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Impact of COVID-19 and Non-COVID-19 Hospitalized Pneumonia on Longer-Term Cardiovascular Mortality in People With Type 2 Diabetes: A Nationwide Prospective Cohort Study From Scotland

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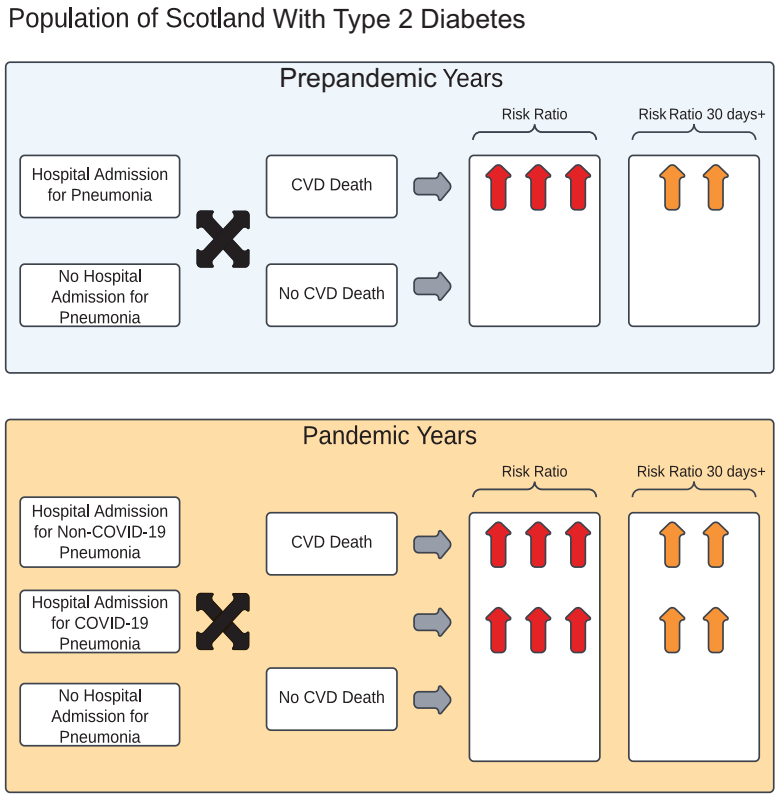

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Individuals at higher risk for cardiovascular disease (CVD) face increased pneumonia risk, with both coronavirus disease 2019 (COVID-19) and non-COVID-19 pneumonia linked to heightened CVD risk, though precise comparisons remain unquantified.
- **What is the specific question(s) we wanted to answer?**
  Does COVID-19 pneumonia raise CVD death risk more than other pneumonias, and does this persist long-term?
- **What did we find?**
  Both COVID-19 and non-COVID-19 pneumonias significantly increase CVD death risk; COVID-19 risk is initially increased, but both lead to an ~4.2-fold increase post–30 days.
- **What are the implications of our findings?**
  A history of pneumonia, from any cause, is a key risk indicator for CVD death in diabetes, emphasizing its importance in prioritization of CVD prevention efforts for people with diabetes.

ORIGINAL ARTICLE

Impact of COVID-19 and Non-COVID-19 Hospitalized Pneumonia on Longer-Term Cardiovascular Mortality in People With Type 2 Diabetes: A Nationwide Prospective Cohort Study From Scotland

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OBJECTIVE

In this study we examine whether hospitalized coronavirus disease 2019 (COVID-19) pneumonia increases long-term cardiovascular mortality more than other hospitalized pneumonias in people with type 2 diabetes and aim to quantify the relative cardiovascular disease (CVD) mortality risks associated with COVID-19 versus non-COVID-19 pneumonia.

RESEARCH DESIGN AND METHODS

With use of the SCI-Diabetes register, two cohorts were identified: individuals with type 2 diabetes in 2016 and at the 2020 pandemic onset. Hospital and death records were linked for determination of pneumonia exposure and CVD deaths. Poisson regression estimated rate ratios (RRs) for CVD death associated with both pneumonia types, with adjustment for confounders. Median follow-up durations were 1,461 days (2016 cohort) and 700 days (2020 cohort).

RESULTS

The adjusted RR for CVD death following non-COVID-19 pneumonia was 5.51 (95% CI 5.31–5.71) prepandemic and 7.3 (6.86–7.76) during the pandemic. For COVID-19 pneumonia, the RR was 9.13 (8.55–9.75). Beyond 30 days post pneumonia, the RRs converged, to 4.24 (3.90–4.60) for non-COVID-19 and 3.35 (3.00–3.74) for COVID-19 pneumonia, consistent even with exclusion of prior CVD cases.

CONCLUSIONS

Hospitalized 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.

There are concerns that the coronavirus disease 2019 (COVID-19) pandemic will lead to an explosion in the incidence of cardiovascular morbidity and mortality well beyond

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the pandemic, particularly in those with diabetes. The factors that could lead to such an explosion in cardiovascular disease (CVD) are complex including not only reduced diabetes and cardiovascular care during and beyond the pandemic (1), reduced operative interventions (2), and potential effects of vaccines on myocarditis (though this seems very modest) but also long-term effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection itself on the cardiovascular system (3). In the U.K. excess all-cause mortality has continued well into 2023 partly due to an excess in CVD mortality and deaths where diabetes is mentioned in reporting (4).

Regarding the long-term direct effects of severe SARS-CoV-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. Answering this question is complicated by the fact that risk of developing COVID-19 pneumonia is increased with prior frailty including prior CVD and diabetes. In the overall population increased risks associated with COVID-19, in comparison with risks for historical control subjects, 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 are 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; in some, outcomes were examined after a positive COVID-19 test, and some focused on those hospitalized. In a recent report from the U.S. Centers for Disease Control and Prevention (8) with use of insurance claims data, increased risk of CVD was found to be associated with prior COVID-19 diagnosis codes in comparison with the risk for those without COVID-19 over a mean follow-up time of 8.5 months, with risk slightly greater for 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. For an understanding of 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 with 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 hospitalized COVID-19 because it has been estimated that up to one-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. While both relative risks for CVD mortality for COVID-19 and relative risks for 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 for 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.

RESEARCH DESIGN AND METHODS

Data Sources

SCI-Diabetes (Scottish Care Information-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 previously been described in detail (10). Included in the database are data collected from various sources, information regarding clinical episodes, laboratory data from primary care, and data from diabetes clinics in the National Health Service hospitals, community care, and the national retinopathy screening program. With use of a unique health service identifier, hospital admissions data (SMR01 [Scottish Morbidity Record 01]) and mortality data from the National Records of Scotland have been linked to SCI-Diabetes.

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 1 January 2016 to 31 December 2019 (N = 263,922, follow-up 946,547 years) and 1 January 2020 to 30 November 2021 (N = 284,801, follow-up 515,226 years), respectively. For categorization of 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 according to a hospital admission with bacterial or viral pneumonia. We selected Scottish Morbidity Record inpatient and day case procedure records (SMR01), for which World Health Organization ICD-10 codes are used. In the study, pneumonia was subset as ICD-10 coding in any primary or secondary position of the SMR01 hospital episode. ICD-10 codes used for non-COVID-19 and COVID-19 pneumonia are provided in Supplementary Table 6.

A discharge including only a non-COVID-19 ICD-10 pneumonia code, but where there was a positive RT-PCR test for COVID-19 during the admission, was assigned into the COVID-19 pneumonia category. We categorized cases where both non-COVID-19 and COVID-19 codes were present on the discharge summary as COVID-19 pneumonia.

CVD during the study and prior look back windows was identified using hospital discharge ICD-10 codes. The codes used can be found in Supplementary Table 9.

The outcome of cardiovascular mortality in the study window was ascertained from the Medical Certificate of Cause of Death data provided by the National Records of Scotland. Cause-specific information for the cause of death was defined according to the presence of ICD-10 coding at any position on a Medical Certificate of Cause of Death. The codes used are provided in Supplementary Table 10.

Other covariate and risk factor data were obtained from SCI-Diabetes on HbA_{1c} body weight, BMI, blood pressure, estimated glomerular filtration rate (eGFR), plasma total cholesterol, albuminuria, retinopathy, smoking status, treatment for hypertension or dyslipidemia, ever having atrial fibrillation, and the number of Anatomical Therapeutic Chemical (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. A longer look back period, of 10 years, was used for other ever/never risk factors such as prior CVD, immune

disease, chronic kidney disease, asthma, liver disease, and neurological diseases.

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 organized 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 occured later. 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, with the pneumonia exposure index date being that of hospital admission. There was 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 postinfection.

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

Information Governance

This research was conducted with approval from the Public Benefit and Privacy Panel (PBPP) (reference no. 1617-0147), originally set up under Privacy Advisory Committee (PAC) 33/11, with approval from the Scotland A Research Ethics Committee (reference no. 11/AL/0225 & 21/WS/0047). All data sets were de-identified before analysis.

Data and Resource Availability

National Health Service data governance rules do not permit us to secondarily share the data directly. However, bone fide researchers can apply to the Scottish Public Benefit and Privacy Panel for Health and Social Care for access to these data.

RESULTS

Table 1 shows baseline characteristics by pneumonia status for the 2020–2021 (COVID-19 era) cohort. A similar table for 2016–2019 (pre-COVID-19 era) is also provided (Supplementary Table 2). The data demonstrate the importance of adjusting for confounders in assessing the association of pneumonias with CVD death, since those who developed pneumonia were older, with 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-19 pneumonia were older than the COVID-19 pneumonia group, and the interquartile range of their Charlson comorbidity index was 4–7 vs. 1–6 for the COVID-19 group.

Table 2 illustrates the large numbers of people in the cohorts and of events in this study. The minimally adjusted (age, sex, and diabetes duration adjusted) rate ratios (RRs) 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 RR prior to adjustment for additional potential confounders. As shown, both non-COVID-19 and COVID-19 pneumonias were associated with a >10-fold elevation in risk of CVD death with adjustment for age, sex, and diabetes duration.

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

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

We also examined the relationship of non-COVID-19 and COVID-19 pneumonia with all-cause mortality during follow-up (Supplementary Tables 6 and 7). The magnitude of RR for all-cause mortality was similar to that for CVD mortality. A

Table 1—Cohort characteristics at 1 January 2020, study entry

	No pneumonia	Non-COVID-19 pneumonia	COVID-19 pneumonia	Total
Total included	272,730 (95.78)	5,533 (1.94)	6,483 (2.28)	284,801
Follow-up duration (days)	700 (700, 700)	700 (428, 700)	700 (451, 700)	700 (700, 700)
Sociodemographic characteristics				
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	154,161 (56.5)	3,153 (57.0)	3,734 (57.6)	161,081 (56.6)
Female	118,569 (43.5)	2,380 (43.0)	2,749 (42.4)	123,720 (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	199,717 (73.2)	4,410 (79.7)	4,955 (76.4)	209,127 (73.4)
Non-White	11,419 (4.2)	90 (1.6)	335 (5.2)	11,848 (4.2)
Other/unknown	61,594 (22.6)	1,033 (18.7)	1,193 (18.4)	63,826 (22.4)
Deprivation index				
Quintile 1 (most deprived)	62,604 (23.0)	1,399 (25.3)	2,108 (32.5)	66,125 (23.2)
Quintile 2	61,302 (22.5)	1,355 (24.5)	1,573 (24.3)	64,245 (22.6)
Quintile 3	55,271 (20.3)	1,077 (19.5)	1,074 (16.6)	57,431 (20.2)
Quintile 4	49,294 (18.1)	921 (16.6)	906 (14.0)	51,128 (18.0)
Quintile 5 (least deprived)	39,739 (14.6)	656 (11.9)	691 (10.7)	41,095 (14.4)
Unknown	4,520 (1.7)	125 (2.3)	131 (2.0)	4,777 (1.7)
Other clinical measures				
HbA_{1c} (mmol/mol)	55 (48, 67)	54 (47, 66)	57 (48, 71)	55 (48, 67)
HbA_{1c} (%)	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–to–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 ($mL/min/1.73\ m^2$)	83 (65, 95)	67 (48, 85)	73 (54, 90)	82 (65, 95)
Albuminuria status				
Normal	113,851 (41.7)	1,752 (31.7)	2,364 (36.5)	117,982 (41.4)
Microalbuminuria	42,941 (15.7)	1,441 (26.0)	1,432 (22.1)	45,828 (16.1)
Macroalbuminuria	7,750 (2.8)	415 (7.5)	373 (5.8)	8,545 (3.0)
Unknown	108,188 (39.7)	1,925 (34.8)	2,314 (35.7)	112,446 (39.5)
Retinopathy				
None	174,707 (64.1)	3,430 (62.0)	4,046 (62.4)	182,213 (64.0)
Nonreferable	36,997 (13.6)	857 (15.5)	987 (15.2)	38,850 (13.6)
Referable/eye clinic	18,168 (6.7)	506 (9.1)	703 (10.8)	19,387 (6.8)
Unknown	42,858 (15.7)	740 (13.4)	747 (11.5)	44,351 (15.6)
Tobacco smoking status				
Never smoked	95,542 (35.0)	1,263 (22.8)	2,028 (31.3)	98,847 (34.7)
Ever smoked	174,544 (64.0)	4,236 (76.6)	4,412 (68.1)	183,233 (64.3)
Unknown	2,644 (1.0)	34 (0.6)	43 (0.7)	2,721 (1.0)
Comorbidities				
Prior CVD	51,293 (18.8)	2,150 (38.9)	2,073 (32.0)	55,536 (19.5)
Atrial fibrillation	18,235 (6.7)	1,026 (18.5)	852 (13.1)	20,122 (7.1)
Treated for dyslipidemia	174,213 (63.9)	4,129 (74.6)	4,651 (71.7)	183,033 (64.3)
Treated for hypertension	163,832 (60.1)	3,902 (70.5)	4,326 (66.7)	172,098 (60.4)
Immune disease or on immunosuppressants	599 (0.2)	26 (0.5)	32 (0.5)	657 (0.2)
Chronic kidney disease	5,666 (2.1)	439 (7.9)	434 (6.7)	6,545 (2.3)
Asthma or chronic lower-airway disease	33,663 (12.3)	1,832 (33.1)	1,511 (23.3)	37,020 (13.0)
Liver disease	1,350 (0.5)	72 (1.3)	71 (1.1)	1,493 (0.5)
Neurological and dementia (excluding epilepsy)	9,280 (3.4)	530 (9.6)	503 (7.8)	10,320 (3.6)
No. 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 as *N* (%) and continuous values as median (interquartile range). BP, blood pressure.

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.

CONCLUSIONS

Statement of Principal Findings

The key findings of this study are that for those with diabetes prior to the pandemic era, non-COVID-19 pneumonias were associated with a 5.5-fold elevation in risk of CVD death with adjustment for CVD risks factors. This elevation in risk worsened

Table 2—Age-, sex-, and diabetes duration–adjusted RRs for CVD death associated with pneumonia type in the Scottish population with type 2 diabetes

Cohort	Subgroup	Total (*N*)	CVD deaths (*N*)	Crude CVD death rate (per 1,000/py)	RR (95% CI)	*P*
2016–2019	All	263,922	19,672	20.78		
	No pneumonia	248,660	15,564	16.76	Reference	
	Pneumonia	15,262	4,108	230.27	7.96 (7.68, 8.24)	<0.001
2020–2021	All	284,801	10,817	20.99		
	No pneumonia	272,730	8,522	16.79	Reference	
	Non–COVID-19 pneumonia	5,533	1,250	329.81	11.8 (11.11, 12.53)	<0.001
	COVID-19 pneumonia	6,483	1,034	262.77	12.93 (12.12, 13.79)	<0.001

py, person-years.

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 with 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 pneumonia was not associated with a greater elevation in CVD death compared with non-COVID-19 pneumonia over an average follow-up of 21 months.

Thus, regardless of the cause of pneumonia, prior hospitalization for pneumonia remains an important risk marker for CVD death in people with diabetes. Therefore, in 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 is associated with a much greater long-term risk for 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 includes the comparison of the relative risks with those seen for other pneumonias. We have shown that using prepandemic data for other pneumonias could exaggerate apparent COVID-19 effects, as the relative risks for other pneumonias themselves increased during the pandemic period. A further strength is that we noted a very similar pattern for all-cause mortality such that competing risks do not account for our observations.

Limitations of this study include the following: 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 hospitalized pneumonia is at the least an important risk marker for future CVD. As another limitation, with respect to comparing the impact of different pneumonia causes, the analysis assumes that COVID-19 codes were correctly assigned, and nonassigned, for 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 hospitalization is a collider in the analysis. We chose CVD mortality (regardless of the death involving hospitalization 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 hospitalization cannot be a collider. However, in the first 30 days, some hospitalizations may have been triggered by underlying CVD that eventually led to CVD death. This could introduce collider bias in the estimates of the RR for CVD mortality associated with pneumonias during this period. Thus, the most valid estimates for considering the main hypothesis of whether COVID-19 pneumonia has a greater long-term impact on CVD mortality than non-COVID-19 pneumonias are those pertaining to the post–30-day period.

We focused on hospitalized pneumonias as the exposure of interest rather than a positive RT-PCR result for SARS-CoV-2 because although there was extensive free of charge RT-PCR testing for SARS-CoV-2 (including self-referral), this information will not result in correct classification of SARS-CoV-2 exposure, since it has been estimated that up to one-third of infections were asymptomatic (9). We note that use of RT-PCR community tests as the basis for exposure definition 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, With Discussion of Important Differences in Results

Our results are not entirely consistent with findings of other studies of initial elevations in CVD incidence shortly after COVID-19 that did not persist after the first few months (6). We found that with exclusion of the first 30 days, risks fell but

Table 3—Multivariable-adjusted RRs for CVD death associated with pneumonia type in Scottish population with type 2 diabetes from 2020 to 2021

Covariate	RR	2.5% CI	97.5% CI	*P*
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
HbA_{1c} (mmol/mol)	1.004	1.003	1.005	<0.001
HbA_{1c} (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 (m)	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/1.73 m^2)	1.123	1.079	1.169	<0.001
Albuminuria status ref = normal				
Microalbuminuria	1.305	1.242	1.371	<0.001
Macroalbuminuria	1.640	1.523	1.764	<0.001
Retinopathy status ref = none				
Nonreferable	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 disorders and dementia (excluding epilepsy)	1.306	1.225	1.392	<0.001
No. 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

BP, blood pressure; ref, reference.

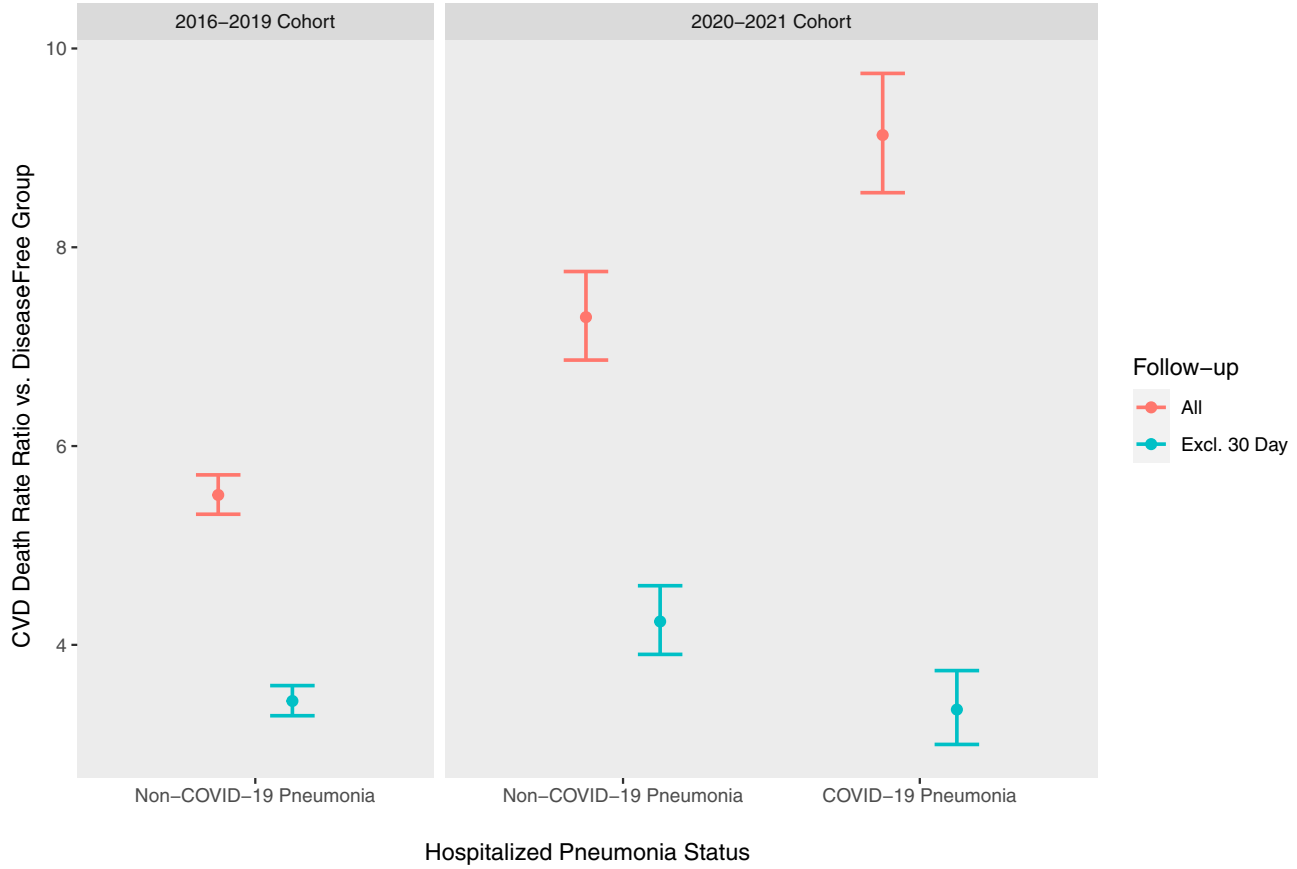

Figure 1—RRs for CVD death associated with COVID-19 and non-COVID-19 pneumonia, with all follow-up time included and with exclusion of the first 30 days postinfection.

continued to be elevated in the two- to fourfold range. In a recent review focused on post–30-day outcomes, heterogeneity was found in existing evidence with lack of adjustment for confounders and relatively short follow-up (7). Our study follow-up period was longer and sample size larger than many of these studies. In most studies investigators have simply compared CVD incidence in those with and without prior COVID-19. We chose to also conduct a comparison with risks associated with other pneumonias, since the potential for residual confounding by prior risk should be at least as great for COVID-19 as for 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 include consideration of the effect on different constellations of CVD events.

In previous studies where investigators have compared the effect of COVID-19 pneumonia with that of other pneumonias, studies have usually been focused on historical prepandemic control subjects (17), with fairly short follow-up. For example, in a French study a higher 90-day mortality rate was reported for COVID-19 than for 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 U.S. Centers for Disease Control and Prevention. In that study, over a median of 8.5 months excluding the first 30 days, there were also findings of 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 for 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 prepandemic. However, as we have shown, using a prepandemic comparator may not be valid, since the pandemic period itself seems to have worsened the outcomes associated with pneumonias other 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 comorbidity index for those admitted during the pandemic in comparisons with the prepandemic 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 cardiovascular event and subsequent death due to effects on risk pathways, particularly hemostatic 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

In terms of practical implications, there have been concerns about significantly

elevated rates of CVD in the long term after the pandemic due to direct effects of COVID-19 on the CVD system. However, these effects may be less severe than has been feared. What remains cruical is careful risk factor management and optimizing primary and secondary prevention and management for anyone with diabetes who has had a prior hospitalization for 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 of which is, what is the mechanism of this association? 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 is needed postpandemic to determine the long-term effects of COVID-19 on CVD with certainty. 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.

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References

1. Carr MJ, Wright AK, Leelarathna L, et al. Impact of COVID-19 restrictions on diabetes health checks and prescribing for people with type 2 diabetes: a UK-wide cohort study involving 618 161 people in primary care. BMJ Qual Saf 2022;31:503–514
2. Wright FL, Cheema K, Goldacre R, et al. Effects of the COVID-19 pandemic on secondary care for cardiovascular disease in the UK: an electronic health record analysis across three countries. Eur Heart J Qual Care Clin Outcomes 2023;9:377–388
3. Patone M, Mei XW, Handunnetthi L, et al. Risk of myocarditis after sequential doses of COVID-19 vaccine and SARS-CoV-2 infection by age and sex. Circulation 2022;146:743–754
4. Office for National Statistics. Monthly mortality analysis, England and Wales: May 2023. Accessed 19 January 2024. Available from https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/monthlymortalityanalysisenglandandwales/may2023/
5. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. Nat Med 2022;28:583–590
6. Rezel-Potts E, Douiri A, Sun X, Chowienczyk PJ, Shah AM, Gulliford MC. Cardiometabolic outcomes up to 12 months after COVID-19 infection. A matched cohort study in the UK. PLoS Med 2022;19:e1004052
7. Parhizgar P, Yazdankhah N, Rzepka AM, et al. Beyond acute COVID-19: a review of long-term cardiovascular outcomes. Can J Cardiol 2023;39:726–740
8. Koyama AK, Imperatore G, Rolka DB, et al. Risk of cardiovascular disease after COVID-19 diagnosis among adults with and without diabetes. J Am Heart Assoc 2023;12:e029696
9. Sah P, Fitzpatrick MC, Zimmer CF, et al. Asymptomatic SARS-CoV-2 infection: a systematic review and meta-analysis. Proc Natl Acad Sci U S A 2021;118:e2109229118
10. McGurnaghan SJ, Blackbourn LAK, Caparrotta TM, et al. Cohort profile: the Scottish Diabetes Research Network national diabetes cohort - a population-based cohort of people with diabetes in Scotland. BMJ Open 2022;12:e063046
11. McGurnaghan SJ, McKeigue PM, Read SH, et al.; Swedish National Diabetes Register and the Scottish Diabetes Research Network Epidemiology Group. Development and validation of a cardiovascular risk prediction model in type 1 diabetes. Diabetologia 2021;64:2001–2011
12. Mellor J, Jiang W, Fleming A, et al.; Scottish Diabetes Research Network Epidemiology Group. Can deep learning on retinal images augment known risk factors for cardiovascular disease prediction in diabetes? A prospective cohort study from the national screening programme in Scotland. Int J Med Inform 2023;175:105072
13. McGurnaghan SJ, Weir A, Bishop J, et al.; Public Health Scotland COVID-19 Health Protection Study Group; Scottish Diabetes Research Network Epidemiology Group. Risks of and risk factors for COVID-19 disease in people with diabetes: a cohort study of the total population of Scotland. Lancet Diabetes Endocrinol 2021;9:82–93
14. Honaker J, King G, Blackwell M. Amelia II: a program for missing data. J Stat Softw 2011;45:1–47
15. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria, R Foundation for Statistical Computing. Accessed 19 January 2024. Available from https://www.R-project.org/
16. Griffith GJ, Morris TT, Tudball MJ, et al. Collider bias undermines our understanding of COVID-19 disease risk and severity. Nat Commun 2020;11:5749
17. Ritsinger V, Bodegård J, Kristofi R, et al. History of heart failure and chronic kidney disease and risk of all-cause death after COVID-19 during the first three waves of the pandemic in comparison with influenza outbreaks in Sweden: a registry-based, retrospective, case-control study. BMJ Open 2023;13:e069037
18. de Marignan D, Vacheron C-H, Ader F, et al. A retrospective comparison of COVID-19 and seasonal influenza mortality and outcomes in the ICUs of a French university hospital. Eur J Anaesthesiol 2022;39:427–435
19. Wallemacq S, Danwang C, Scohy A, et al. A comparative analysis of the outcomes of patients with influenza or COVID-19 in a tertiary hospital in Belgium. J Infect Chemother 2022;28:1489–1493
20. Sorriento D, Iaccarino G. Inflammation and cardiovascular diseases: the most recent findings. Int J Mol Sci 2019;20:3879