in our analysis. We conducted two sets of analysis one including all follow up time and one restricted to 30 days after the admission. In this latter analysis where the death is occurring much after the initial admission the CVD death hospitalisation cannot be a collider. However, in the first 30 day period since some hospitalisations may have been precipitated by underlying CVD that eventually led to CVD death, this could induce collider bias in the estimates for the RR for CVD mortality associated with pneumonias that includes the first 30 day period. Thus, the most valid estimates for considering the main hypothesis of whether COVID-19 has a greater long term impact on CVD mortality than non-COVID-pneumonias are those pertaining to the post 30 day period. We have focused on hospitalised pneumonias as the exposure of interest rather than having had a positive rt-PCR for SARS-CoV-2.

We have done this because although there was extensive free of charge rt-PCR testing for SARS-CoV-2 (including self referral) this will not correctly classify SARS-Co-V-2 exposure since it has been estimated that up to a third of infections were asymptomatic[9]. We note that had we used rt-PCR community tests as the basis for exposure definition this would have precluded comparison with other pneumonias since there was no equivalent testing in the community for these. This comparison was critical to answering the key question of whether there was any extra detrimental effect of SARS-CoV-2 on CVD.

Strengths and weaknesses in relation to other studies, discussing important differences in results;

Our results are not entirely consistent with other studies that found initial elevations in CVD incidence shortly after COVID-19 that did not persist after the first few months[6]. We found that excluding the first 30 days risks fell but continued to be elevated in the 2-4 fold range. A recent review focusing on post 30 day outcomes found heterogeneity in existing evidence with lack of adjustment for confounders and relatively short follow up[7]. Our follow-up was longer than many of these studies and larger. Most studies have simply compared CVD incidence in those with and without prior COVID-19. We chose to also compare to risks associated with other pneumonias since the potential for residual confounding by prior risk should be at least as great for COVID-19 as non-COVID-19 pneumonia, allowing us to assess whether COVID-19 has a particularly great effect. We also chose to focus on the hard outcome of CVD death but future work will consider the effect on different constellations of CVD events.

Previous studies that have compared the effect of COVID-19 with other pneumonias have focused usually on historical pre-pandemic controls[17] and have had fairly short follow-up. For example, a French study reported a greater 90 day mortality for COVID-19 than influenza[18]. Others have focused on in-hospital rather than longer term mortality[19]. One of the largest and longest studies to date, and one of the few examining risks among those with diabetes, is a recent study from the US Centres of Disease Control. That study over a median of 8.5 months excluding the first 30 days also found an elevation in CVD incidence associated with COVID-19. The relative risk was less than we found at 1.66 probably since in that study any COVID-19 diagnosis as an outpatient or inpatient was considered as the exposure whereas we focused on the more severe COVID-19 pneumonia admission. The studies also differed in that the outcome was CVD incidence unlike our study of CVD mortality. Unlike our findings for CVD mortality, CVD incidence was higher after COVID-19 infection than after other acute respiratory infections pre-pandemic. However, as we have shown using a pre-pandemic comparator may not be valid since the pandemic period itself seems to have worsened the outcomes associated with other pneumonias than COVID-19. Given the pressure that health services were under this is not surprising and it may also reflect a higher threshold for admission during the pandemic period as was shown by a slightly worse Charlson index in those admitted during the pandemic than pre-pandemic period. Consistent with our findings they found that relative risks were much higher in the first 30 days after the infection and then fell. This finding is consistent with systemic inflammation acutely worsening risk of a CV event and subsequent death due to effects on risk pathways, perhaps particular

haemostatic status. Notably, acute systemic inflammatory levels are known to be greater with COVID-19 infections versus other infections[20].

Meaning of the study: possible explanations and implications for clinicians and policymakers

The practical implications of this analysis are that the fears of greatly elevated rates of CVD over the long term post-pandemic due to direct effects of COVID-19 on the CVD system may be less than has been feared. What remains important though is careful risk factor management and optimising primary and secondary prevention and management in anyone with diabetes with prior hospitalised pneumonia regardless of cause.

Unanswered questions and future research

There remain many important unanswered questions on the long term effects of respiratory infections on CVD. Not least is what the mechanism of this association is. Does it for example reflect continued systemic inflammation, sequelae of direct myocardial damage at the time of infection, persistent thrombogenesis or other pathways and are there specific interventions that could target the mechanisms involved? More broadly, longer follow-up post pandemic is needed to be certain what the long term effect is of COVID-19 on CVD. Finally, the broader impact of the pandemic period and its attendant controls on health and on health care delivery still need to be understood and reversed.

Declarations

Information governance

This research was conducted with approval from the Public Benefit Privacy Protection Panel (PBPP ref. 1617-0147), originally set up under PAC 33/11, with approval from the Scotland A Research Ethics Committee (ref. 11/AL/0225). All datasets were de-identified before analysis.

Data Availability

NHS Data governance rules do not permit us to secondarily share the data directly. However, *Bone fide* researchers can apply to the Scottish Public Benefits and Privacy Protection Committee for access to these data.

Conflicts of interest

The authors have no conflicts of interest to declare.

Contributions

HMC, SJM and PMM conceived and designed the study. NS, JM, SW, TMC, and BK made important contributions to study design. SJM and LAKB were involved in the cleaning, harmonisation, quality control and databasing of data in Scotland. SJM performed the analyses. NS, JM, SW, and BK contributed to data analysis and interpretation. HMC and PMM developed data analysis methods. SJM and HMC drafted the initial manuscript. All authors made critically important contributions to the manuscript revision. All authors approved the final manuscript. HMC is the guarantor and, as such, is responsible for the integrity of the work as a whole.

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Data validity

Stuart McGurnaghan and Helen Colhoun had full access to the data reported in this paper which they analysed and take responsibility for its validity.

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Table 1: Cohort characteristics at 2020-01-01 study entry

	No Pneumonias	Non-COVID-19 Pneumonia	COVID-19 Pneumonia	Total
Total included	272730(95.78)	5533(1.94)	6483(2.28)	284801
Follow-up (days)	700(700,700)	700(428,700)	700(451,700)	700(700,700)
Sociodemographic				
Current age (years)	67.0(57.8,75.5)	76.3(68.3,83.3)	71.7(61.2,80.0)	67.4(58.0,75.9)
Sex				
Male	154161(56.5)	3153(57.0)	3734(57.6)	161081(56.6)
Female	118569(43.5)	2380(43.0)	2749(42.4)	123720(43.4)
Diabetes duration (years)	10.7(6.1,16.2)	13.1(7.5,18.8)	12.2(7.0,18.2)	10.7(6.2,16.3)
Ethnicity				
White	199717(73.2)	4410(79.7)	4955(76.4)	209127(73.4)
Non White	11419(4.2)	90(1.6)	335(5.2)	11848(4.2)
Other/unknown	61594(22.6)	1033(18.7)	1193(18.4)	63826(22.4)
Deprivation index				
Quintile 1 (most deprived)	62604(23.0)	1399(25.3)	2108(32.5)	66125(23.2)
Quintile 2	61302(22.5)	1355(24.5)	1573(24.3)	64245(22.6)
Quintile 3	55271(20.3)	1077(19.5)	1074(16.6)	57431(20.2)
Quintile 4	49294(18.1)	921(16.6)	906(14.0)	51128(18.0)
Quintile 5 (least deprived)	39739(14.6)	656(11.9)	691(10.7)	41095(14.4)
Unknown	4520(1.7)	125(2.3)	131(2.0)	4777(1.7)
Other clinical measures				
HbA1c (mmol/mol)	55(48,67)	54(47,66)	57(48,71)	55(48,67)
HbA1c (%)	7.18(6.54,8.28)	7.09(6.45,8.23)	7.37(6.54,8.65)	7.18(6.54,8.28)
BMI (kg/m^2)	31(27,35)	30(26,34)	31(27,36)	31(27,35)
Height (meters)	1.68(1.60,1.75)	1.67(1.59,1.74)	1.68(1.60,1.75)	1.68(1.60,1.75)
Weight (kg)	88(75,102)	82(70,97)	89(76,104)	88(75,102)
Systolic BP (mmHg)	134(124,142)	134(122,144)	133(123,142)	134(124,142)
Diastolic BP (mmHg)	78(70,82)	74(67,80)	76(70,81)	78(70,82)
Total cholesterol / HDL ratio (mmol/L)	3.56(2.87,4.42)	3.38(2.70,4.26)	3.54(2.86,4.44)	3.55(2.87,4.42)
eGFR (mL/min/1.73m^2)	83(65,95)	67(48,85)	73(54,90)	82(65,95)
Albuminuric status				
Normal	113851(41.7)	1752(31.7)	2364(36.5)	117982(41.4)
Micro	42941(15.7)	1441(26.0)	1432(22.1)	45828(16.1)
Macro	7750(2.8)	415(7.5)	373(5.8)	8545(3.0)
Unknown	108188(39.7)	1925(34.8)	2314(35.7)	112446(39.5)
Retinopathy				
None	174707(64.1)	3430(62.0)	4046(62.4)	182213(64.0)
Non referable	36997(13.6)	857(15.5)	987(15.2)	38850(13.6)
Referable / eye clinic	18168(6.7)	506(9.1)	703(10.8)	19387(6.8)
Unknown	42858(15.7)	740(13.4)	747(11.5)	44351(15.6)
Tobacco smoking status				
Never smoked	95542(35.0)	1263(22.8)	2028(31.3)	98847(34.7)
Ever smoked	174544(64.0)	4236(76.6)	4412(68.1)	183233(64.3)
Unknown	2644(1.0)	34(0.6)	43(0.7)	2721(1.0)
Comorbidities				
No. with prior CVD	51293(18.8)	2150(38.9)	2073(32.0)	55536(19.5)
No. with atrial fibrillation	18235(6.7)	1026(18.5)	852(13.1)	20122(7.1)
No. treated for dyslipidemia	174213(63.9)	4129(74.6)	4651(71.7)	183033(64.3)
No. treated for hypertension	163832(60.1)	3902(70.5)	4326(66.7)	172098(60.4)
Immune disease or on immunosuppressants	599(0.2)	26(0.5)	32(0.5)	657(0.2)
Chronic kidney disease	5666(2.1)	439(7.9)	434(6.7)	6545(2.3)
Asthma or chronic lower airway disease	33663(12.3)	1832(33.1)	1511(23.3)	37020(13.0)
Liver disease	1350(0.5)	72(1.3)	71(1.1)	1493(0.5)
Neurological and dementia (excluding epilepsy)	9280(3.4)	530(9.6)	503(7.8)	10320(3.6)
Number of ATC level 3 drug classes	12.0(7.0,18.0)	17.0(11.0,22.0)	16.0(10.0,22.0)	12.0(7.0,18.0)
Charlson Comorbidity Index	1.0(1.0,5.0)	5.0(4.0,7.0)	4.0(1.0,6.0)	1.0(1.0,5.0)

Categorical values are shown in N (%) and continuous values are median (interquartile range).

Table 2: Age, sex and diabetes duration adjusted risk ratios for CVD death associated with pneumonia type in the Scottish population with type 2 diabetes for 2016-2019 and 2020-2021 cohorts

Cohort	Subgroup	Total (N)	CVD Deaths (N)	Crude CVD Death Rate (Per 1k/py)	RR (95% CI)	P-Value
2016-2019	All	263922	19672	20.78		
	No Pneumonia	248660	15564	16.76	(reference)	
	Pneumonia	15262	4108	230.27	7.96 (7.68, 8.24)	<0.001
2020-2021	All	284801	10817	20.99		
	No Pneumonias	272730	8522	16.79	(reference)	
	Non-COVID-19 Pneumonia	5533	1250	329.81	11.8 (11.11, 12.53)	<0.001
	COVID-19 Pneumonia	6483	1034	262.77	12.93 (12.12, 13.79)	<0.001

Table 3: Multivariable adjusted risk ratios for CVD death associated with pneumonia types in Scottish T2 population from 2020 to 2021

Covariate	RR	2.5%	97.5%	P-Value
Pneumonia status ref=No Pneumonias				
Non-COVID-19 Pneumonia	7.297	6.865	7.756	<0.001
COVID-19 Pneumonia	9.129	8.549	9.749	<0.001
Current age (years)	0.969	0.879	1.068	0.524
Current age^2 (years^2)	1.001	1.000	1.002	0.153
(Current age/100)^3 (years/100^3)	1.000	0.999	1.000	0.326
Sex ref=Male				
Female	0.831	0.798	0.866	<0.001
Diabetes duration (years)	1.010	1.007	1.013	<0.001
Ethnicity ref=White				
Other/unknown	0.980	0.934	1.029	0.422
Non White	0.660	0.564	0.772	<0.001
Deprivation Index ref=Quintile 1 (most deprived)				
Quintile 2	0.920	0.870	0.972	0.003
Quintile 3	0.940	0.887	0.995	0.033
Quintile 4	0.874	0.823	0.928	<0.001
Quintile 5 (least deprived)	0.830	0.778	0.886	<0.001
HbA1c (mmol/mol)	1.004	1.003	1.005	<0.001
HbA1c (3 year average) (mmol/mol)	1.000	0.999	1.001	0.761
log BMI (kg/m^2)	0.645	0.578	0.719	<0.001
Height (meters)	1.011	0.969	1.055	0.599
Systolic BP (mmHg)	0.999	0.999	1.000	0.064
log Total cholesterol (mmol/L)	1.024	0.945	1.108	0.565
log eGFR (mL/min/1.73m^2)	1.123	1.079	1.169	<0.001
Albuminuria Status ref=Normal				
Micro	1.305	1.242	1.371	<0.001
Macro	1.640	1.523	1.764	<0.001
Retinopathy Status ref=None				
Non referable	1.124	1.066	1.185	<0.001
Referable or eye clinic	1.343	1.262	1.429	<0.001
Smoking Status ref=Never				
Ever smoked	1.162	1.111	1.216	<0.001
Unknown	1.080	0.816	1.429	0.590
Treated for hypertension	1.119	1.067	1.173	<0.001
Treated for dyslipidemia	1.053	1.000	1.109	0.051
Ever atrial fibrillation	1.755	1.677	1.836	<0.001
Prior CVD	1.676	1.604	1.752	<0.001
Immune disease or on immunosuppressants	0.795	0.558	1.132	0.204
Chronic kidney disease	1.657	1.536	1.787	<0.001
Asthma or chronic lower airway disease	1.292	1.235	1.352	<0.001
Liver disease	1.474	1.253	1.733	<0.001
Neurological and dementia (excluding epilepsy)	1.306	1.225	1.392	<0.001
Number of ATC level 3 drug classes	1.004	1.001	1.007	0.002
Charlson Comorbidity Index	1.128	1.120	1.137	<0.001

Figure Legends

Figure 1: Risk ratios for CVD death associated with COVID-19 and Non-COVID-19 pneumonia. Including all follow-up time and excluding the first 30 days post infection

Electronic Supplementary Material

Table 1: Variable missingness ratio in the 2016-2019 and 2020-2021 type 2 diabetes cohorts

	Missingness 2016-2019	Missingness 2020-2021
Deprivation index	0.02	0.02
BMI (kg/m^2)	0.07	0.10
eGFR (mL/min/1.73m^2)	0.06	0.07
HbA1c (mmol/mol)	0.06	0.06
Systolic BP (mmHg)	0.05	0.07
Diastolic BP (mmHg)	0.05	0.07
Weight (kg)	0.07	0.10
Height (meters)	0.08	0.10
Total cholesterol (mmol/L)	0.06	0.09
Albuminuric grade	0.31	0.39
Retinopathy grading	0.13	0.16

Table 2: Cohort characteristics at 2016-01-01 study entry

	No Hosp Pneumonia	Hosp Pneumonia	Total
Total included	248660(94.22)	15262(5.78)	263922
Follow-up (days)	1461(1461,1461)	1407(775,1461)	1461(1461,1461)
Sociodemographic			
Current age (years)	66.5(57.0,75.0)	75.6(67.5,82.0)	67.0(57.4,75.6)
Sex			
Male	139290(56.0)	8236(54.0)	147526(55.9)
Female	109370(44.0)	7026(46.0)	116396(44.1)
Diabetes duration (years)	11.3(7.3,16.3)	13.3(8.7,18.5)	11.4(7.4,16.4)
Ethnicity			
White	188968(76.0)	12381(81.1)	201349(76.3)
Non White	9414(3.8)	310(2.0)	9724(3.7)
Other/unknown	50278(20.2)	2571(16.8)	52849(20.0)
Deprivation index			
Quintile 1 (most deprived)	56876(22.9)	3999(26.2)	60875(23.1)
Quintile 2	55690(22.4)	3595(23.6)	59285(22.5)
Quintile 3	50264(20.2)	2980(19.5)	53244(20.2)
Quintile 4	44543(17.9)	2451(16.1)	46994(17.8)
Quintile 5 (least deprived)	36080(14.5)	1818(11.9)	37898(14.4)
Unknown	5207(2.1)	419(2.7)	5626(2.1)
Other clinical measures			
HbA1c (mmol/mol)	55(47,67)	54(46,66)	55(47,67)
HbA1c (%)	7.18(6.45,8.28)	7.09(6.36,8.19)	7.18(6.45,8.28)
BMI (kg/m^2)	31(27,35)	30(26,34)	31(27,35)
Height (meters)	1.68(1.60,1.75)	1.66(1.58,1.73)	1.68(1.60,1.75)
Weight (kg)	88(75,102)	82(70,96)	87(75,101)
Systolic BP (mmHg)	133(124,140)	132(122,141)	133(124,140)
Diastolic BP (mmHg)	76(70,80)	72(66,80)	76(70,80)
Total cholesterol / HDL ratio (mmol/L)	3.64(2.93,4.53)	3.44(2.76,4.33)	3.63(2.92,4.51)
eGFR (mL/min/1.73m^2)	81(64,94)	66(48,83)	80(62,93)
Albuminuric status			
Normal	117989(47.4)	5963(39.1)	123952(47.0)
Micro	44374(17.8)	4356(28.5)	48730(18.5)
Macro	7594(3.1)	1284(8.4)	8878(3.4)
Unknown	78703(31.7)	3659(24.0)	82362(31.2)
Retinopathy			
None	158829(63.9)	9470(62.0)	168299(63.8)
Non referable	36463(14.7)	2433(15.9)	38896(14.7)
Referable / eye clinic	19453(7.8)	1895(12.4)	21348(8.1)
Unknown	33915(13.6)	1464(9.6)	35379(13.4)
Tobacco smoking status			
Never smoked	82273(33.1)	3299(21.6)	85572(32.4)
Ever smoked	161949(65.1)	11848(77.6)	173797(65.9)
Unknown	4438(1.8)	115(0.8)	4553(1.7)
Comorbidities			
No. with prior CVD	48163(19.4)	5682(37.2)	53845(20.4)
No. with atrial fibrillation	15194(6.1)	2450(16.1)	17644(6.7)
No. treated for dyslipidemia	164651(66.2)	11735(76.9)	176386(66.8)
No. treated for hypertension	154095(62.0)	11334(74.3)	165429(62.7)
Immune disease or on immunosuppressants	502(0.2)	58(0.4)	560(0.2)
Chronic kidney disease	6074(2.4)	1255(8.2)	7329(2.8)
Asthma or chronic lower airway disease	28055(11.3)	4318(28.3)	32373(12.3)
Liver disease	1152(0.5)	161(1.1)	1313(0.5)
Neurological and dementia (excluding epilepsy)	7831(3.1)	1155(7.6)	8986(3.4)
Number of ATC level 3 drug classes	13.0(8.0,19.0)	18.0(12.0,24.0)	13.0(8.0,19.0)
Charlson Comorbidity Index	1.0(1.0,5.0)	5.0(1.0,6.0)	1.0(1.0,5.0)

Categorical values are shown in N (%) and continuous values are median (interquartile range).

Table 3: Multivariable adjusted risk ratios for CVD death associated with pneumonia types in Scottish T2 population from 2016 to 2019

Covariate	RR	2.5%	97.5%	P-Value
Pneumonia status ref=No Pneumonia				
Non-COVID-19 Pneumonia	5.508	5.314	5.710	<0.001
Current age (years)	0.841	0.787	0.900	<0.001
Current age^2 (years^2)	1.003	1.002	1.004	<0.001
(Current age/100)^3 (years/100^3)	0.999	0.998	0.999	<0.001
Sex ref=Male				
Female	0.880	0.854	0.907	<0.001
Diabetes duration (years)	1.010	1.008	1.012	<0.001
Ethnicity ref=White				
Other/unknown	1.119	1.080	1.160	<0.001
Non White	0.651	0.577	0.735	<0.001
Deprivation Index ref=Quintile 1 (most deprived)				
Quintile 2	0.932	0.895	0.971	0.001
Quintile 3	0.887	0.850	0.925	<0.001
Quintile 4	0.834	0.798	0.872	<0.001
Quintile 5 (least deprived)	0.774	0.737	0.813	<0.001
HbA1c (mmol/mol)	1.006	1.005	1.006	<0.001
HbA1c (3 year average) (mmol/mol)	1.000	0.999	1.000	0.814
log BMI (kg/m^2)	0.658	0.609	0.711	<0.001
Height (meters)	1.008	0.985	1.032	0.515
Systolic BP (mmHg)	0.998	0.997	0.998	<0.001
log Total cholesterol (mmol/L)	0.867	0.817	0.921	<0.001
log eGFR (mL/min/1.73m^2)	1.132	1.101	1.165	<0.001
Albuminuria Status ref=Normal				
Micro	1.348	1.302	1.396	<0.001
Macro	1.798	1.706	1.896	<0.001
Retinopathy Status ref=None				
Non referable	1.112	1.070	1.156	<0.001
Referable or eye clinic	1.261	1.208	1.317	<0.001
Smoking Status ref=Never				
Ever smoked	1.184	1.145	1.225	<0.001
Unknown	0.953	0.785	1.157	0.627
Treated for hypertension	1.171	1.128	1.215	<0.001
Treated for dyslipidemia	1.012	0.974	1.052	0.541
Ever atrial fibrillation	1.664	1.607	1.723	<0.001
Prior CVD	1.621	1.569	1.674	<0.001
Immune disease or on immunosuppressants	1.388	1.099	1.753	0.006
Chronic kidney disease	1.869	1.769	1.976	<0.001
Asthma or chronic lower airway disease	1.224	1.182	1.267	<0.001
Liver disease	1.485	1.287	1.715	<0.001
Neurological and dementia (excluding epilepsy)	1.300	1.234	1.369	<0.001
Number of ATC level 3 drug classes	1.007	1.005	1.009	<0.001
Charlson Comorbidity Index	1.094	1.088	1.100	<0.001

Table 4: Multivariable adjusted risk ratios for CVD death associated with pneumonia types in Scottish T2 population excluding prior CVD

Model	Covariate	RR	2.5%	97.5%	P-Value
Excluding prior CVD					
2016-2019	Pneumonia status ref=No Pneumonia				
	Non-COVID-19 Pneumonia	6.961	6.610	7.332	<0.001
2020-2021	Pneumonia status ref=No Pneumonias				
	Non-COVID-19 Pneumonia	9.052	8.249	9.932	<0.001
	COVID-19 Pneumonia	10.623	9.622	11.729	<0.001

Table 5: Multivariable adjusted risk ratios for CVD death associated with pneumonia types in Scottish T2 population with 30 day post infection exclusion

Model	Covariate	RR	2.5%	97.5%	P-Value
30-Day Post Infection Exclusion					
2016-2019	Pneumonia status ref=No Pneumonia				
	Non-COVID-19 Pneumonia	3.435	3.287	3.590	<0.001
2020-2021	Pneumonia status ref=No Pneumonias				
	Non-COVID-19 Pneumonia	4.235	3.904	4.595	<0.001
	COVID-19 Pneumonia	3.349	2.998	3.741	<0.001

Table 6: Multivariable adjusted risk ratios for all-cause mortality with pneumonia types in Scottish T2 population

Model	Covariate	RR	2.5%	97.5%	P-Value
All cause mortality					
2016-2019	Pneumonia status ref=No Pneumonia				
	Non-COVID-19 Pneumonia	5.039	4.928	5.152	<0.001
2020-2021	Pneumonia status ref=No Pneumonia				
	Non-COVID-19 Pneumonia	8.139	7.790	8.504	<0.001
	COVID-19 Pneumonia	10.946	10.461	11.453	<0.001

Table 7: Multivariable adjusted risk ratios for all-cause mortality associated with pneumonia types in Scottish T2 population with 30 day post infection exclusion

Model	Covariate	RR	2.5%	97.5%	P-Value
30-Day Post Infection Exclusion					
2016-2019	Pneumonia status ref=No Pneumonia				
	Non-COVID-19 Pneumonia	3.623	3.530	3.718	<0.001
2020-2021	Pneumonia status ref=No Pneumonias				
	Non-COVID-19 Pneumonia	4.606	4.343	4.885	<0.001
	COVID-19 Pneumonia	3.937	3.647	4.249	<0.001

Table 8: International classification of diseases coding version 10 codes for hospitalised COVID-19 and non COVID-19 Pneumonia

coding category	icd-10 code	description
Hospitalised COVID-19 Pneumonia		
	U07.1	COVID-19, virus identified
	U07.2	COVID-19, virus not identified
Hospitalised Non-COVID-19 Pneumonia		
	J10.0	Influenza with pneumonia, seasonal influenza virus identified
	J11.0	Influenza with pneumonia, virus not identified
	J12	Viral pneumonia, not elsewhere classified
	J12.0	Adenoviral pneumonia
	J12.1	Respiratory syncytial virus pneumonia
	J12.2	Parainfluenza virus pneumonia
	J12.3	Human metapneumovirus pneumonia
	J12.8	Other viral pneumonia
	J12.9	Viral pneumonia, unspecified
	J13	Pneumonia due to Streptococcus pneumoniae
	J14	Pneumonia due to Haemophilus influenzae
	J15	Bacterial pneumonia, not elsewhere classified
	J15.0	Pneumonia due to Klebsiella pneumoniae
	J15.1	Pneumonia due to Pseudomonas
	J15.2	Pneumonia due to staphylococcus
	J15.20	PNEUMONIA DUE TO STAPHYLOCOCCUS, NOT MRSA
	J15.21	PNEUMONIA DUE TO STAPHYLOCOCCUS, MRSA IDENTIFIED BEFORE ADM THIS EP
	J15.22	PNEUMONIA DUE TO STAPHYLOCOCCUS, MRSA IDENTIFIED AFTER ADM THIS EP
	J15.23	PNEUMONIA DUE TO STAPHYLOCOCCUS, MRSA NOT KNOWN WHEN IDENTIFIED
	J15.29	PNEUMONIA DUE TO STAPHYLOCOCCUS, NOT KNOWN WHETHER MRSA
	J15.3	Pneumonia due to streptococcus, group B
	J15.4	Pneumonia due to other streptococci
	J15.5	Pneumonia due to Escherichia coli
	J15.6	Pneumonia due to other Gram-negative bacteria
	J15.7	Pneumonia due to Mycoplasma pneumoniae
	J15.8	Other bacterial pneumonia
	J15.9	Bacterial pneumonia, unspecified
	J16	Pneumonia due to other infectious organisms, not elsewhere classified
	J16.0	Chlamydial pneumonia
	J16.8	Pneumonia due to other specified infectious organisms
	J17	Pneumonia in diseases classified elsewhere
	J17.0	Pneumonia in bacterial diseases classified elsewhere
	J17.1	Pneumonia in viral diseases classified elsewhere
	J17.2	Pneumonia in mycoses
	J17.3	Pneumonia in parasitic diseases
	J17.8	Pneumonia in other diseases classified elsewhere
	J18	Pneumonia, organism unspecified
	J18.0	Bronchopneumonia, unspecified
	J18.1	Lobar pneumonia, unspecified
	J18.2	Hypostatic pneumonia, unspecified
	J18.8	Other pneumonia, organism unspecified
	J18.9	Pneumonia, unspecified

Table 9: International classification of diseases coding version 10 codes for hospitalised CVD

coding category	icd-10 code	description
Hospitalised CVD	E10.5	Type 1 diabetes mellitus With peripheral circulatory complications
	E11.5	Type 2 diabetes mellitus With peripheral circulatory complications
	E13.5	Other specified diabetes mellitus With peripheral circulatory complications
	E14.5	Unspecified diabetes mellitus With peripheral circulatory complications
	G45	Transient cerebral ischaemic attacks and related syndromes
	G45.0	Vertebro-basilar artery syndrome
	G45.1	Carotid artery syndrome (hemispheric)
	G45.2	Multiple and bilateral precerebral artery syndromes
	G45.3	Amaurosis fugax
	G45.4	Transient global amnesia
	G45.8	Other transient cerebral ischaemic attacks and related syndromes
	G45.9	Transient cerebral ischaemic attack, unspecified
	I20	Angina pectoris
	I20.0	Unstable angina
	I20.00	Unstable angina – Clinical statement - 'troponin positive' - (THIS EXTENSION NOW OBSOLETE)
	I20.01	Unstable angina – Clinical statement - 'troponin negative' - (THIS EXTENSION NOW OBSOLETE)
	I20.02	Unstable angina – Coder knows tropopin was measured but has no clinical statement of 'troponin positive' or 'troponin negative - (THIS EXTENSION NOW OBSOLETE)
	I20.09	Unstable angina – Coder does not know if troponin was measure OR coder knows troponin not measured - (THIS EXTENSION NOW OBSOLETE)
	I20.1	Angina pectoris with documented spasm
	I20.8	Other forms of angina pectoris
	I20.9	Angina pectoris, unspecified
	I21	Acute myocardial infarction
	I21.0	Acute transmural myocardial infarction of anterior wall
	I21.00	Acute transmural myocardial infarction of anterior wall – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I21.01	Acute transmural myocardial infarction of anterior wall – ST Elevated Myocardial Infarction (STEMI)
	I21.09	Acute transmural myocardial infarction of anterior wall – MI with no statement of ST elevation or non-elevation
	I21.1	Acute transmural myocardial infarction of inferior wall
	I21.10	Acute transmural myocardial infarction of inferior wall – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I21.11	Acute transmural myocardial infarction of inferior wall – ST Elevated Myocardial Infarction (STEMI)
	I21.19	Acute transmural myocardial infarction of inferior wall – MI with no statement of ST elevation or non-elevation
	I21.2	Acute transmural myocardial infarction of other sites
	I21.20	Acute transmural myocardial infarction of other sites – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I21.21	Acute transmural myocardial infarction of other sites – ST Elevated Myocardial Infarction (STEMI)
	I21.29	Acute transmural myocardial infarction of other sites – MI with no statement of ST elevation or non-elevation
	I21.3	Acute transmural myocardial infarction of unspecified site
	I21.30	Acute transmural myocardial infarction of unspecified site – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I21.31	Acute transmural myocardial infarction of unspecified site – ST Elevated Myocardial Infarction (STEMI)
	I21.39	Acute transmural myocardial infarction of unspecified site – MI with no statement of ST elevation or non-elevation
	I21.4	Acute subendocardial myocardial infarction
	I21.40	Acute subendocardial myocardial infarction – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I21.41	Acute subendocardial myocardial infarction – ST Elevated Myocardial Infarction (STEMI)

Table 9: International classification of diseases coding version 10 codes for hospitalised CVD *(continued)*

coding category	icd-10 code	description
	I21.49	Acute subendocardial myocardial infarction – MI with no statement of ST elevation or non-elevation
	I21.9	Acute myocardial infarction, unspecified
	I21.90	Acute myocardial infarction, unspecified – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I21.91	Acute myocardial infarction, unspecified – ST Elevated Myocardial Infarction (STEMI)
	I21.99	Acute myocardial infarction, unspecified – MI with no statement of ST elevation or non-elevation
	I22	Subsequent myocardial infarction
	I22.0	Subsequent myocardial infarction of anterior wall
	I22.00	Subsequent myocardial infarction of anterior wall – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I22.01	Subsequent myocardial infarction of anterior wall – ST Elevated Myocardial Infarction (STEMI)
	I22.09	Subsequent myocardial infarction of anterior wall – MI with no statement of ST elevation or non-elevation
	I22.1	Subsequent myocardial infarction of inferior wall
	I22.10	Subsequent myocardial infarction of inferior wall – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I22.11	Subsequent myocardial infarction of inferior wall – ST Elevated Myocardial Infarction (STEMI)
	I22.19	Subsequent myocardial infarction of inferior wall – MI with no statement of ST elevation or non-elevation
	I22.8	Subsequent myocardial infarction of other sites
	I22.80	Subsequent myocardial infarction of other sites – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I22.81	Subsequent myocardial infarction of other sites – ST Elevated Myocardial Infarction (STEMI)
	I22.89	Subsequent myocardial infarction of other sites – MI with no statement of ST elevation or non-elevation
	I22.9	Subsequent myocardial infarction of unspecified site
	I22.90	Subsequent myocardial infarction of unspecified site – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I22.91	Subsequent myocardial infarction of unspecified site – ST Elevated Myocardial Infarction (STEMI)
	I22.99	Subsequent myocardial infarction of unspecified site – MI with no statement of ST elevation or non-elevation
	I23	Certain current complications following acute myocardial infarction
	I23.0	Haemopericardium as current complication following acute myocardial infarction
	I23.1	Atrial septal defect as current complication following acute myocardial infarction
	I23.2	Ventricular septal defect as current complication following acute myocardial infarction
	I23.3	Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction
	I23.4	Rupture of chordae tendineae as current complication following acute myocardial infarction
	I23.5	Rupture of papillary muscle as current complication following acute myocardial infarction
	I23.6	Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction
	I23.8	Other current complications following acute myocardial infarction
	I24	Other acute ischaemic heart diseases
	I24.0	Coronary thrombosis not resulting in myocardial infarction
	I24.1	Dressler syndrome
	I24.8	Other forms of acute ischaemic heart disease
	I24.9	Acute ischaemic heart disease, unspecified
	I25	Chronic ischaemic heart disease
	I25.0	Atherosclerotic cardiovascular disease, so described
	I25.1	Atherosclerotic heart disease
	I25.2	Old myocardial infarction
	I25.3	Aneurysm of heart
	I25.4	Coronary artery aneurysm and dissection
	I25.5	Ischaemic cardiomyopathy

Table 9: International classification of diseases coding version 10 codes for hospitalised CVD *(continued)*

coding category	icd-10 code	description
	I25.50	Ischaemic cardiomyopathy – Reduced Left Ventricular Ejection Fraction
	I25.51	Ischaemic cardiomyopathy – Preserved Left Ventricular Ejection Fraction
	I25.59	Ischaemic cardiomyopathy – No information on Left Ventricular Ejection Fraction
	I25.6	Silent myocardial ischaemia
	I25.8	Other forms of chronic ischaemic heart disease
	I25.9	Chronic ischaemic heart disease, unspecified
	I50	Heart failure
	I50.0	Congestive heart failure
	I50.00	Congestive heart failure – Reduced Left Ventricular Ejection Fraction
	I50.01	Congestive heart failure – Preserved Left Ventricular Ejection Fraction
	I50.09	Congestive heart failure – No information on Left Ventricular Ejection Fraction
	I50.1	Left ventricular failure
	I50.10	Left ventricular failure – Reduced Left Ventricular Ejection Fraction
	I50.11	Left ventricular failure – Preserved Left Ventricular Ejection Fraction
	I50.19	Left ventricular failure – No information on Left Ventricular Ejection Fraction
	I50.9	Heart failure, unspecified
	I50.90	Heart failure, unspecified – Reduced Left Ventricular Ejection Fraction
	I50.91	Heart failure, unspecified – Preserved Left Ventricular Ejection Fraction
	I50.99	Heart failure, unspecified – No information on Left Ventricular Ejection Fraction
	I61	Intracerebral haemorrhage
	I61.0	Intracerebral haemorrhage in hemisphere, subcortical
	I61.1	Intracerebral haemorrhage in hemisphere, cortical
	I61.2	Intracerebral haemorrhage in hemisphere, unspecified
	I61.3	Intracerebral haemorrhage in brain stem
	I61.4	Intracerebral haemorrhage in cerebellum
	I61.5	Intracerebral haemorrhage, intraventricular
	I61.6	Intracerebral haemorrhage, multiple localized
	I61.8	Other intracerebral haemorrhage
	I61.9	Intracerebral haemorrhage, unspecified
	I62	Other nontraumatic intracranial haemorrhage
	I62.0	Subdural haemorrhage (acute)(nontraumatic)
	I62.1	Nontraumatic extradural haemorrhage
	I62.9	Intracranial haemorrhage (nontraumatic), unspecified
	I63	Cerebral infarction
	I63.0	Cerebral infarction due to thrombosis of precerebral arteries
	I63.1	Cerebral infarction due to embolism of precerebral arteries
	I63.2	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
	I63.3	Cerebral infarction due to thrombosis of cerebral arteries
	I63.4	Cerebral infarction due to embolism of cerebral arteries
	I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
	I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
	I63.8	Other cerebral infarction
	I63.9	Cerebral infarction, unspecified
	I64	Stroke, not specified as haemorrhage or infarction
	I70.2	Atherosclerosis of arteries of extremities
	I70.20	Atherosclerosis of arteries of extremities
	I70.21	Atherosclerosis of arteries of extremities
	I70.8	Atherosclerosis of other arteries
	I70.80	Atherosclerosis of other arteries
	I70.81	Atherosclerosis of other arteries
	I70.9	Generalized and unspecified atherosclerosis
	I70.90	Generalized and unspecified atherosclerosis

Table 9: International classification of diseases coding version 10 codes for hospitalised CVD *(continued)*

coding category	icd-10 code	description
	I70.91	Generalized and unspecified atherosclerosis
	I73.9	Peripheral vascular disease, unspecified

Table 10: International classification of diseases coding version 10 codes used for CVD death

coding category	icd-10 code	description
CVD Deaths	I20	Angina pectoris
	I20.0	Unstable angina
	I20.00	Unstable angina – Clinical statement - 'troponin positive' - (THIS EXTENSION NOW OBSOLETE)
	I20.01	Unstable angina – Clinical statement - 'troponin negative' - (THIS EXTENSION NOW OBSOLETE)
	I20.02	Unstable angina – Coder knows tropopin was measured but has no clinical statement of 'troponin positive' or 'troponin negative - (THIS EXTENSION NOW OBSOLETE)
	I20.09	Unstable angina – Coder does not know if troponin was measure OR coder knows troponin not measured - (THIS EXTENSION NOW OBSOLETE)
	I20.1	Angina pectoris with documented spasm
	I20.8	Other forms of angina pectoris
	I20.9	Angina pectoris, unspecified
	I21	Acute myocardial infarction
	I21.0	Acute transmural myocardial infarction of anterior wall
	I21.00	Acute transmural myocardial infarction of anterior wall – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I21.01	Acute transmural myocardial infarction of anterior wall – ST Elevated Myocardial Infarction (STEMI)
	I21.09	Acute transmural myocardial infarction of anterior wall – MI with no statement of ST elevation or non-elevation
	I21.1	Acute transmural myocardial infarction of inferior wall
	I21.10	Acute transmural myocardial infarction of inferior wall – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I21.11	Acute transmural myocardial infarction of inferior wall – ST Elevated Myocardial Infarction (STEMI)
	I21.19	Acute transmural myocardial infarction of inferior wall – MI with no statement of ST elevation or non-elevation
	I21.2	Acute transmural myocardial infarction of other sites
	I21.20	Acute transmural myocardial infarction of other sites – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I21.21	Acute transmural myocardial infarction of other sites – ST Elevated Myocardial Infarction (STEMI)
	I21.29	Acute transmural myocardial infarction of other sites – MI with no statement of ST elevation or non-elevation
	I21.3	Acute transmural myocardial infarction of unspecified site
	I21.30	Acute transmural myocardial infarction of unspecified site – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I21.31	Acute transmural myocardial infarction of unspecified site – ST Elevated Myocardial Infarction (STEMI)
	I21.39	Acute transmural myocardial infarction of unspecified site – MI with no statement of ST elevation or non-elevation
	I21.4	Acute subendocardial myocardial infarction
	I21.40	Acute subendocardial myocardial infarction – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I21.41	Acute subendocardial myocardial infarction – ST Elevated Myocardial Infarction (STEMI)
	I21.49	Acute subendocardial myocardial infarction – MI with no statement of ST elevation or non-elevation
	I21.9	Acute myocardial infarction, unspecified
	I21.90	Acute myocardial infarction, unspecified – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I21.91	Acute myocardial infarction, unspecified – ST Elevated Myocardial Infarction (STEMI)
	I21.99	Acute myocardial infarction, unspecified – MI with no statement of ST elevation or non-elevation
	I22	Subsequent myocardial infarction
	I22.0	Subsequent myocardial infarction of anterior wall
	I22.00	Subsequent myocardial infarction of anterior wall – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I22.01	Subsequent myocardial infarction of anterior wall – ST Elevated Myocardial Infarction (STEMI)
	I22.09	Subsequent myocardial infarction of anterior wall – MI with no statement of ST elevation or non-elevation

Table 10: International classification of diseases coding version 10 codes used for CVD death *(continued)*

coding category	icd-10 code	description
	I22.1	Subsequent myocardial infarction of inferior wall
	I22.10	Subsequent myocardial infarction of inferior wall – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I22.11	Subsequent myocardial infarction of inferior wall – ST Elevated Myocardial Infarction (STEMI)
	I22.19	Subsequent myocardial infarction of inferior wall – MI with no statement of ST elevation or non-elevation
	I22.8	Subsequent myocardial infarction of other sites
	I22.80	Subsequent myocardial infarction of other sites – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I22.81	Subsequent myocardial infarction of other sites – ST Elevated Myocardial Infarction (STEMI)
	I22.89	Subsequent myocardial infarction of other sites – MI with no statement of ST elevation or non-elevation
	I22.9	Subsequent myocardial infarction of unspecified site
	I22.90	Subsequent myocardial infarction of unspecified site – Non-ST Elevated Myocardian Infarction (NSTEMI)
	I22.91	Subsequent myocardial infarction of unspecified site – ST Elevated Myocardial Infarction (STEMI)
	I22.99	Subsequent myocardial infarction of unspecified site – MI with no statement of ST elevation or non-elevation
	I23	Certain current complications following acute myocardial infarction
	I23.0	Haemopericardium as current complication following acute myocardial infarction
	I23.1	Atrial septal defect as current complication following acute myocardial infarction
	I23.2	Ventricular septal defect as current complication following acute myocardial infarction
	I23.3	Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction
	I23.4	Rupture of chordae tendineae as current complication following acute myocardial infarction
	I23.5	Rupture of papillary muscle as current complication following acute myocardial infarction
	I23.6	Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction
	I23.8	Other current complications following acute myocardial infarction
	I24	Other acute ischaemic heart diseases
	I24.0	Coronary thrombosis not resulting in myocardial infarction
	I24.1	Dressler syndrome
	I24.8	Other forms of acute ischaemic heart disease
	I24.9	Acute ischaemic heart disease, unspecified
	I25	Chronic ischaemic heart disease
	I25.0	Atherosclerotic cardiovascular disease, so described
	I25.1	Atherosclerotic heart disease
	I25.2	Old myocardial infarction
	I25.3	Aneurysm of heart
	I25.4	Coronary artery aneurysm and dissection
	I25.5	Ischaemic cardiomyopathy
	I25.50	Ischaemic cardiomyopathy – Reduced Left Ventricular Ejection Fraction
	I25.51	Ischaemic cardiomyopathy – Preserved Left Ventricular Ejection Fraction
	I25.59	Ischaemic cardiomyopathy – No information on Left Ventricular Ejection Fraction
	I25.6	Silent myocardial ischaemia
	I25.8	Other forms of chronic ischaemic heart disease
	I25.9	Chronic ischaemic heart disease, unspecified
	I26	Pulmonary embolism
	I26.0	Pulmonary embolism with mention of acute cor pulmonale
	I26.9	Pulmonary embolism without mention of acute cor pulmonale
	I27	Other pulmonary heart diseases
	I27.0	Primary pulmonary hypertension
	I27.1	Kyphoscoliotic heart disease

Table 10: International classification of diseases coding version 10 codes used for CVD death *(continued)*

coding category	icd-10 code	description
	I27.2	Other secondary pulmonary hypertension
	I27.8	Other specified pulmonary heart diseases
	I27.9	Pulmonary heart disease, unspecified
	I28	Other diseases of pulmonary vessels
	I28.0	Arteriovenous fistula of pulmonary vessels
	I28.1	Aneurysm of pulmonary artery
	I28.8	Other specified diseases of pulmonary vessels
	I28.9	Disease of pulmonary vessels, unspecified
	I30	Acute pericarditis
	I30.0	Acute nonspecific idiopathic pericarditis
	I30.1	Infective pericarditis
	I30.8	Other forms of acute pericarditis
	I30.9	Acute pericarditis, unspecified
	I31	Other diseases of pericardium
	I31.0	Chronic adhesive pericarditis
	I31.1	Chronic constrictive pericarditis
	I31.2	Haemopericardium, not elsewhere classified
	I31.3	Pericardial effusion (noninflammatory)
	I31.8	Other specified diseases of pericardium
	I31.9	Disease of pericardium, unspecified
	I32	Pericarditis in diseases classified elsewhere
	I32.0	Pericarditis in bacterial diseases classified elsewhere
	I32.1	Pericarditis in other infectious and parasitic diseases classified elsewhere
	I32.8	Pericarditis in other diseases classified elsewhere
	I33	Acute and subacute endocarditis
	I33.0	Acute and subacute infective endocarditis
	I33.9	Acute endocarditis, unspecified
	I34	Nonrheumatic mitral valve disorders
	I34.0	Mitral (valve) insufficiency
	I34.1	Mitral (valve) prolapse
	I34.2	Nonrheumatic mitral (valve) stenosis
	I34.8	Other nonrheumatic mitral valve disorders
	I34.9	Nonrheumatic mitral valve disorder, unspecified
	I35	Nonrheumatic aortic valve disorders
	I35.0	Aortic (valve) stenosis
	I35.1	Aortic (valve) insufficiency
	I35.2	Aortic (valve) stenosis with insufficiency
	I35.8	Other aortic valve disorders
	I35.9	Aortic valve disorder, unspecified
	I36	Nonrheumatic tricuspid valve disorders
	I36.0	Nonrheumatic tricuspid (valve) stenosis
	I36.1	Nonrheumatic tricuspid (valve) insufficiency
	I36.2	Nonrheumatic tricuspid (valve) stenosis with insufficiency
	I36.8	Other nonrheumatic tricuspid valve disorders
	I36.9	Nonrheumatic tricuspid valve disorder, unspecified
	I37	Pulmonary valve disorders
	I37.0	Pulmonary valve stenosis
	I37.1	Pulmonary valve insufficiency
	I37.2	Pulmonary valve stenosis with insufficiency
	I37.8	Other pulmonary valve disorders
	I37.9	Pulmonary valve disorder, unspecified
	I38	Endocarditis, valve unspecified

Table 10: International classification of diseases coding version 10 codes used for CVD death *(continued)*

coding category	icd-10 code	description
	I39	Endocarditis and heart valve disorders in diseases classified elsewhere
	I39.0	Mitral valve disorders in diseases classified elsewhere
	I39.1	Aortic valve disorders in diseases classified elsewhere
	I39.2	Tricuspid valve disorders in diseases classified elsewhere
	I39.3	Pulmonary valve disorders in diseases classified elsewhere
	I39.4	Multiple valve disorders in diseases classified elsewhere
	I39.8	Endocarditis, valve unspecified, in diseases classified elsewhere
	I40	Acute myocarditis
	I40.0	Infective myocarditis
	I40.1	Isolated myocarditis
	I40.8	Other acute myocarditis
	I40.9	Acute myocarditis, unspecified
	I41	Myocarditis in diseases classified elsewhere
	I41.0	Myocarditis in bacterial diseases classified elsewhere
	I41.1	Myocarditis in viral diseases classified elsewhere
	I41.2	Myocarditis in other infectious and parasitic diseases classified elsewhere
	I41.8	Myocarditis in other diseases classified elsewhere
	I42	Cardiomyopathy
	I42.0	Dilated cardiomyopathy
	I42.00	Dilated cardiomyopathy – Reduced Left Ventricular Ejection Fraction
	I42.01	Dilated cardiomyopathy – Preserved Left Ventricular Ejection Fraction
	I42.09	Dilated cardiomyopathy – No information on Left Ventricular Ejection Fraction
	I42.1	Obstructive hypertrophic cardiomyopathy
	I42.2	Other hypertrophic cardiomyopathy
	I42.3	Endomyocardial (eosinophilic) disease
	I42.4	Endocardial fibroelastosis
	I42.5	Other restrictive cardiomyopathy
	I42.6	Alcoholic cardiomyopathy
	I42.7	Cardiomyopathy due to drugs and other external agents
	I42.8	Other cardiomyopathies
	I42.81	Other cardiomyopathies – Tako-tsubo cardiomyopathy
	I42.9	Cardiomyopathy, unspecified
	I42.90	Cardiomyopathy, unspecified – Reduced Left Ventricular Ejection Fraction
	I42.91	Cardiomyopathy, unspecified – Preserved Left Ventricular Ejection Fraction
	I42.99	Cardiomyopathy, unspecified – No information on Left Ventricular Ejection Fraction
	I43	Cardiomyopathy in diseases classified elsewhere
	I43.0	Cardiomyopathy in infectious and parasitic diseases classified elsewhere
	I43.1	Cardiomyopathy in metabolic diseases
	I43.2	Cardiomyopathy in nutritional diseases
	I43.8	Cardiomyopathy in other diseases classified elsewhere
	I44	Atrioventricular and left bundle-branch block
	I44.0	Atrioventricular block, first degree
	I44.1	Atrioventricular block, second degree
	I44.2	Atrioventricular block, complete
	I44.3	Other and unspecified atrioventricular block
	I44.4	Left anterior fascicular block
	I44.5	Left posterior fascicular block
	I44.6	Other and unspecified fascicular block
	I44.7	Left bundle-branch block, unspecified
	I45	Other conduction disorders
	I45.0	Right fascicular block
	I45.1	Other and unspecified right bundle-branch block

Table 10: International classification of diseases coding version 10 codes used for CVD death *(continued)*

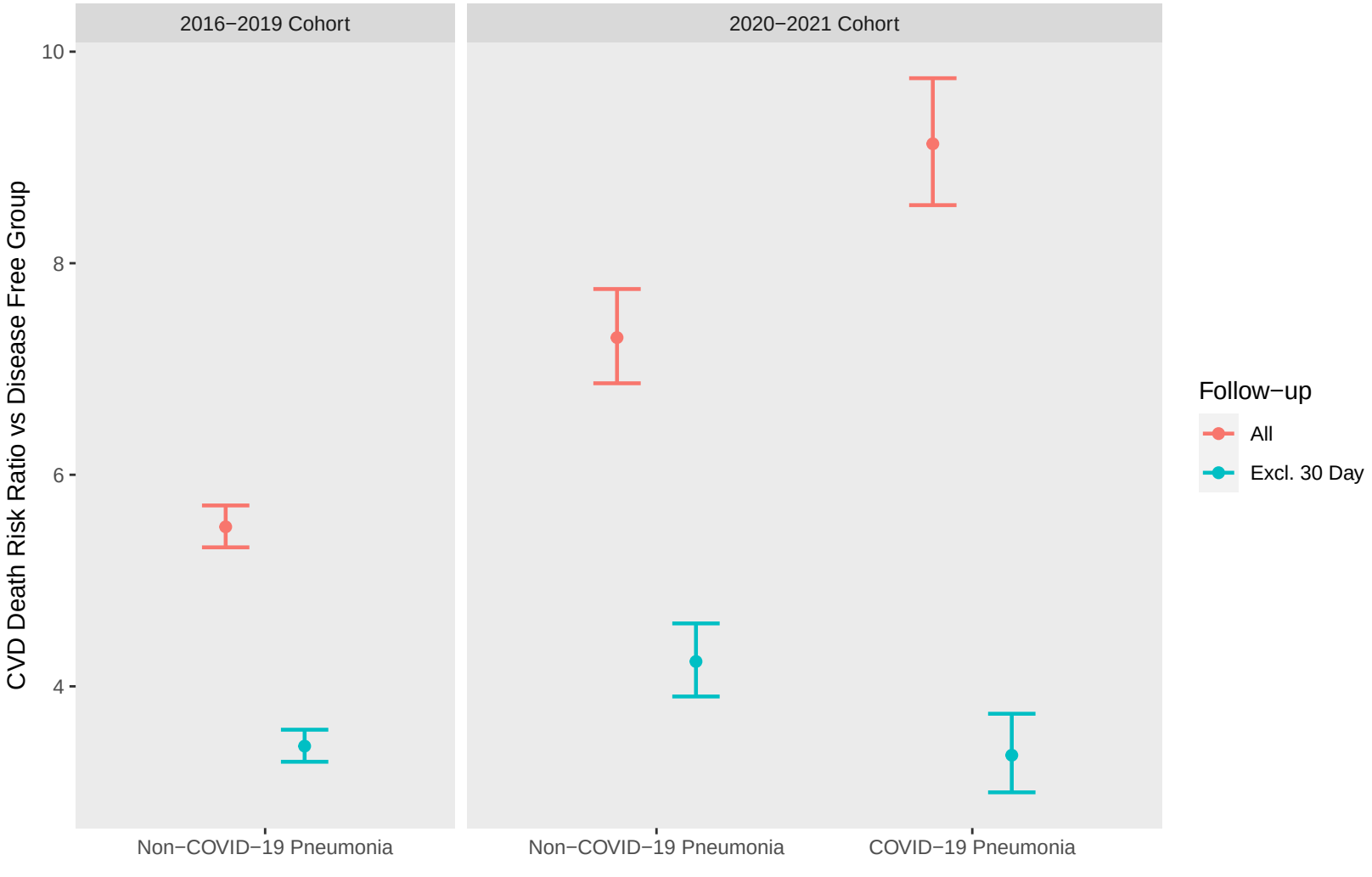
coding category	icd-10 code	description
	I45.2	Bifascicular block
	I45.3	Trifascicular block
	I45.4	Nonspecific intraventricular block
	I45.5	Other specified heart block
	I45.6	Pre-excitation syndrome
	I45.8	Other specified conduction disorders
	I45.9	Conduction disorder, unspecified
	I46	Cardiac arrest
	I46.0	Cardiac arrest with successful resuscitation
	I46.1	Sudden cardiac death, so described
	I46.9	Cardiac arrest, unspecified
	I47	Paroxysmal tachycardia
	I47.0	Re-entry ventricular arrhythmia
	I47.1	Supraventricular tachycardia
	I47.2	Ventricular tachycardia
	I47.9	Paroxysmal tachycardia, unspecified
	I48	Atrial fibrillation and flutter
	I48.0	Paroxysmal atrial fibrillation
	I48.1	Persistent atrial fibrillation
	I48.2	Chronic atrial fibrillation
	I48.3	Typical atrial flutter
	I48.4	Atypical atrial flutter
	I48.9	Atrial fibrillation and atrial flutter, unspecified
	I49	Other cardiac arrhythmias
	I49.0	Ventricular fibrillation and flutter
	I49.1	Atrial premature depolarization
	I49.2	Junctional premature depolarization
	I49.3	Ventricular premature depolarization
	I49.4	Other and unspecified premature depolarization
	I49.5	Sick sinus syndrome
	I49.8	Other specified cardiac arrhythmias
	I49.9	Cardiac arrhythmia, unspecified
	I50	Heart failure
	I50.0	Congestive heart failure
	I50.00	Congestive heart failure – Reduced Left Ventricular Ejection Fraction
	I50.01	Congestive heart failure – Preserved Left Ventricular Ejection Fraction
	I50.09	Congestive heart failure – No information on Left Ventricular Ejection Fraction
	I50.1	Left ventricular failure
	I50.10	Left ventricular failure – Reduced Left Ventricular Ejection Fraction
	I50.11	Left ventricular failure – Preserved Left Ventricular Ejection Fraction
	I50.19	Left ventricular failure – No information on Left Ventricular Ejection Fraction
	I50.9	Heart failure, unspecified
	I50.90	Heart failure, unspecified – Reduced Left Ventricular Ejection Fraction
	I50.91	Heart failure, unspecified – Preserved Left Ventricular Ejection Fraction
	I50.99	Heart failure, unspecified – No information on Left Ventricular Ejection Fraction
	I51	Complications and ill-defined descriptions of heart disease
	I51.0	Cardiac septal defect, acquired
	I51.1	Rupture of chordae tendineae, not elsewhere classified
	I51.2	Rupture of papillary muscle, not elsewhere classified
	I51.3	Intracardiac thrombosis, not elsewhere classified
	I51.4	Myocarditis, unspecified
	I51.5	Myocardial degeneration

Table 10: International classification of diseases coding version 10 codes used for CVD death *(continued)*

coding category	icd-10 code	description
	I51.6	Cardiovascular disease, unspecified
	I51.7	Cardiomegaly
	I51.8	Other ill-defined heart diseases
	I51.9	Heart disease, unspecified
	I52	Other heart disorders in diseases classified elsewhere
	I52.0	Other heart disorders in bacterial diseases classified elsewhere
	I52.1	Other heart disorders in other infectious and parasitic diseases classified elsewhere
	I52.8	Other heart disorders in other diseases classified elsewhere
	I60	Subarachnoid haemorrhage
	I60.0	Subarachnoid haemorrhage from carotid siphon and bifurcation
	I60.1	Subarachnoid haemorrhage from middle cerebral artery
	I60.2	Subarachnoid haemorrhage from anterior communicating artery
	I60.3	Subarachnoid haemorrhage from posterior communicating artery
	I60.4	Subarachnoid haemorrhage from basilar artery
	I60.5	Subarachnoid haemorrhage from vertebral artery
	I60.6	Subarachnoid haemorrhage from other intracranial arteries
	I60.7	Subarachnoid haemorrhage from intracranial artery, unspecified
	I60.8	Other subarachnoid haemorrhage
	I60.9	Subarachnoid haemorrhage, unspecified
	I61	Intracerebral haemorrhage
	I61.0	Intracerebral haemorrhage in hemisphere, subcortical
	I61.1	Intracerebral haemorrhage in hemisphere, cortical
	I61.2	Intracerebral haemorrhage in hemisphere, unspecified
	I61.3	Intracerebral haemorrhage in brain stem
	I61.4	Intracerebral haemorrhage in cerebellum
	I61.5	Intracerebral haemorrhage, intraventricular
	I61.6	Intracerebral haemorrhage, multiple localized
	I61.8	Other intracerebral haemorrhage
	I61.9	Intracerebral haemorrhage, unspecified
	I62	Other nontraumatic intracranial haemorrhage
	I62.0	Subdural haemorrhage (acute)(nontraumatic)
	I62.1	Nontraumatic extradural haemorrhage
	I62.9	Intracranial haemorrhage (nontraumatic), unspecified
	I63	Cerebral infarction
	I63.0	Cerebral infarction due to thrombosis of precerebral arteries
	I63.1	Cerebral infarction due to embolism of precerebral arteries
	I63.2	Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
	I63.3	Cerebral infarction due to thrombosis of cerebral arteries
	I63.4	Cerebral infarction due to embolism of cerebral arteries
	I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
	I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
	I63.8	Other cerebral infarction
	I63.9	Cerebral infarction, unspecified
	I64	Stroke, not specified as haemorrhage or infarction
	I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
	I65.0	Occlusion and stenosis of vertebral artery
	I65.1	Occlusion and stenosis of basilar artery
	I65.2	Occlusion and stenosis of carotid artery
	I65.3	Occlusion and stenosis of multiple and bilateral precerebral arteries
	I65.8	Occlusion and stenosis of other precerebral artery
	I65.9	Occlusion and stenosis of unspecified precerebral artery
	I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction

Table 10: International classification of diseases coding version 10 codes used for CVD death *(continued)*

coding category	icd-10 code	description
	I66.0	Occlusion and stenosis of middle cerebral artery
	I66.1	Occlusion and stenosis of anterior cerebral artery
	I66.2	Occlusion and stenosis of posterior cerebral artery
	I66.3	Occlusion and stenosis of cerebellar arteries
	I66.4	Occlusion and stenosis of multiple and bilateral cerebral arteries
	I66.8	Occlusion and stenosis of other cerebral artery
	I66.9	Occlusion and stenosis of unspecified cerebral artery
	I67	Other cerebrovascular diseases
	I67.0	Dissection of cerebral arteries, nonruptured
	I67.1	Cerebral aneurysm, nonruptured
	I67.2	Cerebral atherosclerosis
	I67.3	Progressive vascular leukoencephalopathy
	I67.4	Hypertensive encephalopathy
	I67.5	Moyamoya disease
	I67.6	Nonpyogenic thrombosis of intracranial venous system
	I67.7	Cerebral arteritis, not elsewhere classified
	I67.8	Other specified cerebrovascular diseases
	I67.9	Cerebrovascular disease, unspecified
	I68	Cerebrovascular disorders in diseases classified elsewhere
	I68.0	Cerebral amyloid angiopathy
	I68.1	Cerebral arteritis in infectious and parasitic diseases classified elsewhere
	I68.2	Cerebral arteritis in other diseases classified elsewhere
	I68.8	Other cerebrovascular disorders in diseases classified elsewhere
	I69	Sequelae of cerebrovascular disease
	I69.0	Sequelae of subarachnoid haemorrhage
	I69.1	Sequelae of intracerebral haemorrhage
	I69.2	Sequelae of other nontraumatic intracranial haemorrhage
	I69.3	Sequelae of cerebral infarction
	I69.4	Sequelae of stroke, not specified as haemorrhage or infarction
	I69.8	Sequelae of other and unspecified cerebrovascular diseases


2016–2019 Cohort
2020–2021 Cohort
CVD Death Risk Ratio vs Disease Free Group
10
8
6
4
Non–COVID–19 Pneumonia
Non–COVID–19 Pneumonia
COVID–19 Pneumonia
Hospitalised Pneumonia Status
Follow–up
All
Excl. 30 Day

Impact of COVID-19 and non-COVID-19 hospitalised pneumonia on longer term cardiovascular mortality in people with type 2 diabetes: A nationwide prospective cohort study from Scotland

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Tweet: Pneumonia hospitalisation significantly raises long-term CVD death risk in people with diabetes, irrespective of COVID-19 or other causes.

Running Title: Pneumonia, COVID-19 & CVD Mortality in Diabetes

Keywords: Type 2 Diabetes, COVID-19, Pneumonia, Cardiovascular Mortality

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Word count: 3985

Commented [SM1]: Clarified hospitalisation

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Abstract

Objective: This study examines if hospitalised COVID-19 pneumonia increases long-term cardiovascular mortality more than other hospitalised pneumonias in people with type 2 diabetes and aims to quantify the relative cardiovascular disease (CVD) mortality risks associated with COVID-19 versus non-COVID-19 pneumonia.

Research Design and Methods: Using the SCI-Diabetes register, two cohorts were identified: people with type 2 diabetes in 2016 and at the 2020 pandemic onset. Hospital and death records were linked to determine pneumonia exposure and CVD deaths. Poisson regression estimated hazard ratios (HR) for CVD death associated with both pneumonia types, adjusted for confounders. The median follow-up was 1461 days (2016 cohort) and 700 days (2020 cohort).

Results and Conclusions: The adjusted HR for CVD death following non-COVID-19 pneumonia was 5.51 (95% CI 5.31-5.71) pre-pandemic and 7.3 (95% CI 6.86-7.76) during the pandemic. For COVID-19 pneumonia, the HR was 9.13 (95% CI 8.55-9.75). Beyond 30 days post-pneumonia, the HRs converged to 4.24 (95% CI 3.90-4.60), for non-COVID-19 and 3.35 (95% CI 3.00-3.74) for COVID-19 pneumonia, consistent even when excluding prior CVD cases. Hospitalised pneumonia, irrespective of causal agent, marks an increased risk for CVD death immediately and over the long term. COVID-19 pneumonia poses a higher CVD death risk than other pneumonias in the short term, but this distinction diminishes over time. These insights underscore the need for including pneumonia in CVD risk assessments, with particular attention to the acute impact of COVID-19 pneumonia.

Research in Context

What is already known about this subject?

- Individuals at higher risk for CVD face increased pneumonia risk, with both COVID-19 and non-COVID pneumonia linked to heightened CVD risk, though precise comparisons remain unquantified.

- ~~Those at increased risk of CVD are also at increased risk of developing pneumonia~~

What is the key question?

- Does COVID-19 pneumonia raise CVD death risk more than other pneumonias, and does this persist long-term?~~Does COVID-19 pneumonia increase risk of CVD death more than other pneumonias and if so is this only in the short-term or also over the longer-term?~~

What are the new findings?

- Both COVID and non-COVID pneumonia significantly increase CVD death risk; COVID-19 risk is initially increased but both lead to around a 4.2 fold increase post-30 days.

- ~~COVID-19 and non-COVID-19 pneumonia are associated with a substantial increased risk of CVD death even when prior CVD risk is considered~~

~~The risk associated with non-COVID-19 pneumonia increased during the pandemic period but was lower than for COVID-19 pneumonia even during the pandemic period~~

- ~~However, beyond the first 30 days of pneumonia the longer-term elevation in risk of CVD death associated with pneumonia was similar regardless of the cause being approximately 4.2 fold~~

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

- A history of pneumonia, from any cause, is a key risk indicator for CVD death in diabetes, emphasising its importance in prioritising CVD prevention efforts for people with diabetes.~~Prior history of pneumonia regardless of cause is an important risk marker for CVD death in diabetes and should be considered when prioritising interventions for primary and secondary prevention of CVD in people with diabetes~~

Introduction

There are concerns that the COVID-19 pandemic will lead to an explosion in the incidence of cardiovascular morbidity and mortality well beyond the pandemic, particularly in those with diabetes. The factors that could lead to such an explosion in CVD are complex including reduced diabetes and cardiovascular care during and beyond the pandemic[1], reduced operative interventions[2], potential effects of vaccines on myocarditis (though this seems very modest) but also long term effects of SARS-CoV-2 infection itself on the cardiovascular system[3]. In the UK excess all-cause mortality has continued well into 2023 partly due to an excess in CVD mortality and deaths mentioning diabetes[4].

Regarding the long term direct effects of severe SARS-Co-V-2 infection, as evidenced by COVID-19 pneumonia, on the cardiovascular system an important question is the extent to which prior COVID-19 pneumonia is associated with cardiovascular mortality in the immediate aftermath of pneumonia as well as subsequently. This question is complicated by the fact that risk of developing COVID-19 pneumonia is increased by prior frailty including prior CVD and diabetes. In the overall population increased risks associated with COVID-19 compared to historical controls have been found in some studies after 30 days[5] but not in all[6]. Systematic reviews of the literature on CVD incidence after COVID-19 pneumonia suggest that there is strong evidence of short term increased risk but there is insufficient data on whether this elevation in risk is sustained as most studies are of very short duration[7]. These studies differed in how COVID-19 was captured with some examining outcomes after testing positive for COVID-19 and some focusing on those hospitalised. A recent report from the U.S Centers for Disease Control[8] using insurance claims data found an increased risk of CVD associated with prior COVID-19 diagnosis codes compared to those without COVID-19 over a mean follow-up time of 8.5 months that was slightly greater in those without than with diabetes[8]. The aim of this study is therefore to examine the longer term relative risk of CVD death associated with COVID-19 pneumonia in the population with diabetes in Scotland since the start of the pandemic up to November 2021. To understand the extent to which any increased risk of CVD death is specific to COVID-19 as a cause of pneumonia, the relative risk of CVD death was compared to the relative risk for CVD death associated with non-COVID-19 pneumonia prior to and since the start of the COVID-19 pandemic. We focused on hospitalised COVID-19 because it has been estimated that up to a third of COVID-19 infections were asymptomatic so that accurate classification of infection status is not possible outside of a surveillance setting[9]. Furthermore, this allowed a more comparable inclusion for non-COVID-19 pneumonias since self referral community testing systems akin to that provided nationally for SARS-CoV-2 do not exist. Whilst both relative risks for CVD mortality for COVID-19 and other pneumonias will be subject to confounding by frailty, we reasoned that if we found a much higher relative risk for CVD mortality for COVID-19 pneumonias than other pneumonias this would be consistent with an especially detrimental effect of SARS-CoV-2 on the cardiovascular system that could have implications for milder infections.

Methods

Data Sources

The Scottish Care Information-Diabetes (SCI-Diabetes) serves as a comprehensive register and database encompassing the vast majority (> 99%) of individuals in Scotland who have been diagnosed with diabetes. It has been described in detail previously[10]. The database collects data from various sources, including clinical episodes, laboratory data from primary care, diabetes clinics in the National Health Service (NHS) hospitals, community care, and the national retinopathy screening program. By utilising a unique health service identifier, it has been linked to hospital admissions data (Scottish Morbidity Record 01) and mortality data from the National Records of Scotland.

Participants

We defined two cohorts including all people alive and observable with a clinical diagnosis of Type 2 diabetes in pre-COVID-19 and intra COVID-19 pandemic time windows January 1st, 2016 to December 31st, 2019 (N=263922, follow-up 946547 years) and January 1st, 2020 to November 30th, 2021 (N=284801, follow-up 515226 years) respectively. To define a cohort free of recent pneumonia at baseline, for each time window, we excluded individuals who were admitted to hospital with any bacterial or viral pneumonia infection in the preceding 3 years.

Exposure to pneumonia

Exposure was defined as a hospital admission with bacterial or viral pneumonia. We selected Scottish Morbidity Records inpatient and day case procedure records (SMR01) which use the World Health Organisation (WHO) International Classification of Disease version 10 (ICD-10). In the study, pneumonia was subset as ICD-10 coding in any position of the SMR01 hospital episode. ICD-10 codes used for Non-COVID-19 and COVID-19 pneumonia are provided in ESM Table 6.

Where a discharge included only a non-COVID ICD-10 pneumonia code but where there was a positive rt-PCR test for COVID-19 during the admission, we assigned that into the COVID-19 pneumonia category. Where both non-COVID and COVID-19 codes were present on the discharge summary we assigned that as COVID-19 pneumonia

Cardiovascular disease during the study and prior lookback windows was determined using hospital discharge ICD10 codes. The codes used are provided in ESM Table 9.

The outcome of cardiovascular mortality in the study window was ascertained from the Medical Certificate of Cause of Death (MCCD) data provided by the National Records of Scotland (NRS). Cause-specific information for the cause of death was defined by ICD-10 coding present at any position on an MCCD. The codes used are provided in ESM Table 10.

Other covariate and risk factor data were obtained from SCI-Diabetes on HbA1c, body weight, BMI, blood pressure, estimated GFR (eGFR), plasma total cholesterol, albuminuria, retinopathy, smoking status, treated for hypertension or dyslipidaemia, ever having atrial fibrillation and the number of ATC level 3 drug classes. The value for these routine measurement variables at the nearest time prior to each cohort entry point was used, with a maximum look-back period of 3 years. Other ever/never risk factors such as prior CVD, immune disease, chronic kidney disease, asthma, liver disease and neurological diseases had a greater lookback period of 10 years.

Observability

The observability status of individuals was defined using a proxy of routine observations and receipt of any prescriptions during the study period. If individuals became unobservable during the study period, they were censored on the date at which they first became unobservable.

Statistical methods

The analyses consisted of multivariable Poisson regression, with each cohort organised in longitudinal survival table format consisting of 28 day intervals. Individuals entered the study at the study entry date, or when they were diagnosed with type 2 diabetes, whichever was sooner. Individuals were right-censored when there was either a loss of observability or death. The exposure variable was constructed as a time updated exposure variable denoting any prior exposure to COVID-19 pneumonia, since the start of follow-up, any prior non COVID-19 pneumonia since start of follow-up or exposure to neither, the pneumonia exposure index date being that of hospital admission. There were a small number of individuals who during the COVID-19 era had first one type of pneumonia and then in a later separate admission had another type but for simplicity, these were excluded from the analysis as numbers were low (N=271). The regression coefficient in each model was used to estimate the association between pneumonia and cardiovascular death, considering all time and 30 days post infection.

Adjustment was carried out in two stages. Firstly, a simple model was used, which included age, sex, and diabetes duration as covariates. Secondly, a more complex model was employed, incorporating several additional covariates expected to confound the association between pneumonia exposure and cardiovascular death. The adjustment covariates were entered into the model at baseline and not time updated. The adjustment covariates were derived from previously developed cardiovascular[11,12] and COVID-19[13] risk prediction models (see Table 3 for list of covariates).

Missing covariate data as detailed in ESM Table 1 were imputed using a multiple imputation approach. The imputation process involved utilising an expectation-maximization with bootstrapping (EMB) algorithm, assuming that the missing data were random conditional on the covariates and independent of the cardiovascular death outcome. The imputation was performed using the Amelia II package in R[14,15]. Multiple imputation was used, where five imputed datasets were generated, and for continuous variables, the mean of the imputed values was utilised in the regression model. Categorical variables were converted into probabilities for each category, representing the frequency of occurrence across the five imputations.

Results

Table 1 shows the baseline characteristics by pneumonia status for the 2020-2021 (COVID-19 era) cohort. A similar table for the 2016-2019 (pre-COVID-19 era) is contained in ESM Table 2. The data demonstrate the importance of adjusting for confounders when assessing the association of pneumonias with CVD death since those who developed pneumonia were older, had more deprived socioeconomic status and more prior comorbid conditions including CVD, were on more drugs and were more likely to have smoked. Those developing non-COVID pneumonia were older than COVID-pneumonia and the interquartile range of their Charlson index was 4 to 7 versus 1-6 for the COVID-19 group.

Table 2 illustrates the large numbers of people in the cohorts and large number of events in this study. The minimally adjusted (age, sex and diabetes duration adjusted) risk ratios for CVD death associated with pneumonia type in the Scottish population with type 2 diabetes for 2016-2019 and 2020-2021 cohorts are given as a baseline risk ratio ~~for~~ prior to adjustment for additionaal potential confounders. As shown both non-COVID-19 and COVID-19 pneumonia were associated with a more than 10 fold elevation in risk of CVD death adjusted for age sex and diabetes duration.

Table 3 illustrates the effect of adjusting for potential confounders on the risk ratio for CVD death associated with pneumonias. Even with this adjustment pneumonias are associated with a large elevation in risk that was somewhat greater for COVID-19 (9.13) than non-COVID-19 (7.3) pneumonia. A broadly similar degree of reduction in the risk ratio with adjustment for potential confounders was seen regardless of pneumonia type. The multivariate adjusted risks ratio for pneumonia in the pre-COVID-19 era is given in ESM Table 3; the RR for non-COVID-19-pneumona was lower than for non-COVID-19 during the pandemic years even after adjusting for the difference in frailty in the two eras as evidenced by the increase in the Charlson index interquartile range from the pre-pandemic to pandemic period in those with non-COVID-19 pneumonia. A similar reduction in the relative risk with covariate adjustment was found (5.51). As shown in ESM Table 4 a similar pattern was found when the analyses were restricted to those without prior CVD at baseline- exposure to any pneumonia being associated with an increased risk of CVD.

ESM Table 5 and Figure 1 show the risk ratios for CVD death when the analysis is restricted to the period beyond 30 days post pneumonia, or in other words conditional upon surviving the first 30 days post-pneumonia. The relative risk of CVD death remains high but is much less than that for the total period including the immediate post pneumonia period. Furthermore, as shown, conditional on surviving the first 30 days post exposure, the subsequent relative risk of CVD death associated with prior exposure to COVID-19 pneumonia alone are somewhat lower than for non-COVID-19 pneumonia RR (3.35 and 4.24 respectively).

We also examined the relationship of non-COVID-19 and COVID-19 pneumonia to all cause mortality during follow up (ESM Tables 6 and 7). The magnitude of RR for all cause mortality was similar to that for CVD mortality. A very similar pattern was also found i.e. a slightly higher RR for COVID-19 than non-COVID-19 pneumonia overall but slightly lower after the first 30 days.

Discussion

Statement of principal findings

The key findings of this study are that in those with diabetes, prior to the pandemic era non-COVID-19-pneumonias were associated with a 5.5-fold elevation in risks of CVD death adjusted for CVD risks factors. This elevation in risk worsened during the pandemic period. The increased risk associated with COVID-19 pneumonia (9.1 fold) was somewhat higher than that associated with other pneumonias (7.3 fold) during the pandemic period. However, most of this greater elevation in risk of CVD death with COVID-19 than non-COVID-19 pneumonia reflected a greater impact of COVID-19 in the short term after pneumonia. From the first 30 days after pneumonia, COVID-19 was not associated with a greater elevation in CVD death than non-COVID-19 pneumonia over an average follow-up of 21 months.

Thus, regardless of the cause of pneumonia, having had a prior hospitalisation for pneumonia remains an important risk marker for CVD death in people with diabetes. Therefore, when developing risk scores for incident CVD events in future, researchers should consider the potential for pneumonia history to improve prediction. However, the concern that COVID-19 has a much greater long term risk on the cardiovascular system than other causes of pneumonia is not supported by these data.

Strengths and weaknesses of the study

The strengths of this study are the comprehensive capture of data from everyone with type 2 diabetes in Scotland and the comprehensive capture of all deaths. Other strengths are the extensive covariate data from the clinical records. Strengths in the design is the comparison of the relative risks with those seen for other pneumonias and that we have shown that using pre-pandemic data for other pneumonias could exaggerate

apparent COVID-19 effects since the relative risks for other pneumonias themselves increased during the pandemic period.

A further strength is that we noted very similar pattern was noted for all cause mortality such that competing risks do not account for our observations.

Limitations of this study include that for both causes of pneumonia one cannot rule out residual confounding by prior risk of CVD or subclinical CVD being a risk factor for COVID-19 from a direct effect of pneumonia on subsequent CVD. However, that the relative risks were only moderately reduced by adjustment for a large set of known confounders makes it unlikely that residual confounding alone could account for the observed effects. Furthermore, regardless of whether elevated risks partly reflect confounding the data clearly show that a prior history of hospitalised pneumonia is at the least an important risk marker for future CVD. Another limitation is that with respect to comparing the impact of different pneumonia causes the analysis assumes that COVID-19 codes were correctly assigned, and non-assigned, to pneumonias during the pandemic and we cannot externally validate this coding. If random misclassification of cause occurred, this would tend to make the relative risks associated with the different types of pneumonia more similar.

Another important limitation is the potential for collider bias[16]. A collider is a factor that is caused by both the exposure and the outcome under consideration. Conditioning on such a collider can cause a biased estimate of the association. An issue for our analysis is whether hospitalisation is a collider in the analysis. We chose CVD mortality (regardless of the death being hospitalised or not) as the outcome in our analysis. We conducted two sets of analysis one including all follow up time and one restricted to 30 days after the admission. In this latter analysis where the death is occurring much after the initial admission the CVD death hospitalisation cannot be a collider. However in the first 30 day period since some hospitalisations may have been precipitated by underlying CVD that eventually led to CVD death this could induce collider bias in the estimates for the RR for CVD mortality associated with pneumonias that includes the first 30 day period. Thus the most valid estimates for considering the main hypothesis of whether COVID-19 has a greater long term impact on CVD mortality than non-COVID-pneumonias are those pertaining to the post 30 day period. We have focused on hospitalised pneumonias as the exposure of interest rather than having had a positive rt-PCR for SARS-CoV-2.

We have done this because although there was extensive free of charge rt-PCR testing for SARS-CoV-2 (including self referral) this will not correctly classify SARS-Co-V-2 exposure since it has been estimated that up to a third of infections were asymptomatic[9]. We note that had we used rt-PCR community tests as the basis for exposure definition this would have precluded comparison with other pneumonias since there was no equivalent testing in the community for these. This comparison was critical to answering the key question of whether there was any extra detrimental effect of SARS-CoV-2 on CVD.

Strengths and weaknesses in relation to other studies, discussing important differences in results;

Our results are not entirely consistent with other studies that found initial elevations in CVD incidence shortly after COVID-19 that did not persist after the first few months[6]. We found that excluding the first 30 days risks fell but continued to be elevated in the 2-4 fold range. A recent review focusing on post 30 day outcomes found heterogeneity in existing evidence with lack of adjustment for confounders and relatively short follow up[7]. Our follow-up was longer than many of these studies and larger. Most studies have simply compared CVD incidence in those with and without prior COVID-19. We chose to also compare to risks associated with other pneumonias since the potential for residual confounding by prior risk should be at least as great for COVID-19 as non-COVID-19 pneumonia, allowing us to assess whether COVID-19 has a particularly great effect. We also chose to focus on the hard outcome of CVD death but future work will consider the effect on different constellations of CVD events.

Previous studies that have compared the effect of COVID-19 with other pneumonias have focused usually on historical pre-pandemic controls[17] and have had fairly short follow-up. For example, a French study reported a greater 90 day mortality for COVID-19 than influenza[18]. Others have focused on in-hospital rather than longer term mortality[19]. One of the largest and longest studies to date, and one of the few examining risks among those with diabetes, is a recent study from the US Centres of Disease Control. That study over a median of 8.5 months excluding the first 30 days also found an elevation in CVD incidence associated with COVID-19. The relative risk was less than we found at 1.66 probably since in that study any COVID-19 diagnosis as an outpatient or inpatient was considered as the exposure whereas we focused on the more severe COVID-19 pneumonia admission. The studies also differed in that the outcome was CVD incidence unlike our study of CVD mortality. Unlike our findings for CVD mortality, CVD incidence was higher after COVID-19 infection than after other acute respiratory infections pre-pandemic. However, as we have shown using a pre-pandemic comparator may not be valid since the pandemic period itself seems to have worsened the outcomes associated with other pneumonias than COVID-19. Given the pressure that health services were under this is not surprising and it may also reflect a higher threshold for admission during the pandemic period as was shown by a slightly worse Charlson index in those admitted during the pandemic than pre-pandemic period. Consistent with our findings they found that relative risks were much higher in the first 30 days after the infection and then fell. This finding is consistent with systemic inflammation

acutely worsening risk of a CV event and subsequent death due to effects on risk pathways, perhaps particular haemostatic status. Notably, acute systemic inflammatory levels are known to be greater with COVID-19 infections versus other infections[20].

Meaning of the study: possible explanations and implications for clinicians and policymakers

The practical implications of this analysis are that the fears of greatly elevated rates of CVD over the long term post-pandemic due to direct effects of COVID-19 on the CVD system may be less than has been feared. What remains important though is careful risk factor management and optimising primary and secondary prevention and management in anyone with diabetes with prior hospitalised pneumonia regardless of cause.

Unanswered questions and future research

There remain many important unanswered questions on the long term effects of respiratory infections on CVD. Not least is what the mechanism of this association is. Does it for example reflect continued systemic inflammation, sequelae of direct myocardial damage at the time of infection, persistent thrombogenesis or other pathways and are there specific interventions that could target the mechanisms involved? More broadly, longer follow-up post pandemic is needed to be certain what the long term effect is of COVID-19 on CVD. Finally, the broader impact of the pandemic period and its attendant controls on health and on health care delivery still need to be understood and reversed.

Declarations

Information governance

This research was conducted with approval from the Public Benefit Privacy Protection Panel (PBPP ref. 1617-0147), originally set up under PAC 33/11, with approval from the Scotland A Research Ethics Committee (ref. 11/AL/0225). All datasets were de-identified before analysis.

Data Availability

NHS Data governance rules do not permit us to secondarily share the data directly. However, *Bone fide* researchers can apply to the Scottish Public Benefits and Privacy Protection Committee for access to these data.

Conflicts of interest

The authors have no conflicts of interest to declare.

Contributions

HMC, SJM and PMM conceived and designed the study. NS, JM, SW, TMC, and BK made important contributions to study design. SJM and LAKB were involved in the cleaning, harmonisation, quality control and databasing of data in Scotland. SJM performed the analyses. NS, JM, SW, and BK contributed to data analysis and interpretation. HMC and PMM developed data analysis methods. SJM and HMC drafted the initial manuscript. All authors made critically important contributions to the manuscript revision. All authors approved the final manuscript. HMC is the guarantor and, as such, is responsible for the integrity of the work as a whole.

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Data validity

Stuart McGurnaghan and Helen Colhoun had full access to the data reported in this paper which they analysed and take responsibility for its validity.

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Table 1: Cohort characteristics at 2020-01-01 study entry

	No Pneumonias	Non-COVID-19 Pneumonia	COVID-19 Pneumonia	Total
Total included	272730(95.78)	5533(1.94)	6483(2.28)	284801
Follow-up (days)	700(700,700)	700(428,700)	700(451,700)	700(700,700)
Sociodemographic				
Current age (years)	67.0(57.8,75.5)	76.3(68.3,83.3)	71.7(61.2,80.0)	67.4(58.0,75.9)
Sex				
Male	154161(56.5)	3153(57.0)	3734(57.6)	161081(56.6)
Female	118569(43.5)	2380(43.0)	2749(42.4)	123720(43.4)
Diabetes duration (years)	10.7(6.1,16.2)	13.1(7.5,18.8)	12.2(7.0,18.2)	10.7(6.2,16.3)
Ethnicity				
White	199717(73.2)	4410(79.7)	4955(76.4)	209127(73.4)
Non White	11419(4.2)	90(1.6)	335(5.2)	11848(4.2)
Other/unknown	61594(22.6)	1033(18.7)	1193(18.4)	63826(22.4)
Deprivation index				
Quintile 1 (most deprived)	62604(23.0)	1399(25.3)	2108(32.5)	66125(23.2)
Quintile 2	61302(22.5)	1355(24.5)	1573(24.3)	64245(22.6)
Quintile 3	55271(20.3)	1077(19.5)	1074(16.6)	57431(20.2)
Quintile 4	49294(18.1)	921(16.6)	906(14.0)	51128(18.0)
Quintile 5 (least deprived)	39739(14.6)	656(11.9)	691(10.7)	41095(14.4)
Unknown	4520(1.7)	125(2.3)	131(2.0)	4777(1.7)
Other clinical measures				
HbA1c (mmol/mol)	55(48,67)	54(47,66)	57(48,71)	55(48,67)
HbA1c (%)	7.18(6.54,8.28)	7.09(6.45,8.23)	7.37(6.54,8.65)	7.18(6.54,8.28)
BMI (kg/m^2)	31(27,35)	30(26,34)	31(27,36)	31(27,35)
Height (meters)	1.68(1.60,1.75)	1.67(1.59,1.74)	1.68(1.60,1.75)	1.68(1.60,1.75)
Weight (kg)	88(75,102)	82(70,97)	89(76,104)	88(75,102)
Systolic BP (mmHg)	134(124,142)	134(122,144)	133(123,142)	134(124,142)
Diastolic BP (mmHg)	78(70,82)	74(67,80)	76(70,81)	78(70,82)
Total cholesterol / HDL ratio (mmol/L)	3.56(2.87,4.42)	3.38(2.70,4.26)	3.54(2.86,4.44)	3.55(2.87,4.42)
eGFR (mL/min/1.73m^2)	83(65,95)	67(48,85)	73(54,90)	82(65,95)
Albuminuric status				
Normal	113851(41.7)	1752(31.7)	2364(36.5)	117982(41.4)
Micro	42941(15.7)	1441(26.0)	1432(22.1)	45828(16.1)
Macro	7750(2.8)	415(7.5)	373(5.8)	8545(3.0)
Unknown	108188(39.7)	1925(34.8)	2314(35.7)	112446(39.5)
Retinopathy				
None	174707(64.1)	3430(62.0)	4046(62.4)	182213(64.0)
Non referable	36997(13.6)	857(15.5)	987(15.2)	38850(13.6)
Referable / eye clinic	18168(6.7)	506(9.1)	703(10.8)	19387(6.8)
Unknown	42858(15.7)	740(13.4)	747(11.5)	44351(15.6)
Tobacco smoking status				
Never smoked	95542(35.0)	1263(22.8)	2028(31.3)	98847(34.7)
Ever smoked	174544(64.0)	4236(76.6)	4412(68.1)	183233(64.3)
Unknown	2644(1.0)	34(0.6)	43(0.7)	2721(1.0)
Comorbidities				
No. with prior CVD	51293(18.8)	2150(38.9)	2073(32.0)	55536(19.5)
No. with atrial fibrillation	18235(6.7)	1026(18.5)	852(13.1)	20122(7.1)
No. treated for dyslipidemia	174213(63.9)	4129(74.6)	4651(71.7)	183033(64.3)
No. treated for hypertension	163832(60.1)	3902(70.5)	4326(66.7)	172098(60.4)
Immune disease or on immunosuppressants	599(0.2)	26(0.5)	32(0.5)	657(0.2)
Chronic kidney disease	5666(2.1)	439(7.9)	434(6.7)	6545(2.3)
Asthma or chronic lower airway disease	33663(12.3)	1832(33.1)	1511(23.3)	37020(13.0)
Liver disease	1350(0.5)	72(1.3)	71(1.1)	1493(0.5)
Neurological and dementia (excluding epilepsy)	9280(3.4)	530(9.6)	503(7.8)	10320(3.6)
Number of ATC level 3 drug classes	12.0(7.0,18.0)	17.0(11.0,22.0)	16.0(10.0,22.0)	12.0(7.0,18.0)
Charlson Comorbidity Index	1.0(1.0,5.0)	5.0(4.0,7.0)	4.0(1.0,6.0)	1.0(1.0,5.0)

Categorical values are shown in N (%) and continuous values are median (interquartile range).

Table 2: Age, sex and diabetes duration adjusted risk ratios for CVD death associated with pneumonia type in the Scottish population with type 2 diabetes for 2016-2019 and 2020-2021 cohorts

Cohort	Subgroup	Total (N)	CVD Deaths (N)	Crude CVD Death Rate (Per 1k/py)	RR (95% CI)	P-Value
2016-2019	All	263922	19672	20.78		
	No Pneumonia	248660	15564	16.76	(reference)	
	Pneumonia	15262	4108	230.27	7.96 (7.68, 8.24)	<0.001
2020-2021	All	284801	10817	20.99		
	No Pneumonias	272730	8522	16.79	(reference)	
	Non-COVID-19 Pneumonia	5533	1250	329.81	11.8 (11.11, 12.53)	<0.001
	COVID-19 Pneumonia	6483	1034	262.77	12.93 (12.12, 13.79)	<0.001

Table 3: Multivariable adjusted risk ratios for CVD death associated with pneumonia types in Scottish T2 population from 2020 to 2021

Covariate	RR	2.5%	97.5%	P-Value
Pneumonia status ref=No Pneumonias				
Non-COVID-19 Pneumonia	7.297	6.865	7.756	<0.001
COVID-19 Pneumonia	9.129	8.549	9.749	<0.001
Current age (years)	0.969	0.879	1.068	0.524
Current age^2 (years^2)	1.001	1.000	1.002	0.153
(Current age/100)^3 (years/100^3)	1.000	0.999	1.000	0.326
Sex ref=Male				
Female	0.831	0.798	0.866	<0.001
Diabetes duration (years)	1.010	1.007	1.013	<0.001
Ethnicity ref=White				
Other/unknown	0.980	0.934	1.029	0.422
Non White	0.660	0.564	0.772	<0.001
Deprivation Index ref=Quintile 1 (most deprived)				
Quintile 2	0.920	0.870	0.972	0.003
Quintile 3	0.940	0.887	0.995	0.033
Quintile 4	0.874	0.823	0.928	<0.001
Quintile 5 (least deprived)	0.830	0.778	0.886	<0.001
HbA1c (mmol/mol)	1.004	1.003	1.005	<0.001
HbA1c (3 year average) (mmol/mol)	1.000	0.999	1.001	0.761
log BMI (kg/m^2)	0.645	0.578	0.719	<0.001
Height (meters)	1.011	0.969	1.055	0.599
Systolic BP (mmHg)	0.999	0.999	1.000	0.064
log Total cholesterol (mmol/L)	1.024	0.945	1.108	0.565
log eGFR (mL/min/1.73m^2)	1.123	1.079	1.169	<0.001
Albuminuria Status ref=Normal				
Micro	1.305	1.242	1.371	<0.001
Macro	1.640	1.523	1.764	<0.001
Retinopathy Status ref=None				
Non referable	1.124	1.066	1.185	<0.001
Referable or eye clinic	1.343	1.262	1.429	<0.001
Smoking Status ref=Never				
Ever smoked	1.162	1.111	1.216	<0.001
Unknown	1.080	0.816	1.429	0.590
Treated for hypertension	1.119	1.067	1.173	<0.001
Treated for dyslipidemia	1.053	1.000	1.109	0.051
Ever atrial fibrillation	1.755	1.677	1.836	<0.001
Prior CVD	1.676	1.604	1.752	<0.001
Immune disease or on immunosuppressants	0.795	0.558	1.132	0.204
Chronic kidney disease	1.657	1.536	1.787	<0.001
Asthma or chronic lower airway disease	1.292	1.235	1.352	<0.001
Liver disease	1.474	1.253	1.733	<0.001
Neurological and dementia (excluding epilepsy)	1.306	1.225	1.392	<0.001
Number of ATC level 3 drug classes	1.004	1.001	1.007	0.002
Charlson Comorbidity Index	1.128	1.120	1.137	<0.001

Figure Legends

Figure 1: Risk ratios for CVD death associated with COVID-19 and Non-COVID-19 pneumonia. Including all follow-up time and excluding the first 30 days post infection