Antipsychotic drug prescribing and mortality in people with dementia before and during the COVID-19 pandemic

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Published in:
The Lancet Healthy Longevity

DOI:
10.1016/S2666-7568(23)00105-8

Publication date:
2023

Antipsychotic drug prescribing and mortality in people with dementia before and during the COVID-19 pandemic: a retrospective cohort study in Wales, UK

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Summary

Background Concerns have been raised that antipsychotic drug prescribing, which has been associated with increased mortality in people with dementia, might have increased during the COVID-19 pandemic due to social restrictions imposed to limit the spread of SARS-CoV-2. We used multisource, routinely collected health-care data from Wales, UK to investigate prescribing and mortality variations in people with dementia before and during the COVID-19 pandemic.

Methods In this retrospective cohort study, we used individual-level, anonymised, population-scale linked health data to identify adults aged 60 years and older with a diagnosis of dementia in Wales, UK. We used the CVD-COVID-UK initiative to access Welsh routinely collected electronic health record data from the Secure Anonymised Information Linkage (SAIL) Databank. Patients who were alive and registered with a SAIL general practice on Jan 1, 2016, and who received a dementia diagnosis before the age of 60 years and before or during the study period were included. We explored antipsychotic drug prescribing rate changes over 67 months, between Jan 1, 2016, and Aug 1, 2021, overall and stratified by age and dementia subtype. We used time-series analyses to examine all-cause and myocardial infarction and stroke mortality over the study period and identified the leading causes of death in people with dementia between Jan 1, 2020, and Aug 1, 2021.

Findings Of 3 106 690 participants in SAIL between Jan 1, 2016 and Aug 1, 2021, 57 396 people (35 148 [61·2%] women and 22 248 [38·8%] men) met inclusion criteria for this study and contributed 101 428 person-years of follow-up. Of the 57 396 people with dementia, 11 929 (20·8%) were prescribed an antipsychotic drug at any point during follow-up. Accounting for seasonality, antipsychotic drug prescribing increased during the second half of 2019 and throughout 2020. However, the absolute difference in prescribing rates was small, ranging from 1253 prescriptions per 10 000 person-months in March, 2019, to 1305 per 10 000 person-months in September, 2020. All-cause mortality and stroke mortality increased throughout 2020, while myocardial infarction mortality declined. From Jan 1, 2020, to Aug 1, 2021, 1286 (17·1%) of 7508 participants who died had COVID-19 recorded as the underlying cause of death.

Interpretation During the COVID-19 pandemic, antipsychotic drug prescribing in people with dementia in the UK increased slightly; however, it is unlikely that this was solely related to the pandemic and this increase was unlikely to be a major factor in the substantial increase in mortality during 2020. The long-term increase in antipsychotic drug prescribing in younger people and in those with Alzheimer's disease warrants further investigation using resources with access to more granular clinical data. Although deprescribing antipsychotic medications remains an essential aspect of dementia care, the results of this study suggest that changes in prescribing and deprescribing practices as a result of the COVID-19 pandemic are not required.

Funding British Heart Foundation (via the British Heart Foundation Data Science Centre led by Health Data Research UK), and the Scottish Neurological Research Fund.

Lancet Healthy Longev 2023; 4: e421–30

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Introduction

An estimated 57 million people worldwide live with dementia.[1] The COVID-19 pandemic has disproportionately affected people with dementia, who are more likely than people without dementia to be infected by SARS-CoV-2 and develop severe disease.[2,3] In addition, social restrictions imposed to limit the spread of SARS-CoV-2 might be associated with a worsening of neuropsychiatric symptoms in people with dementia.[4]

Antipsychotic medications can be used to treat symptoms of agitation, aggression, distress, and psychosis in people with dementia. However, antipsychotic use has been associated with an increased risk of adverse outcomes, such as stroke,[5,6] myocardial infarction,[7,8] and death.[9,10] As a result, many countries have restrictions on the use of these drugs in people with dementia.[11,12] The UK National Institute for Health and Care Excellence's clinical guidance states that

Research in context

Evidence before this study

We searched Ovid MEDLINE with no language restrictions for studies describing antipsychotic drug prescribing changes in people with dementia during the COVID-19 pandemic, published between Jan 1, 2020, and March 22, 2022. The following search terms were used: (exp Antipsychotic Agents/ OR antipsychotic.mp OR neuroleptic.mp OR risperidone.mp OR exp Risperidone/ OR quetiapine.mp OR exp Quetiapine Fumarate/ OR olanzapine.mp OR exp Olanzapine/ OR exp Psychotropic Drugs/ or psychotropic.mp) AND (exp Dementia/ OR exp Alzheimer Disease/ or Alzheimer.mp) AND (prescri*.mp OR exp Prescriptions/ OR exp Electronic Prescribing/ OR trend*.mp OR time series.mp). The search identified 128 published studies, of which three were eligible for inclusion. Two studies, based on data from England and the USA, compared antipsychotic drug prescribing in people with dementia before and during the COVID-19 pandemic. Both reported an increase in the proportion of patients prescribed an antipsychotic drug after the onset of the COVID-19 pandemic. A third study, from the Netherlands, reported antipsychotic drug prescription changes in nursing home residents with dementia during the first 4 months of the COVID-19 pandemic, comparing prescribing rates to the timings of lifting social restrictions, showing that antipsychotic drug prescribing rates remained constant throughout this period.

Added value of this study

We did age-standardised time-series analyses using comprehensive, linked, anonymised, individual-level, routinely collected, population-scale health data for the population of Wales, UK. By accounting for seasonal variations in prescribing and mortality, we showed that the absolute increase in antipsychotic drug prescribing in people with dementia of any cause during the COVID-19 pandemic was small. By contrast, antipsychotic drug prescribing in the youngest age group (60–64 years) and in people with a subtype diagnosis of Alzheimer's disease increased throughout the 5-year study period. Accounting for seasonal variation, all-cause mortality rates in people with dementia began to increase in late 2019 and increased sharply during the COVID-19 pandemic. COVID-19 became the leading non-dementia cause of death in people with dementia from 2020 to 2021. Stroke mortality increased during the pandemic, following a similar pattern to that of all-cause mortality, whereas myocardial infarction rates decreased. Our study identified that the increase in antipsychotic drug prescribing in the UK during the COVID-19 pandemic was smaller than suggested by previous studies, and was unlikely to be solely due to the pandemic.

Implications of all the available evidence

During the COVID-19 pandemic, we observed a large increase in all-cause and stroke mortality in people with dementia. When seasonal variations are accounted for, antipsychotic drug prescribing rates in all-cause dementia increased by a small amount before and during the pandemic in the UK, which is unlikely to have been responsible for the large mortality increases seen during the same period. Our results suggest that significant changes in antipsychotic drug prescribing practices as a result of the pandemic are not required. The increased prescribing rates in younger age groups and in people with Alzheimer's disease warrants further investigation.

antipsychotic medications should only be used when alternative approaches have failed, and if the patient is in severe distress or at risk of harming themselves or others.[13]

Concerns have been raised that rates of antipsychotic drug prescribing for people with dementia might have increased in the UK during the early months of the COVID-19 pandemic.[14,15] The National Health Service (NHS) England reports monthly on the proportion of people with dementia who are prescribed an antipsychotic drug—a proportion that remained stable in 2018–19 but that appeared to increase in March, 2020, around the time social restrictions were introduced in England to reduce the spread of SARS-CoV-2.[14] Although such group-level data are useful for the understanding of overall variations, they do not provide detailed information on the demographic details, seasonal variation, and linked health outcomes associated with medication use in this population. In this study, we used individual-level, routinely collected, linked health data from Wales, UK, and aimed to investigate changes in antipsychotic drug prescribing in people with dementia before and during the COVID-19 pandemic. We also aimed to investigate the potential impact of the COVID-19 pandemic on people with dementia and explore changes in all-cause, myocardial infarction, and stroke mortality over the same period.

For the **pre-published protocol** see https://github.com/BHFDSC/CCU016_01

For more on the **CVD-COVID-UK Consortium** see https://www.hdruk.ac.uk/projects/cvd-covid-uk-project/

For the **SAIL Databank** see https://saildatabank.com

Methods

Study design and participants

We did a retrospective cohort study using routinely collected linked health data from Wales, UK. We pre-published the protocol with disease phenotyping codes.

The CVD-COVID-UK Consortium is a UK-wide initiative established to accelerate research on COVID-19 and cardiovascular disease by facilitating access to linked, routinely collected, electronic health record data from England, Scotland, and Wales.[16] For this study, we used the CVD-COVID-UK initiative to access Welsh routinely collected electronic health record data from the Secure Anonymised Information Linkage (SAIL) Databank. SAIL contains anonymised, individual-level, population-scale, linked, routinely collected electronic health record and social care data sources for the population of approximately 3 million people in Wales, UK, who

receive much of their health care through the NHS.[17] Primary care data are available in SAIL for approximately 86% of the Welsh population. Data are accessed via a remotely accessible, privacy-protecting, trusted research environment.

We created a population-based cohort of people with dementia using linked, individual-level, anonymised data sources. The Welsh Longitudinal General Practice dataset was used to obtain primary care diagnoses and prescriptions. The Patient Episode Database for Wales provided diagnostic information arising from hospital admissions. The Annual District Death Extract, Annual District Death Daily, and Consolidated Death Data Source were combined for mortality data. The Lower-layer Super Output Area of residence and associated Welsh Index of Multiple Deprivation (Welsh Demographic Service Dataset) were used for demographic information. The Care Home Dataset was used for care home information. Sex data were collected via a combination of medical records from birth, and self-reported from patients if registering with a new general practice.

We defined the study period from Jan 1, 2016, to Aug 1, 2021 (67 months). Follow-up for each participant started at the earliest date of dementia diagnosis or, if a participant received a dementia diagnosis before the study start date, on Jan 1, 2016. Follow-up for each participant ended at the date of death, deregistration with a SAIL general practice, or Aug 1, 2021, whichever was earliest. For reference, the first case of COVID-19 in the UK was recorded in January, 2020, and the UK's first nationwide lockdown to mitigate the spread of the virus began in March, 2020.

We included all patients who were alive and registered with a SAIL general practice on Jan 1, 2016, and who received a dementia diagnosis before (using all available previous data) or during the study period. We excluded people who received a diagnosis of dementia before age 60 years due to the low rates of dementia and dementia-related mortality and low accuracy of dementia diagnostic coding before this age.[18,19]

We used a validated list of codes, namely Read Codes (version 2) for primary care and International Classification of Diseases (tenth revision) for hospital admissions, to identify people with all-cause dementia (appendix pp 2–4).[20] We defined dementia as the presence of at least one dementia code in either data source, using the date of the first dementia code as the date of diagnosis. We did not use a prescription of a dementia medication (ie, donepezil, rivastigmine, galantamine, or memantine) to identify dementia cases but, for people with a prescription for a dementia medication before the date of their first dementia diagnostic code, we used the date of the first prescription as the date of dementia diagnosis. We defined dementia subtypes (eg, Alzheimer's disease or vascular dementia) as the presence of one or more subtype codes at any point (appendix p 2). Dementia subtype categories were not mutually exclusive.

The North East–Newcastle and North Tyneside 2 research ethics committee provided ethical approval for the CVD-COVID-UK research programme. In accordance with Data Protection Act and the UK General Data Protection Regulation, individual participant consent was not required for this study because the data were anonymised.

Procedures and outcomes

We defined exposure to antipsychotic medications during the study window using prescription data, which are part of primary care data (appendix p 5). We also identified exposure to benzodiazepines, an alternative class of drugs used to treat agitation or distress in people with dementia, to investigate whether any change seen in antipsychotic drug prescribing was specific to that medication class or reflected changes in prescribing rates across all psychotropic medications.

For descriptive purposes, we estimated frailty in participants with a minimum of 5 years of available primary care data before the study start date using the electronic Frailty Index,[21] which uses primary care data to estimate an individual participant's frailty (defined as fit, or mild, moderate, or severe frailty). We used the preceding 5 years of primary care data to calculate the electronic Frailty Index.

We used mortality data to describe changes in all-cause mortality and mortality due to myocardial infarction or ischaemic stroke over the study period. We used fatal ischaemic stroke to investigate cerebrovascular outcomes and myocardial infarction to investigate cardiovascular outcomes, to avoid the uncertainty of whether repeated non-fatal stroke or myocardial infarction codes, such as those identified in hospital admissions data, represent recurrent events or the same event coded multiple times. We used the code lists for stroke and myocardial infarction that were developed during the creation of the SAIL Dementia electronic cohort (appendix p 6).[17]

To identify causes of death, we grouped International Classification of Diseases codes using the same method used by the Office for National Statistics when collating UK mortality figures, with the addition of the new COVID-19 codes (U07.1 and U07.2).[22]

See Online for appendix

Statistical analysis

We calculated the age-standardised monthly rate of antipsychotic and benzodiazepine prescribing between Jan 1, 2016, and Aug 1, 2021 (67 months) in people with dementia. We also stratified antipsychotic drug prescribing by age (in 5-year intervals). We used an autoregressive integrated moving average model to conduct time-series analyses. This model involves decomposing the raw data into seasonal, trend and random and residual components using a moving average with a symmetric window (6 months on either side of the month under study, for a total of 13 months) and an additive decomposition model. We standardised

ages on the basis of the age distribution of the study cohort in January, 2020 (the month in which the first COVID-19 case was identified in the UK), to account for changes in the age distribution of the cohort over the study period. We also stratified the study sample by sex and dementia subtype. We could not stratify by care home versus community residence due to the risk of participant identification in groups with a small number of individuals. We described the prescribing patterns for all antipsychotic drugs combined and for the top three most commonly prescribed antipsychotic drugs (risperidone, olanzapine, and quetiapine). To identify potential associations between the start of the COVID-19 pandemic in 2020 and changes in antipsychotic drug prescribing, we conducted a prespecified outlier analysis in the seasonal autoregressive integrated moving average models based on the method described by Chen and Liu.[23] We identified additive outliers, level shifts, or transitory changes using the R package tsoutlier,[24] with timepoints identified as outliers if the t-statistic exceeded 3·5. We presented demographic data with absolute values and percentages and medians with IQRs.

We conducted an age-standardised time-series analysis to investigate changes in all-cause mortality, fatal stroke, and fatal myocardial infarction between Jan 1, 2016, and Aug 1, 2021. We compared mortality rates in which stroke or myocardial infarction were listed as the primary cause on the death certificate with rates of these diagnoses listed anywhere on the death certificate. As with antipsychotic drug prescribing variations, we also stratified all-cause mortality analysis by sex and dementia subtype and conducted automated outlier detection.

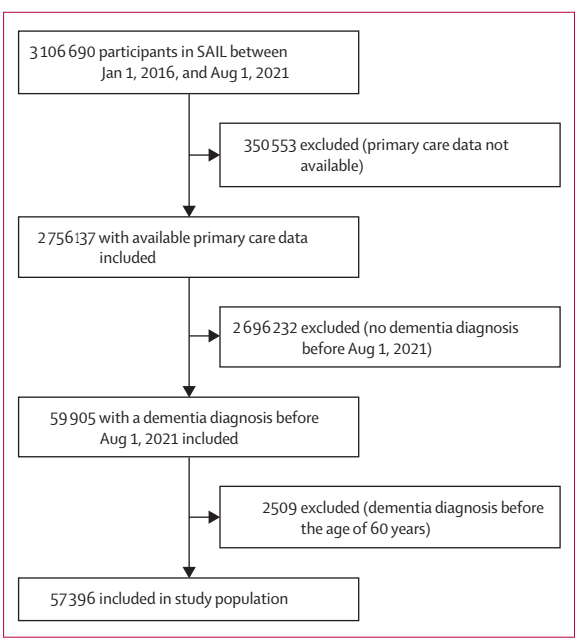

Figure 1: **Study profile**
SAIL=Secure Anonymised Information Linkage Databank

We counted the underlying causes of death in people with dementia who died between Jan 1, 2020, and Aug 1, 2021 (end of follow-up) to only assess the period after the onset of COVID-19. We compared the number of participants for whom COVID-19 was listed as the underlying cause of death with the number in whom COVID-19 was listed anywhere on the death certificate (underlying and secondary).

We used structured query language for data management and R (version 4.1.2) for statistical analysis. The statistical code is publicly available in the aforementioned pre-published protocol.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of 3 106 690 participants included in SAIL between Jan 1, 2016, and Aug 1, 2021, 350 553 (11·3%) did not have primary care data available and 2 696 232 (86·8%) did not have a dementia diagnosis before Aug 1, 2021. A further 2509 (<0·1%) were then excluded for being younger than 60 years at the time of dementia diagnosis, resulting in a final study cohort of 57 396 (1·8%) individuals (figure 1), who contributed 101 428 person-years of follow-up. 35 148 (61·2%) of 57 396 participants were women and 22 248 (38·8%) were men. The median observation time per person was 32 months (IQR 12–66) and the median age at study start date was 82 years (76–87). Participant demographics are displayed in the table. Data on race and ethnicity, which are poorly coded within UK primary routinely collected datasets, were not collected.

Of the 57 396 participants, 11 929 (20·8%) were prescribed an antipsychotic drug at any point during follow-up. The median age of patients who received an antipsychotic drug (80 years [IQR 64–86]) was lower than that of patients who did not (82 years [76–87]), and a higher proportion of patients who received an antipsychotic drug were care-home residents at the study start date (18·5% *vs* 14·4% of those who did not receive antipsychotic medication; table).

The age-standardised prescribing rates for benzodiazepines, the three most prescribed antipsychotic drugs (olanzapine, quetiapine, and risperidone), and total antipsychotic medications are shown in figure 2. Risperidone and olanzapine prescribing rates increased steadily throughout the study period, whereas quetiapine prescribing reduced (appendix p 8). Age-stratified antipsychotic drug prescribing rates appeared relatively static over the entire study period, except for the youngest age group (60–64 years), in whom prescribing rates doubled over the 5 years of the study (appendix p 10).

In March, 2020 (early in the COVID-19 pandemic), 12·9% of people with dementia were prescribed an antipsychotic drug, compared with 12·5% in March, 2019.

	Total cohort (n=57 396)	Subpopulation exposed to antipsychotic drugs (n=11 929)
Total observation time, person-years	101 428	22 699
Age at study start date	82 (76–87)	80 (64–86)
Sex		
Female	35 148 (61·2%)	7115 (59·6%)
Male	22 248 (38·8%)	4814 (40·4%)
Deprivation, quintiles*		
1 (most deprived)	10 624 (18·5%)	2375 (19·9%)
2	11 656 (20·3%)	2513 (21·1%)
3	11 091 (19·3%)	2200 (18·4%)
4	11 425 (19·9%)	2313 (19·4%)
5 (least deprived)	12 600 (21·9%)	2528 (21·2%)
Resident in care home*	8271 (14·4%)	2206 (18·5%)
Dementia subtype†		
Alzheimer's disease	25 407 (44·3%)	5738 (48·1%)
Vascular dementia	17 720 (30·9%)	4302 (36·1%)
Frontotemporal dementia	571 (0·9%)	183 (1·5%)
Dementia with Lewy bodies	1044 (1·8%)	388 (3·3%)
Not specified	17 506 (30·5%)	2835 (23·8%)
Date of dementia diagnosis		
Before Jan 1, 2016	35 940 (62·6%)	6580 (55·2%)
Between Jan 1, 2016 and Aug 1, 2021	21 456 (37·4%)	5349 (44·8%)
Electronic frailty index score*		
Fit	12 255 (21·4%)	1771 (14·8%)
Mild frailty	11 857 (20·7%)	2017 (16·9%)
Moderate frailty	5240 (9·1%)	956 (8·0%)
Severe frailty	576 (1·0%)	100 (0·8%)
Not assessable‡	27 468 (47·9%)	7085 (59·4%)
Previous stroke*	7213 (12·6%)	1441 (12·1%)
Previous myocardial infarction*	6267 (10·9%)	1242 (10·4%)

Data are n (%) or median (IQR), unless otherwise specified. Demographics of the whole cohort and subgroup who were prescribed an antipsychotic drug at any point during follow-up. *Before or at the study start date (Jan 1, 2016). †Categories are not mutually exclusive apart from the not specified category, which reflects the number of participants with no subtype code. ‡Electronic frailty index could only be calculated for participants with 5 years of available primary care data before the study start date.

Table: **Participant characteristics**

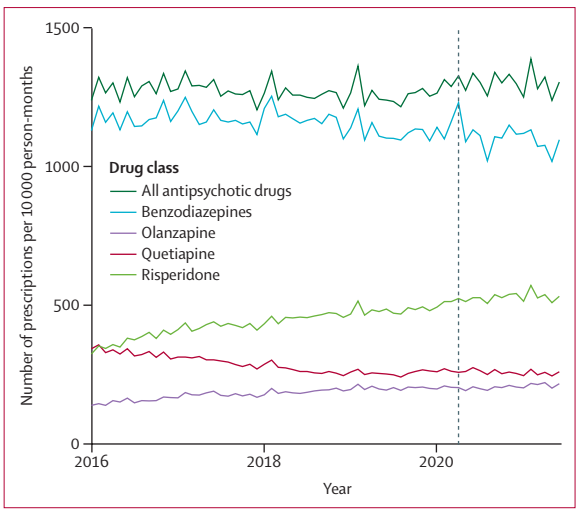

Figure 2: **Antipsychotic drug prescribing rates**
Rates are age-standardised. Benzodiazepine prescribing is included for comparison. Dotted vertical line indicates March, 2020 (start of the first UK-wide lockdown to reduce the spread of SARS-CoV-2).

Accounting for seasonal changes, antipsychotic drug prescribing in people with all-cause dementia fell between 2017 and 2019 (figure 3A), then started to increase in the second half of 2019, continued to increase throughout 2020, and peaked in the second half of 2020. However, the absolute change in prescribing between the lowest and highest rates was relatively small (1253 prescriptions per 10 000 person-months in March, 2019, compared with 1305 per 10 000 person-months in September, 2020). The outlier analysis detected no outliers between March, 2020, and August, 2021. By contrast, antipsychotic drug prescribing in participants with Alzheimer's disease increased steadily throughout the entire study period, with a steep increase during the second half of 2019, peaking in mid-2020 (figure 3B). Antipsychotic drug prescribing changes in the subgroup with vascular dementia showed a similar pattern to that of all-cause dementia (figure 3C).

During the 5-year study period, 35 565 (62·0%) participants died. The median age of death was 87 years (IQR 82–91). Age-standardised all-cause mortality declined from 2018 until late 2019, then increased sharply and continued to increase throughout early and mid-2020 (figure 4A).

The pattern of fatal stroke rates was similar to that of all-cause mortality, with rates declining during 2018 to mid-2019, followed by an increase in the second half of 2019, which continued throughout 2020 (figure 4B). The peak in stroke mortality in August, 2020 (23 deaths per 10 000 person-months) was similar to that in September, 2017 (24 per 10 000 person-months). Two peaks in stroke mortality during the COVID-19 pandemic were noted, coinciding with all-cause mortality peaks. During these peaks, a smaller proportion of strokes were recorded in the primary position of the death certificate than in any position, showing a shift towards stroke as a contributing (rather than underlying) cause of death (appendix p 12).

Fatal myocardial infarction rates declined throughout the study period (figure 4C). After accounting for seasonal effects, there was no noticeable change in myocardial infarction mortality rates following the onset of the COVID-19 pandemic.

Between Jan 1, 2020, and Aug 1, 2021, 7508 (37·5%) of 20 042 participants died. The most frequently recorded underlying cause of death was dementia, whereas COVID-19 was the second most common underlying

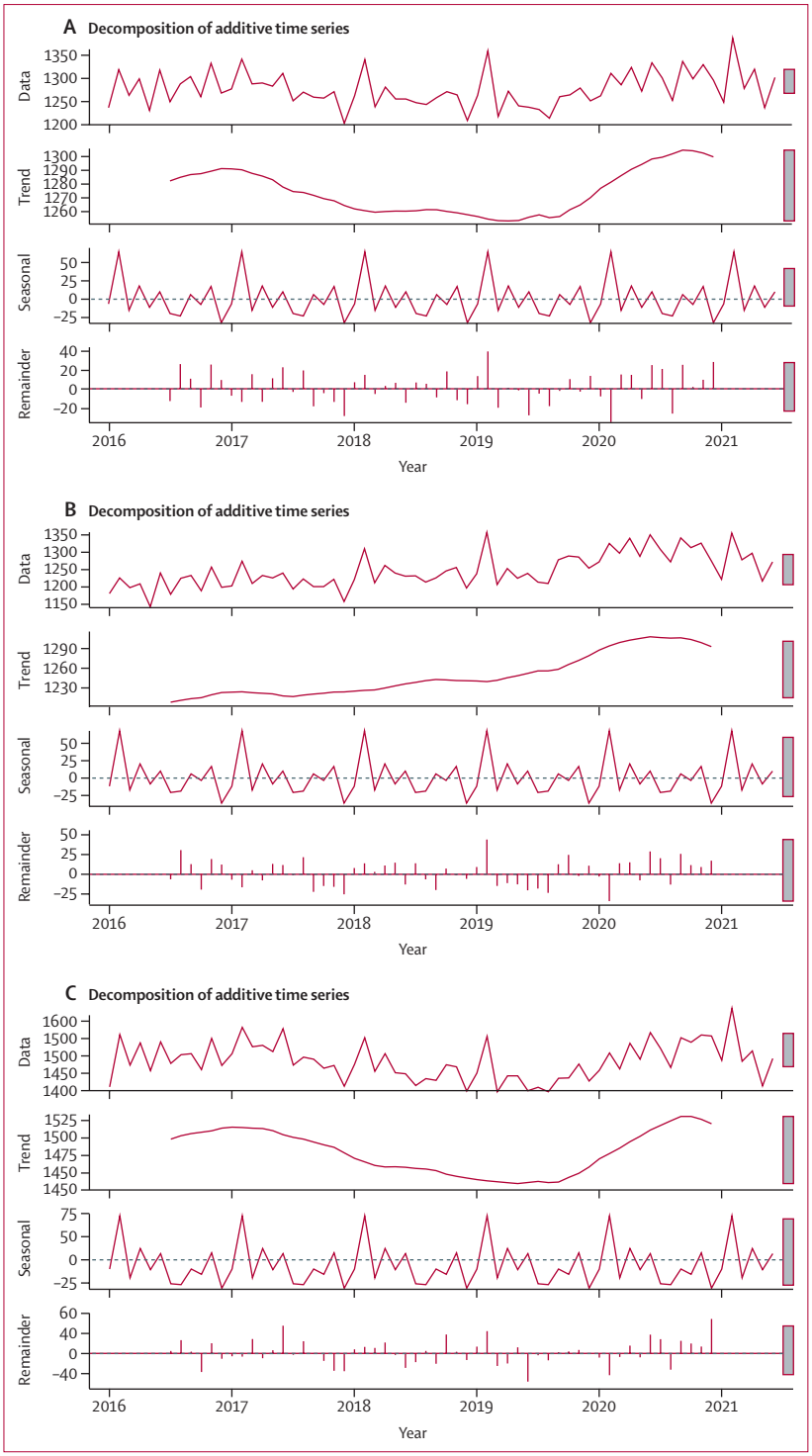

***Figure 3*: Changes in antipsychotic drug prescribing rates in people with all-cause dementia (A), Alzheimer's disease (B), and vascular dementia (C)**

Age-standardised, additive, autoregressive, integrated, moving average time-series model, accounting for seasonal variations in prescribing. The data panel shows age-standardised prescribing rates. The trend panel shows the trend of prescribing rates, accounting for seasonal variations. The seasonal panel shows the seasonal changes in prescribing rates during the study period. The remainder panel shows the difference between the raw data and the seasonal trend. The grey bars to the right of each panel show the relative scales of the components. Each grey bar represents the same length but as the plots are on different scales, the bars vary in size.

cause of death during this period (figure 5). Of the 7508 participants who died, 1451 (19·3%) had COVID-19 listed in any position on the death certificate, and 1286 (17·1%) had COVID-19 recorded as the underlying cause of death, meaning that 1286 (6·4%) of 20 042 participants alive on Jan 1, 2020, died from COVID-19 by Aug 1, 2021.

The median age at death from COVID-19 during this period was the same as for death from any cause (87 years [IQR 81–92]).

Discussion

We used routinely collected health data to examine changes in antipsychotic drug prescribing and mortality before and during the COVID-19 pandemic. Antipsychotic drug prescribing rates for people with dementia increased in 2019 and continued to increase during 2020, but the absolute change was small and on a background of lower rates of prescribing over the previous 2 years. Antipsychotic drug prescribing in people with a subtype diagnosis of Alzheimer's disease increased throughout the 5-year study period. From 2020 onwards, COVID-19 became the leading non-dementia cause of death in people with dementia.

After accounting for seasonal effects on prescribing, we observed a small increase in the proportion of people with dementia prescribed antipsychotic medications following the onset of the COVID-19 pandemic. However, the increased rates of prescribing began in the months before the arrival of COVID-19, suggesting that the COVID-19 pandemic might not have been the only cause of the change. The age-stratified analysis showed a notable increase in antipsychotic drug prescribing in the youngest age group (60–64 years) during the 5-year study period, but the reasons for this finding are unclear and merit further investigation.

Howard and colleagues[14] highlighted an increased proportion of patients with dementia being prescribed antipsychotic drugs in 2020, compared with previous years, on the basis of publicly available NHS safety data in England. Although our study identified an increase in antipsychotic drug prescribing between 2019 and 2020, the use of a time-series analysis showed that, once seasonal variations were accounted for, the absolute increase was minimal and occurred following particularly low prescribing rates over the previous 2 years.

A recent study by Luo and colleagues[25] analysed routine health databases from six countries—France, Germany, Italy, South Korea, the USA, and the UK—to investigate the rates of antipsychotic drug prescribing in people with dementia during the COVID-19 pandemic. In keeping with the findings from our study, after the application of interrupted time series, no substantial changes in prescribing rates were observed before and after the advent of COVID-19 in the UK, France, and South Korea. An immediate increase in prescribing was identified in Italy, and an immediate decrease was observed in

Germany. Conflicting variations were observed in the two included US datasets. The extent to which the differing results across countries in Luo and colleagues' study represent genuine differences in prescribing practices during the pandemic, as opposed to differences in approach to the coding of routine data, issues with data harmonisation, or models of health care, remains unclear.

Harrison and colleagues[15] used routinely collected data from the USA to compare the proportion of people with dementia prescribed an antipsychotic drug in the 30 days before attendance at a health-care organisation (eg, hospital or primary care centre) in 2020, compared with 2019. In Harrison and colleagues' study, 16·4% of patients were prescribed an antipsychotic drug during 2020, compared with 14·7% in 2019. People attending health-care centres in 2020 were on average more likely to be unwell than in the previous year, given the concerns about nosocomial COVID-19 transmission, which might have biased the findings towards increased rates of antipsychotic drug use in this study.

Sizoo and colleagues[26] investigated antipsychotic drug prescribing rates in psychogeriatric residents with dementia in the Netherlands, before and during national lockdowns. The proportion of people prescribed an antipsychotic drug was high (21·0–22·9%), reflecting the known higher rates of antipsychotic drug use in care-home populations than in people not living in care homes, but they did not identify a change in prescribing practices over the study period.

Our analysis showed a marked increase in all-cause mortality from late 2019 onwards, with two peaks in 2020 and early 2021, which coincided with the known peaks in COVID-19 transmission in the UK.[27] Previous studies have shown that people with dementia are at an increased risk of severe symptoms or death from COVID-19.[2]

From January, 2020, to August, 2021, COVID-19 became the leading non-dementia underlying cause of death in people with dementia. According to our analysis, about 6% of all people with dementia who were alive at the start of 2020 died of COVID-19 over the subsequent 19 months. This proportion is likely to be an underestimate due to undertesting of COVID-19 early in the pandemic in the UK, particularly for those not admitted to hospital, which probably led to underreporting of COVID-19 on death certificates.[28]

Stroke mortality rate variations largely followed that of all-cause mortality. Following a reduction in stroke mortality during 2018, we observed an increase in the second half of 2019, which continued throughout 2020,

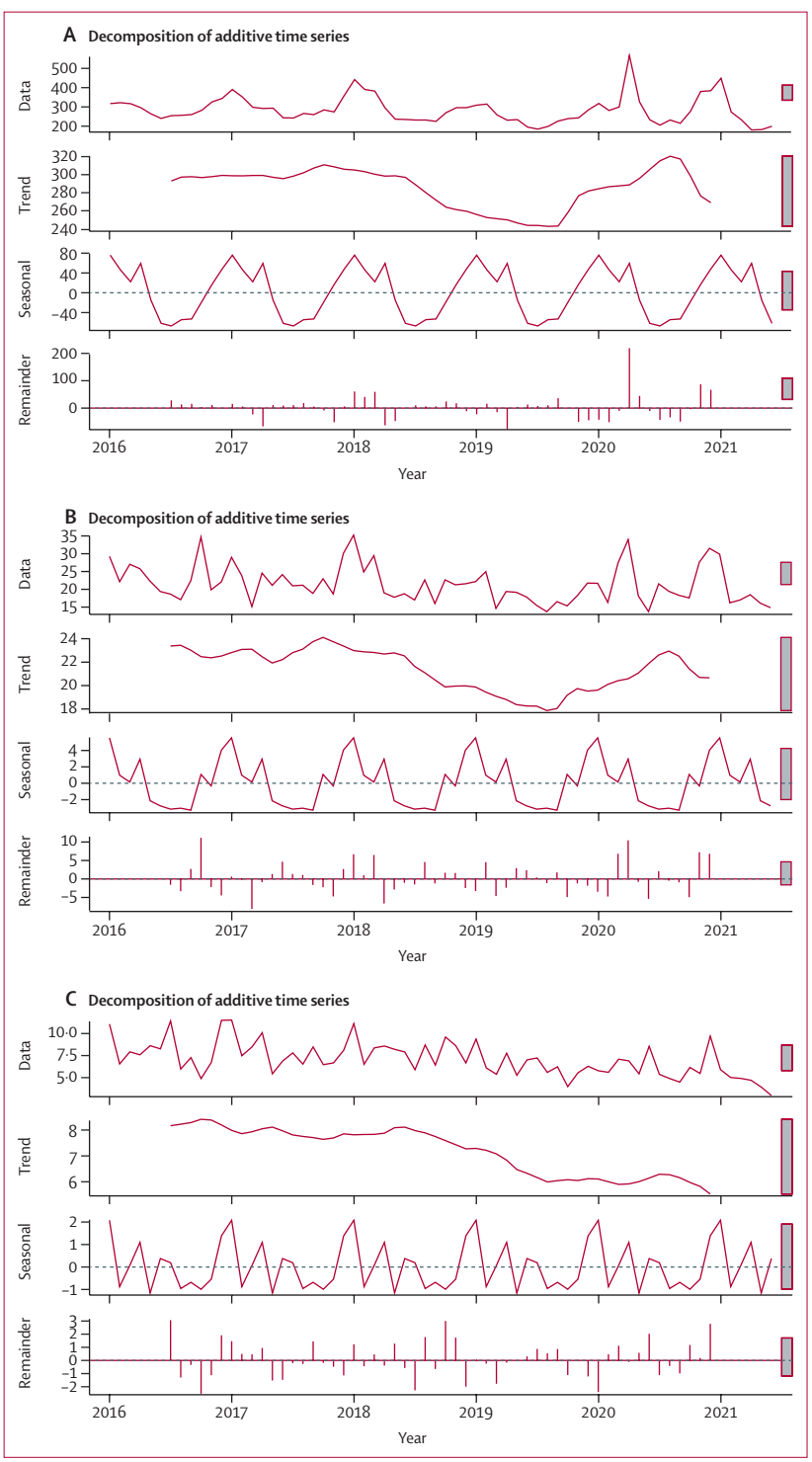

Figure 4: **Changes in all-cause and cause-specific mortality rates**
(A) All-cause mortality. (B) Stroke mortality. (C) Myocardial infarction mortality. Age-standardised, additive, autoregressive, integrated, moving average time-series model, accounting for seasonal variations in mortality. For all-cause mortality, an outlier analysis detected outliers in April, May, and November, 2020, and in January, 2021. The data panel shows the age-standardised mortality rates. The trend panel shows the trend of mortality rates, accounting for seasonal trends. The seasonal panel shows the seasonal changes in prescribing rates during the study period. The remainder panel shows the difference between the raw data and the seasonal trend. The grey bars to the right of each panel show the relative scales of the components. Each grey bar represents the same length but as the plots are on different scales, the bars vary in size.

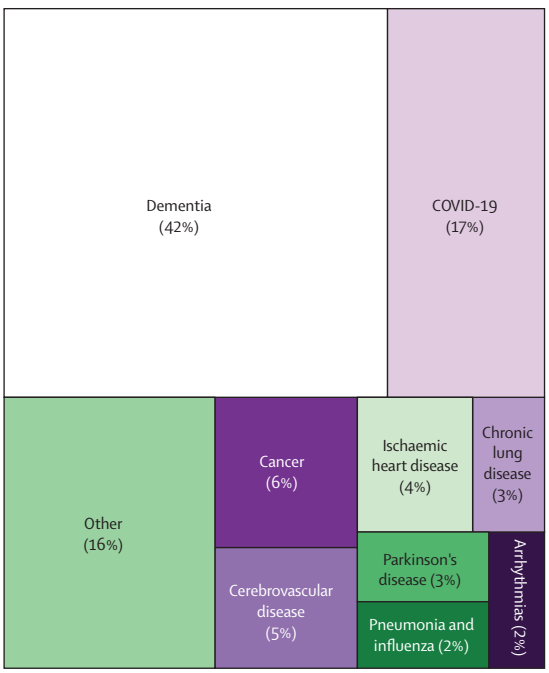

Figure 5: **Treemap of leading underlying causes of death in people with dementia from Jan 1, 2020, to Aug 1, 2021**

albeit with a lower peak than in 2017. During the peaks in mortality, stroke was more frequently listed as a contributing factor, rather than the underlying cause of death, which might in part be due to the increased risk of stroke following COVID-19 infection.[29] In contrast to stroke, the rate of myocardial infarction deaths decreased during the study period, with no increase following the onset of COVID-19.

A previous meta-analysis identified that antipsychotic drug use in people with dementia was consistently associated with a 16% increased risk of stroke across cohort studies.[5] Our study design could not establish whether a causal relationship exists between changes in antipsychotic drug prescribing and resulting stroke and all-cause mortality outcomes. Antipsychotic medications can be prescribed to people who have delirium, which they develop because they are medically unwell. The disease causing the delirium might therefore lead to both an increased likelihood of antipsychotic drug use and increased mortality (termed confounding by indication). Additionally, people might receive antipsychotics palliatively to ease distress (reverse causation). In our view, the small increase in antipsychotic drug prescribing around the onset of the pandemic is unlikely to be responsible for the large increases in stroke and all-cause mortality throughout 2020. We suspect that most of the observed increase in mortality was caused by COVID-19, although this suspicion cannot be refuted or confirmed by this study design. Furthermore, some evidence suggests that older patients prescribed an antipsychotic drug for any indication are at an increased risk of death from COVID-19.[30]

This study benefited from the application of a validated code list to multiple complementary data sources to identify people with dementia.[20] We used individual-level, linked, near-nationwide, routinely collected health data to construct a population-based cohort. The use of time-series analyses allowed us to account for seasonal variations in antipsychotic drug prescribing and mortality, providing a more nuanced interpretation of changes over the 5-year period.

Our study has several limitations. We used mortality data to study fatal stroke and myocardial infarction as outcomes to avoid issues with establishing whether repeated codes reflect recurrent events or duplicate coding of previous events, an approach that can substantially underestimate true rates of stroke and myocardial infarction. Routinely collected health data will not identify disease outcomes with perfect accuracy, and death certificate data often have a lower positive predictive value and sensitivity than other datasets.[19] Given the poor availability of COVID-19 tests in the UK early in the pandemic, the COVID-19 mortality results derived from death registration data are probably underestimates.[28]

Despite these limitations, our study provides evidence of a large increase in stroke and all-cause mortality in people with dementia during the COVID-19 pandemic, although exact causes for this increase cannot be pinpointed from these data, with COVID-19 becoming the most common non-dementia cause of death in this population. A small absolute increase in antipsychotic drug prescribing in people with dementia was noted during the pandemic, but this rise had begun beforehand, suggesting that the pandemic was not the sole cause of this small increase and was unlikely to be a major factor in the large concurrent increase in mortality. Deprescribing antipsychotic medications when possible remains an essential aspect of dementia care, given that these drugs might be associated with increased mortality.

Contributors

CS and AM were responsible for data curation, formal analysis, and creation of figures. CS, AM, and TW accessed and verified the underlying data. All authors were responsible for the methods, participated in the revision of the manuscript, and had access to all the included data. AA and CS were responsible for data curation. AA, CLMS, and TW were responsible for project administration. CLMS and TW were responsible for funding acquisition and supervision. TW was responsible for conceptualisation, writing the original manuscript, and submission for publication. All authors confirm they take full responsibility for the decision to submit for publication.

Declaration of interests

CLMS reports a £10 million research grant from 2020 to 2024 to enable set-up of the British Heart Foundation Data Science Centre within Health Data Research UK, the UK's institute for health data science, which as part of its activities has worked with Secure Anonymised Information Linkage Wales (including a small investment of about £130 000 to enable access to the data relevant to this study); and is the Director of the British Heart Foundation Data Science Centre. CS was a co-investigator on a grant paid by the Benter Foundation to the

University of Edinburgh, Edinburgh, UK, for dementia research. All other authors declare no competing interests.

Data sharing

The North East–Newcastle and North Tyneside 2 research ethics committee provided ethical approval for the CVD-COVID-UK/COVID-IMPACT research programme (REC no 20/NE/0161) to access, within secure trusted research environments, unconsented, whole-population, deidentified data from electronic health records collected as part of patients' routine health care. The CVD-COVID-UK/COVID-IMPACT Approvals & Oversight Board granted approval to this project to access the data within the Secure Anonymised Information Linkage (SAIL) Databank. The deidentified data used in this study were made available to accredited researchers only. Those wishing to gain access to the data should contact bhfdsc@hdruk.ac.uk in the first instance. The data used in this study are available in the SAIL Databank at Swansea University, Swansea, UK but, as restrictions apply, they are not publicly available. 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 considers each project to ensure proper and appropriate use of SAIL data. When access has been granted, it is gained through a privacy protecting safe-haven 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 at https://www.saildatabank.com/application-process.

Acknowledgments

This work was carried out with the support of the British Heart Foundation Data Science Centre led by Health Data Research UK (grant number SP/19/3/34678). This study made use of deidentified data held in the Secure Anonymised Information Linkage (SAIL) Wales Databank and made available via the British Heart Foundation Data Science Centre's CVD-COVID-UK/COVID-IMPACT consortium. This work used data provided by patients and collected by the National Health Service (NHS) as part of their care and support. We would also like to acknowledge all data providers who make health-relevant data available for research. We wish to acknowledge the collaborative partnership that enabled acquisition and access to the deidentified 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 and includes the following groups and organisations: the SAIL Databank, Administrative Data Research Wales, Digital Health and Care Wales, Public Health Wales, NHS Shared Services Partnership, and the Welsh Ambulance Service Trust. All research conducted has been completed under the permission and approval of the SAIL independent Information Governance Review Panel (project number 0911). The British Heart Foundation Data Science Centre (grant number SP/19/3/34678, awarded to Health Data Research UK) funded co-development (with NHS Digital) of the trusted research environment, provision of linked datasets, data access, user software licences, computational usage, and data management and wrangling support, with additional contributions from the Health Data Research UK Data and Connectivity component of the UK Government Chief Scientific Adviser's National Core Studies programme to coordinate national COVID-19 priority research. Consortium partner organisations funded the time of contributing data analysts, biostatisticians, epidemiologists, and clinicians. This work was supported by the Con-COV team funded by the Medical Research Council (grant number MR/V028367/1), and by Health Data Research UK (grant number, 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, and the Wellcome Trust. This work was supported by the Administrative Data Research Wales programme of work. The Administrative Data Research Wales programme of work is aligned to the priority themes as identified in the Welsh Government's national strategy: Prosperity for All. Administrative Data Research Wales brings together data science experts at Swansea University Medical School, staff from the Wales Institute of Social and Economic Research, Data and Methods 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. Administrative Data Research Wales is part of the Economic and Social Research Council (part of UK Research and Innovation) funded Administrative Data Research UK (grant number ES/S007393/1). This work was supported by the Wales COVID-19 Evidence Centre, funded by Health and Care Research Wales. KK is supported by the National Institute for Health Research's Applied Research Collaboration East Midlands and Leicester Biomedical Research Centre. TW was funded by a grant from the Scottish Neurological Research Fund, supported by the RS Macdonald charitable trust, and the Chief Scientist Office.

For more on **CVD-COVID-UK/COVID-IMPACT** see https://www.hdruk.ac.uk/projects/cvd-covid-uk-project/

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