



This is a repository copy of *Direct and indirect effects of the COVID-19 pandemic on mortality: an individual-level population-scale analysis using linked electronic health records, Wales, United Kingdom, 2016 to 2022.*

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/223649/>

Version: Published Version

Article:

Owen, R.K. orcid.org/0000-0001-5977-376X, van Oppen, J.D. orcid.org/0000-0002-2570-7112, Lyons, J. orcid.org/0000-0002-4407-770X et al. (5 more authors) (2024) Direct and indirect effects of the COVID-19 pandemic on mortality: an individual-level population-scale analysis using linked electronic health records, Wales, United Kingdom, 2016 to 2022. *Eurosurveillance*, 29 (50). 2400085. ISSN 1560-7917

<https://doi.org/10.2807/1560-7917.es.2024.29.50.2400085>

Reuse

This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here:

<https://creativecommons.org/licenses/>

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

Direct and indirect effects of the COVID-19 pandemic on mortality: an individual-level population-scale analysis using linked electronic health records, Wales, United Kingdom, 2016 to 2022

Rhiannon K Owen¹, James D van Oppen², Jane Lyons¹, Ashley Akbari¹, Gareth Davies¹, Fatemeh Torabi¹, Keith R Abrams³, Ronan A Lyons¹

1. Population Data Science, Swansea University Medical School, Swansea University, Swansea, United Kingdom

2. Centre for Urgent and Emergency Care Research (CURE), University of Sheffield, Sheffield, United Kingdom

3. Department of Statistics & Warwick Medical School (WMS), University of Warwick, Coventry, United Kingdom

Correspondence: Rhiannon K Owen (r.k.owen@swansea.ac.uk)

Citation style for this article:

Owen Rhiannon K, van Oppen James D, Lyons Jane, Akbari Ashley, Davies Gareth, Torabi Fatemeh, Abrams Keith R, Lyons Ronan A. Direct and indirect effects of the COVID-19 pandemic on mortality: an individual-level population-scale analysis using linked electronic health records, Wales, United Kingdom, 2016 to 2022. *Euro Surveill.* 2024;29(50):pii=2400085. <https://doi.org/10.2807/1560-7917.ES.2024.29.50.2400085>

Article received on 06 Feb 2024 / Accepted on 14 Jul 2024 / Published on 12 Dec 2024

Background: The COVID-19 pandemic resulted in increased mortality directly and indirectly associated with COVID-19. **Aim:** To assess the impact of the COVID-19 pandemic on all-cause and disease-specific mortality and explore potential health inequalities associated with area-level deprivation in Wales. **Methods:** Two population-based cohort studies were derived from multi-sourced, linked demographic, administrative and electronic health record data from 2016 to 2019 (n = 3,113,319) and 2020 to 2022 (n = 3,571,471). Data were analysed using generalised linear models adjusting for age, sex, area-level deprivation and time at risk. **Results:** COVID-19 deaths peaked in January 2021 (54.9/100,000 person-months, 95% confidence interval (CI): 52.4–57.5). The pandemic indirectly affected deaths, with higher than expected maximum relative mortality rates (RR) related to cancer (RR: 1.24, 95% CI: 1.13–1.36), infectious diseases (excluding respiratory infections) (RR: 2.09, 95% CI: 1.27–3.43), circulatory system (RR: 1.41, 95% CI: 1.28–1.56), trauma (RR: 2.04, 95% CI: 1.57–2.65), digestive system (RR: 1.54, 95% CI: 1.25–1.91), nervous system (RR: 1.63; 95% CI: 1.34–2.00) and mental and behavioural disorders (RR: 1.85, 95% CI: 1.58–2.16). Mortality associated with respiratory diseases (unrelated to COVID-19) were lower than expected (minimum RR: 0.52, 95% CI: 0.45–0.60). All-cause mortality was lower in least deprived communities compared with most deprived (RR: 0.61, 95% CI: 0.60–0.62), and the magnitude of this effect increased during the pandemic. **Conclusions:** All-cause and disease-specific mortality directly and indirectly associated with COVID-19 increased during the COVID-19 pandemic. Socioeconomic disparities were exacerbated during this time.

Introduction

The COVID-19 pandemic was declared a public health emergency of international concern on 30 January 2020 [1] and lasted until 5 May 2023 [2]. During this time, nearly 7 million COVID-19 related deaths were reported to the World Health Organization (WHO) [3], with the true death toll estimated to be in excess of 18 million people [4]. The COVID-19 pandemic placed unprecedented pressure on healthcare systems globally [5], leading to reduced healthcare utilisation [6,7] as a result of reduced healthcare services and delivery [7,8] and poorer health outcomes [7]. Following the pandemic, countries across the world have reported ongoing excess deaths from all causes [9]. A substantial proportion of these deaths are likely to be a result of indirect consequences of the pandemic including delayed diagnoses and/or delayed treatment of conditions [10]. These consequential deaths are referred to as indirect effects.

Studies [9,11] have evaluated excess deaths by comparing the number of all-cause or disease-specific deaths over a given time period to the expected number of deaths based on predictions from historical trends. The majority of studies have evaluated excess deaths using aggregated data at a population level. This approach can be prone to aggregation bias when exploring associations with individual-level characteristics such as age, sex, ethnicity and socioeconomic factors [12]. The impact of racial and ethnic disparities on the indirect effects of COVID-19 has been widely explored in the literature [13,14] and demonstrates an excess mortality among racial/ethnic minority groups. However, while it has been suggested that the indirect effects of the COVID-19 pandemic may also have disproportionately impacted those from lower socioeconomic

KEY PUBLIC HEALTH MESSAGE

What did you want to address in this study and why?

The COVID-19 pandemic resulted in increased all-cause mortality. There is a paucity of evidence exploring the impact of socioeconomic status on the direct and indirect effects of the pandemic. We aimed to assess excess all-cause and disease-specific mortality arising from the pandemic and identify potential health inequalities related to area-level deprivation in Wales.

What have we learnt from this study?

Using data from 2016 to 2022, we found that during the pandemic, excess deaths were observed from all-causes including COVID-19, infectious diseases, cancers, circulatory diseases, diseases of digestive and nervous systems, mental disorders and trauma in Wales. Respiratory deaths (excluding COVID-19) were lower than expected. Socioeconomic disparities were exacerbated during the pandemic.

What are the implications of your findings for public health?

The findings of this study could be used to inform further research to understand the aetiology of continued excess deaths and health inequalities in Wales, with a view to inform healthcare policy and implement preventative measures.

backgrounds, there is a paucity of supporting evidence [7].

In this study, we used linked electronic health records to quantify the direct and indirect effects of the COVID-19 pandemic on all-cause and disease-specific mortality, accounting for competing causes of death at the individual level for the population of Wales. We further investigated the impact of potential health inequalities related to socioeconomic status on all-cause and disease-specific mortality.

Methods

Participants and setting

Two population-level cohorts (C16 and C20) were created using multi-sourced administrative, demographic and healthcare data held within the Secure Anonymised Information Linkage (SAIL) Databank (www.saildatabank.com) [15]. The C16 and C20 cohorts contain linked data at the individual participant level using anonymised linkage fields. Full information regarding the curation of the C16 and C20 cohorts and associated methodology have been reported elsewhere [16]. The C16 cohort provides comparative data on population mortality rates and can be used to predict (i.e. calculate expected) mortality for comparison with observed mortality in the C20 cohort.

The C16 cohort included all residents in Wales on 1 January 2016 with follow-up until death, break in Welsh residency, or 31 December 2019. The C16 cohort did not capture individuals migrating to, or born in, Wales between 2016 to 2019, and therefore for analyses involving trends of mortality rates, the population was

assumed to remain constant from 1 January 2016 to 31 December 2019.

The C20 cohort included all individuals resident in Wales from 1 January 2020 with follow-up until death, break in Welsh residency, or cohort end (31 December 2022). The C20 cohort was updated to include individuals migrating to, or born in, Wales after 1 January 2020.

Data sources

Demographic data were obtained from the Welsh Demographic Service Dataset (WDS), which holds administrative information for the population of Wales known to the National Health Service (NHS). Mortality data were obtained from the Annual District Death Extract (ADDE) from the Office for National Statistics (ONS), which holds information regarding the dates and causes of death for all Welsh residents (including those who died outside of Wales). For the C20 cohort, two COVID-19 data sources were added and updated daily to support rapid analysis: the COVID-19 Consolidated Death Data Source (CDDS) created by Digital Health and Care Wales (DHCW) - formerly known as the NHS Wales Informatics Service (NWIS), and the Annual District Death Daily (ADDD) dataset from the ONS. Demographic and mortality data were linked to residential data to identify Lower-layer Super Output Area (LSOA) version 2011. These were used to assign area-level deprivation from 1 (most deprived) to 5 (least deprived) using the Welsh Index of Multiple Deprivation version 2019 (WIMD) [17].

Outcome measures

The primary outcome measure was all-cause mortality. Secondary outcomes were disease-specific mortality grouped by International Classification of Disease

TABLE

Cohort characteristics, Wales, 2016–2022 (n = 6,684,790)

Characteristics	C16 cohort (2016–2019)		C20 cohort (2020–2022)	
	n	%	n	%
Total	3,113,319	NA	3,571,471	NA
All-cause deaths	119,201	3.8	109,735	3.1
Mortality rate per 100,000 person years	957.2	NA	1,024.2	NA
Age (median, IQR)	42	22–60	40	22–60
Missing	0	0.0	0	0.0
Sex				
Female	1,560,206	50.1	1,787,198	50.0
Male	1,553,113	49.9	1,784,273	50.0
Missing	0	0.0	0	0.0
WIMD				
1 – Most deprived	631,648	20.3	679,701	19.0
2	619,494	19.9	657,708	18.4
3	625,620	20.1	667,833	18.7
4	616,888	19.8	649,634	18.2
5 – Least deprived	619,669	19.9	654,193	18.4
Missing	0	0.0	262,402	7.3
ICD-10 chapter (ICD-10 codes) ^a				
1: Infectious and parasitic diseases (A00–B99)	1,226	1.0	1,039	1.0
2: Neoplasms (C00–D48)	33,837	28.4	27,565	25.1
3: Blood and blood forming organs (D50–D89)	237	0.2	192	0.2
4: Endocrine, nutritional, and metabolic (E00–E90)	1,824	1.5	1,812	1.7
5: Mental and behavioural disorders (F00–F99)	9,423	7.9	8,275	7.5
6: Nervous system (G00–G99)	5,186	4.4	6,060	5.5
9: Circulatory system (I00–I99)	30,445	25.5	25,789	23.5
10: Respiratory system (J00–J99)	18,369	15.4	12,353	11.3
11: Digestive system (K00–K93)	6,094	5.1	5,530	5.0
12: Skin and subcutaneous tissue (L00–L99)	482	0.4	395	0.4
13: Musculoskeletal system (M00–M99)	795	0.7	667	0.6
14: Genitourinary system (N00–N99)	2,254	1.9	1,823	1.7
17: Congenital malformations and chromosomal abnormalities (Q00–Q99)	249	0.2	233	0.2
18: Abnormal clinical and laboratory findings (R00–R99)	2,356	2.0	2,749	2.5
20: External causes of morbidity and mortality (V01–Y98)	4,391	3.7	4,089	3.7
22: Codes for special purposes (U00–U99)	88	0.1	9,399	8.6
Other	15	0.0	18	0.0
Missing	1,930	1.6	1,747	1.6

ICD-10: International Classification of Disease tenth revision [ref]; IQR: interquartile range; NA: not applicable; WIMD: Welsh Index of Multiple Deprivation version 2019.

^a Actuarial percentage calculated as the percentage of those who died.

tenth revision (ICD-10) chapter version 2016 [18]. The ICD-10 codes for each chapter are provided in the Table. Deaths from COVID-19 were identified using ICD-10 codes U071, U072, B972, U049, Z038 and Z115. Mortality was primarily identified using the underlying cause of death recorded in ADDE from the ONS, and supplemented by CDDS, WSD and ADDD in that order.

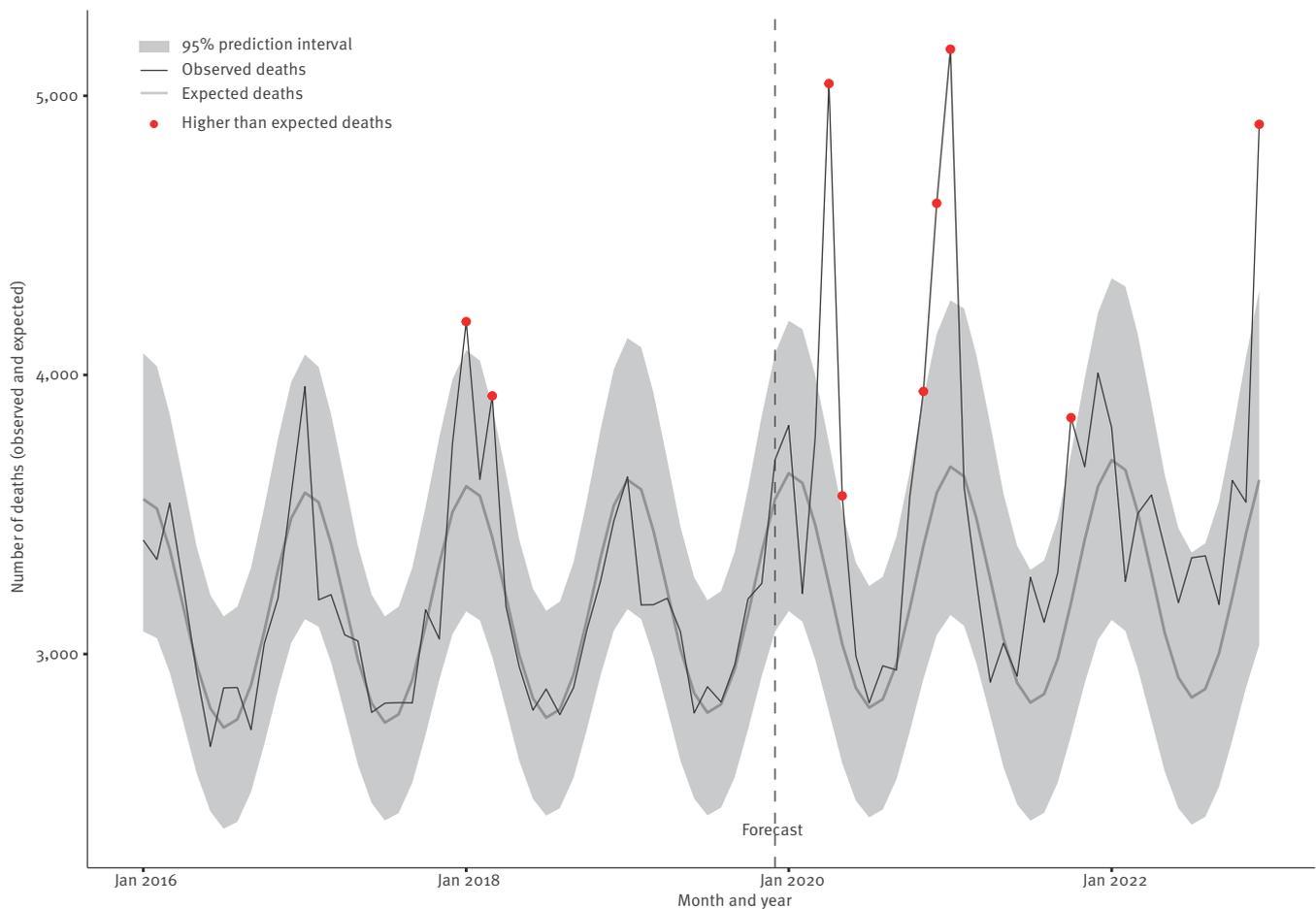
Statistical analysis

Trends in all-cause and disease-specific mortality were expressed as the mortality rate per 100,000 person-months together with their corresponding 95% confidence intervals (CIs). Predicted mortality rates were

calculated to compare observed vs expected mortality. Negative binomial regression models, using an offset for population at risk, were fitted to monthly aggregated data in the C16 cohort accounting for trends using epidemiological month and seasonality using Fourier terms across years, and used to predict expected mortality in the C20 cohort. Outputs were visualised by plotting the observed vs expected mortality counts each month, highlighting where the observed counts are above (red) or below (green) the 95% prediction intervals obtained from the regression model. Prediction intervals were calculated using the upper and lower bounds of the CI in order to obtain quantiles

FIGURE 1

Observed versus expected all-cause mortality obtained from negative binomial regression models, Wales, 2016–2022 (n = 6,684,790)



Vertical dashed line indicates where the C16 cohort ends and the forecasted trend for the C20 cohort.

of the negative binomial distribution, the minimum and maximum of which provided the lower and upper limits of the prediction interval [19]. Relative mortality rates (RR) were calculated as the ratio of observed and expected mortality rates with corresponding 95% CIs.

Zero-inflated Poisson regression models adjusted for age (centred at 50 years), sex (male/female), and WIMD were fitted at the individual participant level to assess the association between cohort and all-cause mortality, using an offset for time at risk [20]. Zero-inflated models were used to account for the high proportion of individuals alive in the cohort. Area-level deprivation was explored adding a main effect for WIMD and an interaction term for cohort and WIMD. Generalised linear models were assessed for overdispersion and model fit. Results were reported as relative risks and corresponding 95% CIs.

Multinomial regression models adjusted for age (centred at 50 years), sex (male/female) and area-level deprivation using WIMD were fitted at the individual participant level to assess the association between

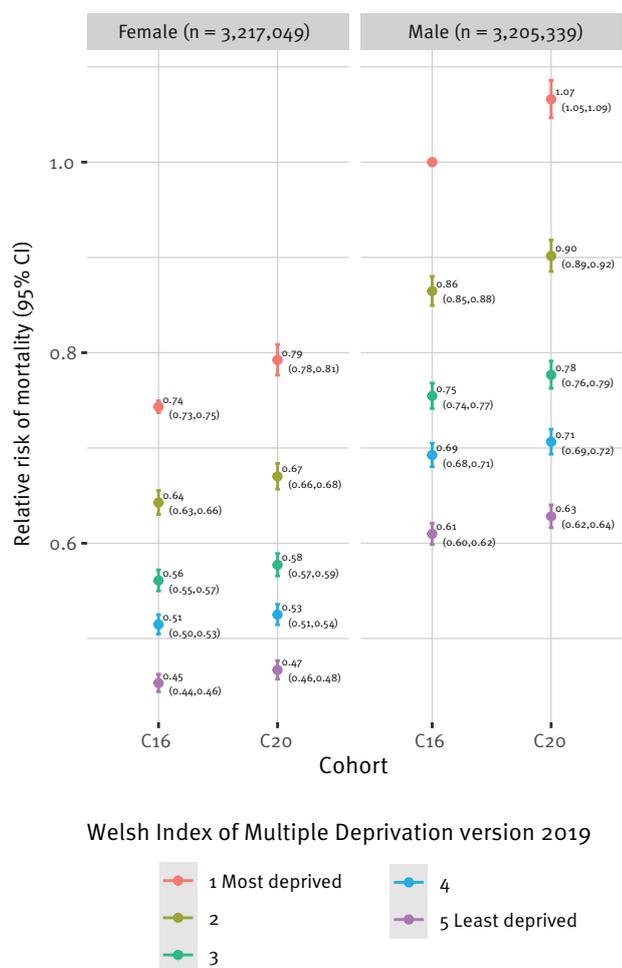
cohort and disease-specific mortality, including an offset for time at risk [20]. This approach accounts for death due to other reasons as a potentially competing risk. Cause-specific deaths of interest were neoplasms, endocrine, nutritional and metabolic diseases, mental and behavioural disorders, diseases of the nervous system, diseases of the circulatory system, diseases of the respiratory system, diseases of the digestive system, external causes and special purposes. Other causes of death were used as the reference group for comparison. Results were reported as odds ratios (OR) and corresponding 95% CIs.

Sensitivity analyses were undertaken in individuals aged 18 years and over to account for potential differences in the populations at risk owing to the C16 cohort not capturing births in Wales between 1 January 2016 and 31 December 2019.

Complete case analyses were undertaken, given the small proportion of missing data for covariates. All statistical analyses were performed using R software version 4.1.3 [21].

FIGURE 2

Relative risk of all-cause mortality by cohort, sex and Welsh Index of Multiple Deprivation obtained from zero-inflated Poisson regression models, Wales, 2016–2022 (n = 6,422,388)



CI: confidence interval.

C16 cohort: 2016–2019.

C20 cohort: 2020–2022.

Results

At cohort start, there were 3,113,319 individuals in C16 and 3,571,471 individuals in C20. The Table shows demographic and other characteristics for the C16 and C20 cohorts. The C16 cohort had a mean follow-up of 12,441,500 person-years and C20 had a mean follow-up of 9,748,397 person-years. During follow-up (4 years for C16 and 3 years for C20), the proportion of all-cause mortality was 3.8% and 3.1%, equivalent to a mortality rate of 957.2 and 1,024.2 per 100,000 person-years, respectively.

The population of Wales remained relatively consistent between C16 and C20 with 50.1% female in C16 and 50.0% female in C20. The C20 cohort was slightly younger with a median age of 40 years (interquartile range (IQR): 22–60) compared with a median age of 42 years (IQR: 22–60) in C16. Deprivation remained

unchanged with ca 20% of the population in the most and least deprived quintiles. However, there was an increased proportion of missing data for deprivation status owing to missing LSOA for individuals in the C20 cohort (7.3%) compared with the C16 cohort (0%). Overall, missing data was low in both C16 and C20 with an actuarial percentage of 1.6% of individuals with a missing cause of death in both cohorts. Of those who died in the C20 cohort, 8.6% of deaths were recorded with codes used for special purposes. The rate of all-cause and COVID-specific deaths from 2016 to 2022 are provided in Supplementary Figure S1. The rate of COVID-19 related deaths peaked in April 2020 (48.9/100,000 person-months, 95% CI: 46.5–51.3) and January 2021 (54.9/100,000 person-months, 95% CI: 52.4–57.5) before plateauing.

Observed vs expected all-cause mortality

Figure 1 illustrates the observed vs expected all-cause mortality over time. The highest observed vs expected relative mortality rate occurred in April 2020 where there appeared to be a 49% increased risk of death compared with that expected (RR: 1.49, 95% CI: 1.42–1.55) (Figure 1). Prior to the COVID-19 pandemic, there appeared to be a higher than expected mortality rate in January 2018, with 16% increased risk of death compared with that expected (RR: 1.16, 95% CI: 1.11–1.22).

Overall, the C20 cohort observed a 7% increased risk of all-cause mortality compared with the C16 cohort having adjusted for differences in age, sex and area-level deprivation (RR: 1.07, 95% CI: 1.05–1.09) (model coefficients are reported in Supplementary Table S1). Individuals in the least deprived communities had a 39% lower all-cause mortality compared with those in the most deprived communities (RR: 0.61, 95% CI: 0.60–0.62) (all-cause mortality rates by deprivation status is provided in Supplementary Figure S2). This socioeconomic disparity appeared to increase during the pandemic (Figure 2). For example, males in the most deprived groups had a significantly higher RR of death in C20 (RR: 1.07, 95% CI: 1.05–1.09) compared with males in the most deprived groups in C16. However, males in the least deprived group in C20 had a similar RR (RR: 0.63, 95% CI: 0.62–0.64), to males in the least deprived group in C16 (RR: 0.61, 95% CI: 0.60–0.62), with overlapping 95% CIs suggesting no statistically significant difference. These findings were robust to sensitivity analyses including using adults aged 18 years and over only (model coefficients for adults only are provided in Supplementary Table S2).

Disease-specific mortality

Figure 3 illustrates trends from 2016 to 2022 in disease-specific mortality rates grouped by cause of death. The observed vs expected cause-specific mortality rates, adjusting for trend and seasonality, are presented in Figure 4. From 2020, deaths due to neoplasms (maximum RR in March 2020: 1.24, 95% CI: 1.13–1.36), circulatory disease (maximum RR in December 2022: 1.41, 95% CI: 1.28–1.56) and the digestive system (maximum

FIGURE 3

Trends and 95% confidence intervals in disease-specific mortality grouped by ICD-10 chapter, Wales, 2016–2022 (n = 6,684,790)



RR in November 2021: 1.54, 95% CI: 1.25–1.91) were consistently higher than expected. Deaths due to respiratory diseases (excluding COVID-19) were mostly lower than expected (minimum RR in February 2021: 0.52, 95% CI: 0.45–0.60) until December 2022 (RR: 1.52, 95% CI: 1.36–1.69). Deaths due to endocrine, nutritional and metabolic diseases were within the expected range. Deaths due to mental and behavioural disorders (RR: 1.85, 95% CI: 1.58–2.16) and the nervous system (RR: 1.63, 95% CI: 1.34–2.00) were higher than expected and peaked during the first lockdown period in April 2020. Deaths due to infectious and parasitic diseases were higher than expected and peaked in July 2021 (RR: 2.09, 95% CI: 1.27–3.43). Deaths due to external causes were consistently higher than expected throughout 2021 and 2022 and also peaked in July 2021 (maximum RR in July 2021: 2.04, 95% CI: 1.57–2.65). The majority of deaths due to external causes during this period were as a result of falls (ICD-10 code: W00–W19), and intent to self-harm (ICD-10 code: X60–X84). Further investigation found that there was higher than expected mortality due to falls throughout 2021 and 2022 (observed versus expected number of deaths from falls are provided in Supplementary Figure S3). The highest peak was observed in December 2022 where individuals were four times as likely to die as result of a fall than expected (RR: 4.41, 95% CI: 2.68–7.29). The majority of secondary causes of deaths in individuals in C20 with falls as their primary cause of death were injuries to the head (ICD-10 code: S00–S09, 42%) and injuries to the hip and thigh (ICD-10 code: S70–S79, 25%). Deaths due to self-harm were as expected throughout 2020 to 2022 (observed versus expected number of deaths from self-harm are provided in Supplementary Figure S4).

Effect estimates obtained from multinomial models, accounting for competing causes of death, are provided in Supplementary Table S3. Compared with deaths from other causes, there appeared to be an 11% increased odds of death from neoplasms (OR: 1.11, 95% CI: 1.09–1.13), 31% increased odds of mortality from endocrine, nutritional and metabolic diseases (OR: 1.31, 95% CI: 1.23–1.39), 38% increased odds of mortality from diseases of the nervous system (OR: 1.38, 95% CI: 1.33–1.43), 11% increased odds of mortality from diseases of the circulatory system (OR: 1.11, 95% CI: 1.09–1.13), 22% increased odds from diseases of the digestive system (OR: 1.22, 95% CI: 1.18–1.27) and 11% increased odds from external causes (OR: 1.11, 95% CI: 1.06–1.15) in the C20 cohort compared with C16 cohort. Compared with deaths from other causes, the C20 cohort had 12% decreased odds of mortality from diseases of the respiratory system excluding COVID-19 (OR: 0.88, 95% CI: 0.86–0.90) compared with C16, and 6% decreased odds of mortality due to mental and behavioural disorders (OR: 0.94, 95% CI: 0.92–0.97). There was 29% increased odds of survival compared with deaths from other causes in the C20 cohort compared with the C16 cohort (OR: 1.28, 95% CI: 1.28–1.30). The predicted

probabilities of each cause of death by cohort, sex and age are provided in Supplementary Figure S5.

The odds of death from endocrine, nutritional and metabolic diseases, diseases of the respiratory system, diseases of the digestive system and deaths due to special codes decreased by 18% (OR: 0.82, 95% CI: 0.74–0.90), 24% (OR: 0.76, 95% CI: 0.73–0.79), 17% (OR: 0.83, 95% CI: 0.79–0.88) and 17% (OR: 0.83, 95% CI: 0.78–0.88), respectively, compared with deaths from other causes, for most deprived compared with least deprived communities (model coefficients are provided in Supplementary Table S3). However, the odds of death due to neoplasms, mental and behavioural disorders and diseases of the nervous system increased by 16% (OR: 1.16, 95% CI: 1.13–1.20), 15% (OR: 1.09, 95% CI: 1.09–1.20) and 65% (OR: 1.65, 95% CI: 1.56–1.75), respectively, compared with deaths from other causes, for most deprived compared with least deprived communities. Deaths due to diseases of the circulatory system and external causes did not appear to differ with deprivation. There was 89% increased odds of survival compared with deaths from other causes in individuals from least deprived compared with most deprived communities (OR: 1.89, 95% CI: 1.86–1.91). Results were robust to sensitivity analyses including adults only (model coefficients for adults only are provided Supplementary Table S4).

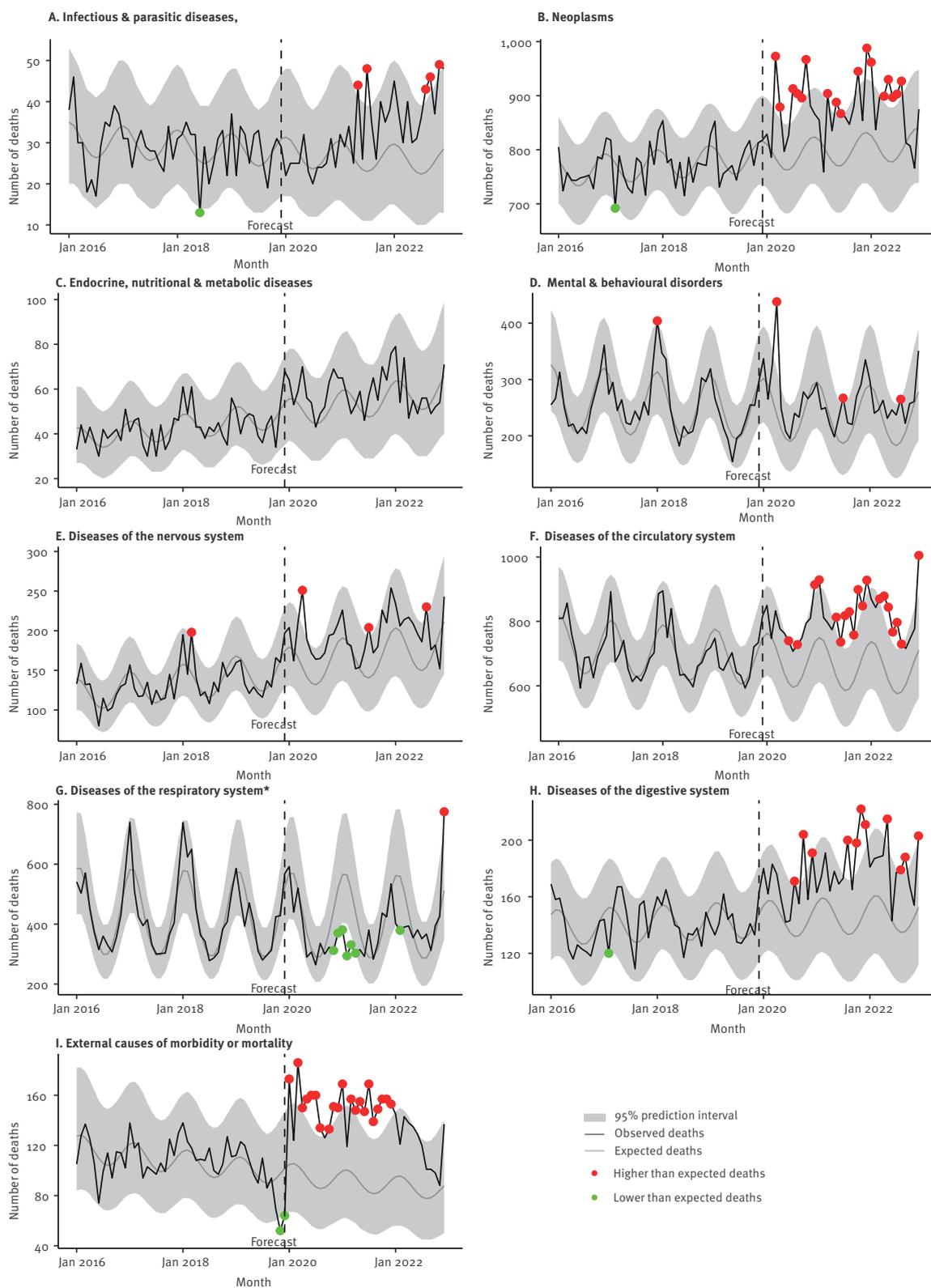
Discussion

This study found that all-cause deaths were higher than expected during the COVID-19 pandemic in Wales. The rate of COVID-19 deaths peaked in April 2020 and January 2021. In addition to COVID-19, excess deaths were observed from infectious and parasitic diseases, cancers, circulatory disease, diseases of the digestive and nervous systems, mental and behavioural disorders and trauma. The majority of trauma-related deaths were as a result of falls and intent to self-harm. Deaths due to respiratory diseases (excluding COVID-19) were consistently lower than expected until December 2022. This is consistent with previous analyses of morbidity in patients with chronic obstructive pulmonary disease (COPD) during lockdown in Scotland and Wales which showed a 48% reduction in primary care attendances and hospital admission. Suggested underlying causes were reduced transmission of respiratory infections overall, due to social distancing and reduced exposure to air pollution [22].

Increases in deaths due to cancers and digestive illnesses during the pandemic period may reflect their later identification due to personal or public messaging-inspired reluctance to attend healthcare settings, or possibly poorer diagnostic sensitivity due to increased healthcare delivery using remote consultation methods. Following diagnosis, delayed medical or surgical intervention due to hospital capacity and professional redeployments may also have contributed to higher mortality.

FIGURE 4

Observed versus expected disease-specific mortality by ICD-10 chapter from negative binomial regression models, Wales, 2016–2022 (n = 6,684,790)



There appeared to be consistently higher (up to four times as many) fall-related deaths during the pandemic than expected. The majority of secondary causes of death in these individuals were recorded as injuries to the head and fractures to the hip and thigh. The higher fall-related deaths may be associated with frailty, based on older people with frailty having more frequent head injuries (due to unprotected falls) and poorer outcomes following fractures of the hip and thigh. The increase in fall-related deaths appeared to peak in December 2022. This suggests ongoing factors following the rapid decrease in COVID-19 related deaths. The increase in fall-related deaths during this time may be a result of delays in urgent care in Wales, including ambulance attendance and subsequent ramping, overcrowding in emergency departments [23] and delayed admissions [24]. Deaths due to femoral fractures may be attributable to delays in surgery and subsequent therapy, and/or change in incidence. Deaths directly due to head injuries and hip fractures may also suggest more proactive identification of frailty and delivery of palliative-focussed trauma care. Pandemic-associated loss of function and physiological resilience due to social isolation and disrupted management of chronic illnesses may have also caused increased susceptibility to falls. Similar increases in fall-related mortality during the pandemic have been reported in the United States and China [25,26].

It is likely that most of the excess deaths during the pandemic period were a result of several factors including changes in health-seeking behaviours during the pandemic [27], excess pressures placed on stretched health systems [28] and disrupted health service delivery [29]. Over the course of the pandemic period, several healthcare professions in Wales participated in industrial action which may have also adversely affected health service delivery and capacity. However, previous research has found that strike action does not result in excess mortality [30].

There appeared to be a disparity in all-cause mortality by area-level deprivation. Overall, individuals from most deprived communities had a higher risk of death compared with those from least deprived communities, and this disparity was exacerbated during the pandemic. However, there were higher odds of mortality from cancer, mental and behavioural disorders and diseases of the nervous system compared with deaths from other causes for least deprived individuals compared with most deprived. It is well-documented that these are considered more affluent diseases [31,32], and previous research has found that mortality rates for specific cancer types including breast [33], ovarian and prostate cancer [34] were higher in mid-least deprived areas of England and Wales compared with the most deprived areas. The models were adjusted to account for potential differences in age and sex across deprivation groups, so differences in mortality related to individuals in the least deprived communities potentially living longer and thus dying from diseases

associated with ageing are unlikely to explain these findings. The discrepancy in cause of death between deprivation groups may be related to potential differences in access to care, education, lifestyle and/or living conditions.

Future work should aim to understand socioeconomic inequalities contributing to disparities in healthcare service and delivery needs. In particular, potential barriers to accessing and delivering emergency care services should be further explored to inform adequate provision. Further research is needed to understand potential differences in healthcare behaviours and access to healthcare services during the pandemic for individuals from different deprivation groups in Wales. This study's strength is its use of population-scale, individual-level, linked electronic health records to adjust for differences in age, sex, area-level deprivation and competing events of mortality at the individual-level, thereby reducing the risk of potential aggregation biases and providing unbiased estimates for cause of death. Further studies using population-scale linked electronic health records at the individual-level should be used in other countries to provide a basis for comparison to inform potential healthcare policy and decision-making at the system-level.

In this study, we were unable to capture individuals born in or migrating to Wales in the C16 cohort and thus we assumed that the C16 cohort remained constant. Sensitivity analyses were undertaken to explore the robustness of results to adults aged 18 years or older only. However, this analysis would not capture migration of adults to Wales. A large proportion of adults migrating to Wales are university students. It is unclear whether this would have an important impact on the analysis since during the COVID-19 pandemic many students remained at their family home and therefore may not have migrated into Wales in the C20 cohort. In the C20 cohort, 329,859 (10.2%) of the cohort were born in, or migrated to, Wales. However, the C20 cohort was younger (median 40 years) than C16 (median 42 years), and therefore may be healthier. This potential limitation is concerning since if this theory holds true, the study findings would underestimate the true indirect effects of the pandemic.

Conclusion

The COVID-19 pandemic had a direct and indirect effect on mortality in Wales. Socioeconomic disparities were also exacerbated during this time. As communities and healthcare systems recover from COVID-19, it is essential to understand the aetiology of increased all-cause deaths and health inequalities.

*Erratum

The title of Figure 4G was corrected on 13 December 2024.

Ethical statement

All research conducted has been completed under the permission and approval of the SAIL independent Information Governance Review Panel (IGRP) project number 0911.

Funding statement

This work is supported by the Academy of Medical Sciences/ the Wellcome Trust/ the Government Department of Business, Energy and Industrial Strategy/the British Heart Foundation/Diabetes UK Springboard Award (SBFoo6/1122) and the Con-COV team funded by the Medical Research Council (MR/V028367/1). This work was supported by Health Data Research UK, which receives its funding from HDR UK Ltd (HDR-9006) funded by the UK Medical Research Council, Engineering and Physical Sciences Research Council, Economic and Social Research Council, Department of Health and Social Care (England), Chief Scientist Office of the Scottish Government Health and Social Care Directorates, Health and Social Care Research and Development Division (Welsh Government), Public Health Agency (Northern Ireland), British Heart Foundation (BHF) and the Wellcome Trust. This work was supported by the ADR Wales programme of work. The ADR Wales programme of work is aligned to the priority themes as identified in the Welsh Government's national strategy: Prosperity for All. ADR Wales brings together data science experts at Swansea University Medical School, staff from the Wales Institute of Social and Economic Research, Data and Methods (WISERD) at Cardiff University and specialist teams within the Welsh Government to develop new evidence which supports Prosperity for All by using the SAIL Databank at Swansea University, to link and analyse anonymised data. ADR Wales is part of the Economic and Social Research Council (part of UK Research and Innovation) funded ADR UK (grant ES/S007393/1). The funders have no role in study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication. Researchers are independent of the funders.

Use of artificial intelligence tools.

None declared.

Data availability

The data used in this study are available in the SAIL Databank at Swansea University, Swansea, UK. All proposals to use SAIL data are subject to review by an independent Information Governance Review Panel (IGRP). Before any data can be accessed, approval must be given by the IGRP. The IGRP carefully considers each project to ensure the proper and appropriate use of SAIL data. When approved, access is gained through a privacy-protecting trusted research environment (TRE) and remote access system referred to as the SAIL Gateway. SAIL has established an application process to be followed by anyone who would like to access data via SAIL <https://www.saildatabank.com/application-process>. This study has been approved by the IGRP as project 0911.

Acknowledgements

We would like to thank Rowena Griffiths for helping with data checking and quality assurance of the C16 and C20 cohorts. This study makes use of anonymised data held in the Secure Anonymised Information Linkage (SAIL) Databank. This work uses data provided by patients and collected by the NHS as part of their care and support. We would also like to acknowledge all data providers who make anonymised

data available for research. We wish to acknowledge the collaborative partnership that enabled acquisition and access to the de-identified data, which led to this output. The collaboration was led by the Swansea University Health Data Research UK team under the direction of the Welsh Government Technical Advisory Cell (TAC) and includes the following groups and organisations: the SAIL Databank, Administrative Data Research (ADR) Wales, Digital Health and Care Wales (DHCW), Public Health Wales, NHS Shared Services Partnership (NWSSP) and the Welsh Ambulance Service Trust (WAST).

Conflict of interest

RKO is a member of the National Institute for Health and Care Excellence (NICE) Technology Appraisal Committee, member of the NICE Decision Support Unit (DSU), and associate member of the NICE Technical Support Unit (TSU). She has served as a paid consultant providing unrelated methodological advice to international reimbursement agencies and the pharmaceutical industry generally. She reports teaching fees from the Association of British Pharmaceutical Industry (ABPI) and the University of Bristol. RAL was a member of the Welsh Government COVID-19 Technical Advisory Group. KRA is a member of the NICE Diagnostic Advisory Committee, member of the NICE Decision Support Unit (DSU), and member of the NICE Technical Support Unit (TSU), and a National Institute for Health and care Research (NIHR) Senior Investigator Emeritus (NF-SI-0512-10159). He has served as a paid consultant providing unrelated methodological advice to the pharmaceutical industry generally, and is a partner and director of Visible Analytics Limited, a health technology assessment consultancy company. He has received unrelated research funding from Association of the British Pharmaceutical Industry (ABPI), European Federation of Pharmaceutical Industries and Associations (EFPIA), Pfizer, Sanofi and Swiss Precision Diagnostics. He reports teaching fees from the Association of British Pharmaceutical Industry (ABPI) and the University of Bristol.

The remaining authors have no conflict of interest to declare.

Authors' contributions

RKO and RAL conceptualised the project. JL, AA, GD, FT and RKO curated the data. RKO, JL, AA, GD, FT and RAL had full access to the data in this study and take full responsibility for the integrity of the data. RKO analysed the data and wrote the first draft. RKO is the guarantor. RKO, JDvO, JL, AA, GD, FT, KRA and RAL critically revised and approved the manuscript.

References

1. World Health Organization (WHO). Novel Coronavirus (2019-nCoV): situation report, 11. Geneva: WHO; 2020. Available from: <https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200131-sitrep-11-ncov.pdf>
2. World Health Organization (WHO). The transition from the acute phase of COVID-19: working towards a paradigm shift for pandemic preparedness and response in the WHO European Region. Geneva: WHO; 2023. Available from: <https://www.who.int/europe/publications/i/item/WHO-EURO-2023-7637-47404-69640>
3. Wise J. Covid-19: WHO declares end of global health emergency. *BMJ*. 2023;381:1041. <https://doi.org/10.1136/bmj.p1041> PMID: 37160309
4. Wang H, Paulson KR, Pease SA, Watson S, Comfort H, Zheng P, et al. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21. *Lancet*. 2022;399(10334):1513-36. [https://doi.org/10.1016/S0140-6736\(21\)02796-3](https://doi.org/10.1016/S0140-6736(21)02796-3) PMID: 35279232

5. Turner S, Botero-Tovar N, Herrera MA, Borda Kuhlmann JP, Ortiz F, Ramirez JC, et al. Systematic review of experiences and perceptions of key actors and organisations at multiple levels within health systems internationally in responding to COVID-19. *Implement Sci.* 2021;16(1):50. <https://doi.org/10.1186/s13012-021-01114-2> PMID: 33962635
6. Moynihan R, Sanders S, Michaleff ZA, Scott AM, Clark J, To EJ, et al. Impact of COVID-19 pandemic on utilisation of healthcare services: a systematic review. *BMJ Open.* 2021;11(3):e045343. Epub 20210316. PMID: 33727273
7. Roy CM, Bollman EB, Carson LM, Northrop AJ, Jackson EF, Moresky RT. Assessing the indirect effects of COVID-19 on healthcare delivery, utilization and health outcomes: a scoping review. *Eur J Public Health.* 2021;31(3):634-40. <https://doi.org/10.1093/eurpub/ckabo47> PMID: 33755130
8. Singleton G, Dowrick A, Manby L, Fillmore H, Syverson A, Lewis-Jackson S, et al. UK Healthcare Workers' Experiences of Major System Change in Elective Surgery During the COVID-19 Pandemic: Reflections on Rapid Service Adaptation. *Int J Health Policy Manag.* 2022;11(10):2072-82. Epub 20210901. PMID: 34523860
9. Alicandro G, La Vecchia C, Islam N, Pizzato M. A comprehensive analysis of all-cause and cause-specific excess deaths in 30 countries during 2020. *Eur J Epidemiol.* 2023;38(11):1153-64. <https://doi.org/10.1007/s10654-023-01044-x> PMID: 37684387
10. Dale CE, Takhar R, Carragher R, Katsoulis M, Torabi F, Duffield S, et al. The impact of the COVID-19 pandemic on cardiovascular disease prevention and management. *Nat Med.* 2023;29(1):219-25. <https://doi.org/10.1038/s41591-022-02158-7> PMID: 36658423
11. Pearson-Stuttard J, Caul S, McDonald S, Whamond E, Newton JN. Excess mortality in England post COVID-19 pandemic: implications for secondary prevention. *Lancet Reg Health Eur.* 2023;36:100802. <https://doi.org/10.1016/j.lanepe.2023.100802> PMID: 38188277
12. Duffy SW, Jonsson H, Agbaje OF, Pashayan N, Gabe R. Avoiding bias from aggregate measures of exposure. *J Epidemiol Community Health.* 2007;61(5):461-3. <https://doi.org/10.1136/jech.2006.050203> PMID: 17435216
13. Zalla LC, Mulholland GE, Filiatreau LM, Edwards JK. Racial/Ethnic and Age Differences in the Direct and Indirect Effects of the COVID-19 Pandemic on US Mortality. *Am J Public Health.* 2022;112(1):154-64. <https://doi.org/10.2105/AJPH.2021.306541> PMID: 34936406
14. Webb Hooper M, Nápoles AM, Pérez-Stable EJ. COVID-19 and racial/ethnic disparities. *JAMA.* 2020;323(24):2466-7. <https://doi.org/10.1001/jama.2020.8598> PMID: 32391864
15. Ford DV, Jones KH, Verplancke J-P, Lyons RA, John G, Brown G, et al. The SAIL Databank: building a national architecture for e-health research and evaluation. *BMC Health Serv Res.* 2009;9(1):157. <https://doi.org/10.1186/1472-6963-9-157> PMID: 19732426
16. Lyons J, Akbari A, Torabi F, Davies GI, North L, Griffiths R, et al. Understanding and responding to COVID-19 in Wales: protocol for a privacy-protecting data platform for enhanced epidemiology and evaluation of interventions. *BMJ Open.* 2020;10(10):e043010. <https://doi.org/10.1136/bmjopen-2020-043010> PMID: 33087383
17. Statistics for Wales. Welsh index of multiple deprivation (WIMD) 2019. Technical report. Welsh Government; 2019. Available from: <https://www.gov.wales/sites/default/files/statistics-and-research/2023-10/welsh-index-multiple-deprivation-2019-technical-report.pdf>
18. World Health Organization (WHO). ICD-10: international statistical classification of diseases and related health problems: tenth revision. Geneva: WHO; 2016. Available from: <https://icd.who.int/browse10/2016/en>
19. Taylor T, Schumacher D, Jombart T. trending: Model Temporal Trends. 3 Apr 2023. Available from: <https://cran.r-project.org/package=trending>
20. Agresti A. Categorical data analysis. Oxford: John Wiley & Sons; 2012.
21. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020. Available from: <http://www.Rproject.org/>
22. Alsallakh MA, Sivakumaran S, Kennedy S, Vasileiou E, Lyons RA, Robertson C, et al. Impact of COVID-19 lockdown on the incidence and mortality of acute exacerbations of chronic obstructive pulmonary disease: national interrupted time series analyses for Scotland and Wales. *BMC Med.* 2021;19(1):124. Epub 20210517. PMID: 33993870
23. Pearce S, Marchand T, Shannon T, Ganshorn H, Lang E. Emergency department crowding: an overview of reviews describing measures causes, and harms. *Intern Emerg Med.* 2023;18(4):1137-58. Epub 20230301. PMID: 36854999
24. Jones S, Moulton C, Swift S, Molyneux P, Black S, Mason N, et al. Association between delays to patient admission from the emergency department and all-cause 30-day mortality. *Emerg Med J.* 2022;39(3):168-73. Epub 20220118. PMID: 35042695
25. He J, Ning P, Schwebel DC, Yang Y, Li L, Cheng P, et al. Injury mortality and morbidity changes due to the COVID-19 pandemic in the United States. *Front Public Health.* 2022;10:1001567. Epub 20221102. . PMID: 36408028
26. Liu J, Zhang L, Yan Y, Zhou Y, Yin P, Qi J, et al. Excess mortality in Wuhan city and other parts of China during the three months of the covid-19 outbreak: findings from nationwide mortality registries. *BMJ.* 2021;372(415):n415. <https://doi.org/10.1136/bmj.n415> PMID: 33627311
27. Abraham SA, Agyare DF, Yeboah NK, Owusu-Sarpong AA, Banulanzeki ES, Doku DT, et al. The Influence of COVID-19 Pandemic on the Health Seeking Behaviors of Adults Living With Chronic Conditions: A View Through the Health Belief Model. *J Prim Care Community Health.* 2023;14:21501319231159459. <https://doi.org/10.1177/21501319231159459> PMID: 36935563
28. O'Dowd A. Around 11 000 ambulances are waiting more than an hour at A&E every week, analysis finds. *BMJ.* 2022;379:02911. <https://doi.org/10.1136/bmj.02911> PMID: 36455967
29. Propper C, Stoye G, Zaranko B. The Wider Impacts of the Coronavirus Pandemic on the NHS. *Fisc Stud.* 2020;41(2):345-56. <https://doi.org/10.1111/1475-5890.12227> PMID: 32836538
30. Essex R, Weldon SM, Thompson T, Kalocsányiová E, McCrone P, Deb S. The impact of health care strikes on patient mortality: A systematic review and meta-analysis of observational studies. *Health Serv Res.* 2022;57(6):1218-34. <https://doi.org/10.1111/1475-6773.14022> PMID: 35791855
31. Luthar SS. The culture of affluence: psychological costs of material wealth. *Child Dev.* 2003;74(6):1581-93. <https://doi.org/10.1046/j.1467-8624.2003.00625.x> PMID: 14669883
32. Kivimäki M, Batty GD, Pentti J, Shipley MJ, Sipilä PN, Nyberg ST, et al. Association between socioeconomic status and the development of mental and physical health conditions in adulthood: a multi-cohort study. *Lancet Public Health.* 2020;5(3):e140-9. [https://doi.org/10.1016/S2468-2667\(19\)30248-8](https://doi.org/10.1016/S2468-2667(19)30248-8) PMID: 32007134
33. Office for National Statistics. How does deprivation vary by leading cause of death? Newport: Office for National Statistics; 2017. Available from: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/howdoesdeprivationvarybyleadingcauseofdeath/2017-11-01#:~:text=Analysis%20into%20how%20deprivation%20impacts%20cause%20of%20death%20in%20England%20and%20Wales.&text=The%20more%20deprived%20areas%20in,Blackpool%20by%20almost%20seven%20years>
34. Romeri E, Baker A, Griffiths C. Mortality by deprivation and cause of death in England and Wales, 1999-2003. *Health Stat Q.* 2006;60(32):19-34. PMID: 17165467

License, supplementary material and copyright

This is an open-access article distributed under the terms of the Creative Commons Attribution (CC BY 4.0) Licence. You may share and adapt the material, but must give appropriate credit to the source, provide a link to the licence and indicate if changes were made.

Any supplementary material referenced in the article can be found in the online version.

This article is copyright of the authors or their affiliated institutions, 2024.