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ORIGINAL REPORT

# The association between benzodiazepines and influenza-like illness-related pneumonia and mortality: a survival analysis using UK Primary Care data

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## ABSTRACT

**Purpose**  Bacterial superinfections, including pneumonia, are frequent complications of influenza-like illness (ILI). Clinical and laboratory evidence suggests that benzodiazepines and Z-drugs may influence susceptibility to infections and mortality. We investigated whether benzodiazepines and zopiclone modify the occurrence of ILI-related pneumonia and mortality.
**Methods**  We obtained data on 804 051 ILI patients from a comprehensive primary care database, the Clinical Practice Research Datalink. The follow-up period started from the diagnosis of ILI for 30 days. Pneumonia and deaths occurring within the 30-day follow-up period were considered as potentially 'ILI related'. Exposure to benzodiazepines and zopiclone was determined in the period preceding a diagnosis of ILI with current use defined as a prescription for benzodiazepines in the month prior to ILI diagnosis. Cox regression was used for the analyses. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) are presented.
**Results**  Influenza-like illness-related pneumonia and mortality were noted in 1117 and 707 ILI patients, respectively. Current exposure to benzodiazepines was associated with increased occurrence of both ILI-related pneumonia and mortality (ILI-related pneumonia adjusted HR 4.24, 95%CI [2.27, 7.95]; ILI-related mortality adjusted HR 20.69, 95%CI [15.54, 27.54]). A similar increase in ILI-related mortality but not pneumonia was observed with current zopiclone use (ILI-related mortality adjusted HR 10.86, 95%CI [6.93, 17.02]; ILI-related pneumonia adjusted HR 1.97, 95%CI [0.63, 6.12]).
**Conclusion**  Benzodiazepines may increase the likelihood of pneumonia and mortality related to ILI. A cautionary approach to prescribing benzodiazepine is suggested in people known to be at increased risk of pneumonia or mortality. Copyright © 2016 John Wiley & Sons, Ltd.

KEY WORDS—benzodiazepines; zopiclone; influenza-like illness; pneumonia; mortality; pharmacoepidemiology

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## INTRODUCTION

Influenza-like illness (ILI) is a common diagnosis in primary care and exerts considerable morbidity and mortality worldwide. In the UK, in a typical winter, primary care consultations for influenza and ILI rise from a baseline of less than 30 to 200 per 100 000 population per week.[1] Approximately three to five million cases of severe influenza illness and about 250 000 to 500 000 deaths are estimated from annual epidemics of influenza worldwide.[2]

Influenza-like illness is frequently complicated with bacterial superinfection, predominantly *Streptococcus pneumoniae*, attributed to a number of factors including increased bacterial cell adherence to epithelial lining and tissue invasion because of damage to respiratory epithelium and impaired ciliary clearance, decreased polymorphonuclear and alveolar macrophage chemotaxis and suppression of other host immune responses caused by influenza virus infection.[3,4] A potentially important strategy to reduce this is to identify modifiable risk factors, including commonly prescribed drugs that influence ILI outcomes.

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The benzodiazepines, a class of psychoactive drugs generally used in the treatment of anxiety and sleep disorders, have recently been suggested as having detrimental effects on immune response to infection, predisposing users to increased risk of infection and mortality.[5] In animal studies, benzodiazepines increased mortality from *Klebsiella pneumoniae*,[6] *Streptococcal pneumoniae*,[5] *Mycobacterium bovis*[7] and *Salmonella typhimurium*.[8] In addition, mice treated with diazepam at anxiolytic (non-sedative) doses during influenza alone had an increased burden of spontaneous bacterial superinfections in their lungs and increased mortality from bacterial superinfection of influenza.[5] Treatment of C57BL/6 mice with diazepam was shown to increase the hazard ratio (HR) of death from combined influenza and streptococcal pneumonia infection (HRs 5.86; 95% confidence interval (CI) [1.37, 25.10]; $p = 0.02$).[5] Mechanistic studies have shown that diazepam acts via bicarbonate-permeable gamma-amino butyric type A ($GABA_A$) receptors located on immune cells.[5,9] Activation of $GABA_A$ receptors leads to cytoplasmic acidification in macrophages, resulting in impaired cytokine production, phagocytosis and bacteria killing.[5] This delays the innate immune response leading to subsequent cytokine storm from increased bacterial replication, culminating in increased infection risk and mortality. Furthermore, the GABAergic system is regulated by bacterial toll-like receptor signalling indicating an endogenous role in immunity, which is opposed by administration of exogenous $GABA_A$ modulators such as benzodiazepines and Z-drugs.[10] Importantly, human and mouse immune cells, including alveolar macrophage, express $GABA_A$ receptors,[5,9] leading to translational evidence that humans may be at risk. In sum, accumulating data from laboratory studies suggest that benzodiazepines impair the host response to bacterial infection[5,11] and hence may increase susceptibility to secondary consequences of influenza including pneumonia and mortality.

Clinical correlates of these preclinical studies have been reported. In critical care patients, sedation with the benzodiazepine midazolam was associated with a doubling of secondary infection compared with the non-GABAergic dexmedetomidine (19.7 vs 10.2%; $p = 0.02$).[12] Furthermore, sedation with lorazepam, compared with dexmedetomidine, has been associated with increased mortality in septic patients.[13]

In the community, meta-analysis of evidence from randomised controlled trials of commonly prescribed Z-drugs (zopiclone, zolpidem, ramelteon and zaleplon) found increased risk of infection with Z-drugs compared with placebo (risk ratio 1.44; 95%CI [1.25, 1.64]).[14] In a recent general population study, benzodiazepine use was associated with increased pneumonia risk (odds ratio (OR) 1.54; 95%CI [1.42, 1.67]).[15] On the other hand, a study in elderly patients did not find a statistically significant association between benzodiazepines and pneumonia (OR 1.08; 95%CI [0.84, 1.47]), although wide CIs were reported, which may partly be due to low numbers of patients exposed to benzodiazepines in this study.[16] In regard to mortality risk, evidence from large general population studies reports increased mortality with hypnotic use.[15,17,18]

Based on the apparent increased susceptibility to spontaneous bacterial infection[5,15,19] and mortality related to benzodiazepines in the setting of infection,[5,6,8] we aimed to investigate these effects in patients with ILI. We hypothesised that benzodiazepine use would increase the risk of developing ILI-related pneumonia and ILI-related death. The same hypothesis was tested among users of zopiclone, a hypnotic drug that also acts on $GABA_A$ receptors.

## METHODS

This study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency for database research (reference number: 11_098R).

### Data source

This study used data from the Clinical Practice Research Datalink (CPRD), which contains anonymised medical records of over 13 million patients prospectively collected from over 600 general practices across the UK. Given that general practitioners are the gatekeepers of primary care and specialist referrals in the UK, CPRD is a rich source of health data for research, including data on demographics, test, diagnoses, therapies and health-related behaviours. The range of data available for research is greatly enhanced by linkage of CPRD with datasets from disease-specific cohorts, secondary care and mortality records. This study utilised CPRD linkages to the Office of National Statistics (ONS) mortality database.

### Study design and population

A retrospective cohort study was undertaken to assess the association between benzodiazepines and ILI-related pneumonia and ILI-related mortality. This study included 804 337 patients of all ages with a recorded diagnosis of ILI within the study period (2005–2011 (Appendix S1)). These were identified

using a defined set of medical Read codes (disease diagnostic codes). To be included in the study, patients were required to be registered with the general practice for at least 2 years. Patient outcomes were ascertained over a 30-day follow-up period starting at the point of ILI diagnosis. Patients who developed the outcome at the start of follow-up (i.e. day of ILI diagnosis or consultation) were also included in the analysis to overcome potential biases due to exclusion of delayed ILI diagnoses or more severe cases.

## Outcome definition

There were two outcomes of interest: (1) ILI-related pneumonia and (2) ILI-related mortality. ILI-related pneumonia was defined as clinically diagnosed pneumonia occurring within 30 days after the diagnosis of ILI. Data on pneumonia were identified using relevant disease diagnostic codes, and the first ever eligible record of pneumonia in the study period was retained in the analyses.

Deaths occurring within the 30-day follow-up period, regardless of cause, were considered as potentially 'ILI related'. For patients with death records in both CPRD and ONS mortality data, the date of death was preferentially determined from ONS data if in conflict. Death data for the remaining subjects were obtained solely from CPRD records (as ONS mortality data are available only for subjects registered with English practices that consent to CPRD–ONS data linkage). The 30-day window used to define ILI-related death is in keeping with the convention used in previous mortality studies, which treated deaths within 30 days of an event to be event-related deaths.[20]

## Exposure definition

Data on all recorded prescriptions of benzodiazepines/zopiclone for study patients were extracted from the patient records. Benzodiazepines were considered both as a class and as individual drugs, represented by the three most frequently prescribed benzodiazepines in the study population, namely, diazepam, temazepam and lorazepam. Exposure was considered current when the most recent prescription was within 30 days prior to the ILI diagnosis date. The presence of a repeat prescription was used as a proxy indicator of long-term drug use, whereas the absence of it was considered short-term use. Prescriptions in the period of 31–90 days and >90 days before ILI diagnosis date were classified as recent and past exposures, respectively. No evidence of prescribing

at any point in the patient's past primary care records defined 'non-users'.

## Study covariates

A wide range of potential confounders was considered including depression, anxiety, stress, psychosis, insomnia and other sleep disorders (as conditions in which benzodiazepines/zopiclone may be indicated and that have been identified as important confounders in previous related studies)[15,17] and co-morbidity burden measured by Charlson's co-morbidity index score, which is a weighted co-morbidity score that is an indicator of the patient's disease burden.[21] The following co-morbidities are included in the derivation of Charlson's co-morbidity index: congestive heart failure, myocardial infarction, peripheral vascular disease, dementia, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, renal disease, diabetes, hemiplegia, cancers and AIDS. Table S3 includes the weights associated with each co-morbidity. Furthermore, current prescriptions of opioids, corticosteroids, statins, antibiotics, antivirals and influenza vaccination in the year preceding the diagnosis of ILI were considered. The absence of a record for the aforementioned covariate in the patient's primary care record defined the non-exposure state to the respective covariate. Additional covariates included were current smoking, alcohol consumption, body mass index, gender, age at ILI diagnosis and Index of Multiple Deprivation (IMD). IMD data relate to patient residence postcode and are only available for a subset of English practices consenting to CPRD data linkage system. Therefore, not all patients included in the analysis had IMD data, and a dummy variable category for missing IMD data was created for the analyses.

## Statistical analyses

The Cox proportional hazards regression analysis was used in both the analyses for ILI-related pneumonia and ILI-related mortality after checking that the proportional hazards assumption was met. Validity of the proportional hazards assumption was tested using log–log plots and the global test for proportional hazards. Missing data on current smoking, alcohol consumption, body mass index and IMD were included in the analysis as dummy variable categories. Two multivariable models (Models 1 and 2) were constructed for each exposure variable. Model 2 included all *a priori* confounders, while Model 1 included all variables that were either

Table 1. Characteristics of exposed (benzodiazepine users) and unexposed (benzodiazepine non-users) patients ($n = 804\,051$)

| Characteristics | Benzodiazepine exposure | | p-value* |
| --- | --- | --- | --- |
| | No ($n = 743\,769$) (%) | Yes ($n = 60\,282$) (%) | |
| Age (years) | | | |
| <18 | 343 128 (46.13) | 675 (1.12) | |
| 18–44 | 218 717 (29.41) | 21 794 (36.15) | |
| 45–65 | 113 376 (15.24) | 23 498 (38.98) | |
| >65 | 68 548 (9.22) | 14 315 (23.75) | $p$ trend < 0.001 |
| Gender | | | |
| Male | 326 670 (43.92) | 18 455 (30.61) | |
| Female | 417 099 (56.08) | 41 827 (69.39) | <0.001 |
| Index of Multiple Deprivation score in quintiles | | | |
| 1 (least deprived) | 100 914 (13.57) | 8184 (13.58) | |
| 2 | 96 764 (13.01) | 8257 (13.70) | |
| 3 | 77 532 (10.42) | 6663 (11.05) | |
| 4 | 89 771 (12.07) | 6960 (11.55) | |
| 5 (most deprived) | 81 874 (11.01) | 5962 (9.89) | $p$ trend < 0.001 |
| Missing | 296 914 (39.92) | 24 256 (40.24) | |
| Current smoking | | | |
| No | 240 337 (32.31) | 33 048 (54.82) | |
| Yes | 67 022 (9.01) | 12 593 (20.89) | <0.001 |
| Missing | 436 410 (58.68) | 14 641 (24.29) | |
| Alcohol consumption | | | |
| ≤Alcohol weekly limit | 150 076 (20.18) | 24 043 (39.88) | |
| >Alcohol weekly limit | 14 875 (2.00) | 2665 (4.42) | <0.001 |
| Missing | 578 818 (77.82) | 33 574(55.69) | |
| Sleep disorders | | | |
| No | 715 381 (96.18) | 52 399 (86.92) | |
| Yes | 28 388 (3.82) | 7883 (13.08) | <0.001 |
| Anxiety | | | |
| No | 737 374 (99.14) | 58 282 (96.68) | |
| Yes | 6395 (0.86) | 2000 (3.32) | <0.001 |
| Stress | | | |
| No | 741 232 (99.66) | 59 622 (98.91) | |
| Yes | 2537 (0.34) | 660 (1.09) | <0.001 |
| Depression | | | |
| No | 738 895 (99.34) | 59 209 (98.22) | |
| Yes | 4874 (0.66) | 1073 (1.78) | <0.001 |
| Psychosis | | | |
| No | 743 683 (99.99) | 60 269 (99.98) | |
| Yes | 86 (0.01) | 13 (0.02) | 0.033 |
| Charlson's co-morbidity index score | | | |
| 0 | 593 787 (79.83) | 35 530 (58.94) | |
| 1–2 | 131 932 (17.74) | 19 960 (33.11) | |
| 3–5 | 15 097 (2.03) | 3891 (6.45) | |
| >5 | 2953 (0.40) | 901 (1.49) | $p$ trend < 0.001 |
| Body mass index | | | |
| Normal weight | 108 723 (14.62) | 16 419 (27.24) | |
| Underweight | 7436 (1.00) | 946 (1.57) | |
| Overweight | 79 443 (10.68) | 13 870 (23.01) | |
| Obesity | 56 079 (7.54) | 10 995 (18.24) | $p$ trend < 0.001 |
| Missing | 492 088 (66.16) | 18 052 (29.95) | |
| Corticosteroids | | | |
| No | 736 027 (98.96) | 59 499 (98.70) | |
| Yes | 7742 (1.04) | 783 (1.30) | <0.001 |
| Opioids | | | |
| No | 739 100 (99.37) | 59 657 (98.96) | |
| Yes | 4669 (0.63) | 625 (1.04) | <0.001 |
| Statins | | | |
| No | 742 569 (99.84) | 60 009 (99.55) | |
| Yes | 1200 (0.16) | 273 (0.45) | <0.001 |
| Antivirals | | | |
| No | 738 977 (99.36) | 59 975 (99.49) | |
| Yes | 4792 (0.64) | 307 (0.51) | <0.001 |
| Antibiotics | | | |

*(Continues)*

Table 1.   (Continued)

| Characteristics | Benzodiazepine exposure | | p-value* |
|---|---|---|---|
| | No (n = 743 769) (%) | Yes (n = 60 282) (%) | |
| No | 743 282 (99.93) | 60 234 (99.92) | |
| Yes | 487 (0.07) | 48 (0.08) | 0.195 |
| Influenza vaccination | | | |
| No | 739 386 (99.41) | 59 475 (98.66) | |
| Yes | 4383 (0.59) | 807 (1.34) | <0.001 |

In bold are statistically significant differences (i.e. $p < 0.05$) between benzodiazepine users and non-users with regard to covariates.
*p-values from chi-squared test.

a  significantly associated with both ILI-related pneumonia or ILI-related mortality and benzodiazepines ($p < 0.05$) or
b  variables that modified the unadjusted effect of benzodiazepine on the outcomes of interest by at least 10%.

Given that benzodiazepines and other GABAergic drugs are commonly used as hypnotics and anxiolytics in adults,[22,23] we conducted a sensitivity analysis among study subjects aged 18 years and older. We further stratified the analyses of the effects of benzodiazepines on ILI-related pneumonia and death according to the following age groups: <25, 25–44, 45–64 and ≥65 years.

A subgroup analysis was undertaken for the outcome ILI-related death, to account for severity of ILI, defined as a diagnosis of pneumonia within 30 days following an ILI diagnosis. The sensitivity analysis for diagnosed influenza was not possible as only 5% of ILI cases were influenza (as identified by influenza Read codes).

All data handling and analysis were performed in STATA v12 SE (StataCorp, College Station, Texas, USA). Results are presented as unadjusted and adjusted HRs, with accompanying 95%CIs.

## RESULTS

### Patient characteristics

Of the 804 337 ILI patients identified in the study period, 804 051 were included in the analyses after exclusion of those with anomalous data (Appendix S1). The median age at ILI diagnosis was 25 years (interquartile range: 4–48 years). During the 30 days of follow-up, 1117 (0.14%) patients developed pneumonia, while 707 (0.09%) died with an overall incidence rate of 4.67 per 100 000 person-days and 2.96 per 100 000 person-days for ILI-related pneumonia and death, respectively.
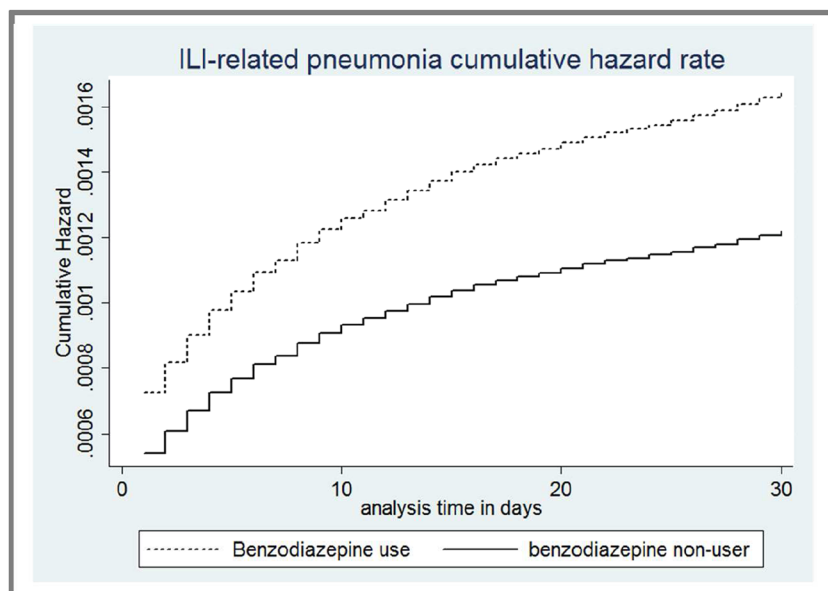


Figure 1.   Influenza-like illness (ILI)-related pneumonia adjusted cumulative hazard rate during 30 days of follow-up period

Table 2.   Association between benzodiazepine/zopiclone use and ILI-related pneumonia in all ages (n = 804 051)

| Drug | ILI-related pneumonia Yes (n = 1117) | Unadjusted model HR [95%CI] | Adjusted model HR [95%CI] | |
|---|---|---|---|---|
| | | | Model 1 | Model 2 |
| Benzodiazepines | | | | |
| Non-use | 981 (0.13) | 1.00 | 1.00 | 1.00 |
| Use | 136 (0.23) | 1.72 [1.43, 2.05] | 1.33 [1.10, 1.60] | 1.35 [1.12, 1.63] |
| Benzodiazepines* | | | | |
| Current | 10 (0.70) | 5.43 [2.91, 10.12] | 4.17 [2.23, 7.79] | 4.24 [2.27, 7.95] |
| Recent | 6 (0.30) | 2.28 [1.02, 5.09] | 1.79 [0.80, 4.00] | 1.84 [0.82, 4.11] |
| Past | 120 (0.21) | 1.60 [1.33, 1.94] | 1.24 [1.02, 1.51] | 1.26 [1.03, 1.54] |
| Benzodiazepines duration | | | | |
| Short-term use | 124 (0.21) | 1.61 [1.34, 1.94] | 1.26 [1.04, 1.53] | 1.28 [1.05, 1.56] |
| Long-term use | 12 (0.68) | 5.21 [2.95, 9.21] | 3.10 [1.74, 5.51] | 3.14 [1.76, 5.60] |
| Diazepam | | | | |
| Non-use | 1016 (0.13) | 1.00 | 1.00 | 1.00 |
| Use | 101 (0.21) | 1.61 [1.31, 1.97] | 1.25 [1.01, 1.54] | 1.27 [1.03, 1.57] |
| Diazepam timing* | | | | |
| Current | 4 (0.42) | 3.17 [1.19, 8.47] | 2.46 [0.92, 6.57] | 2.52 [0.94, 6.76] |
| Recent | 6 (0.39) | 2.95 [1.32, 6.59] | 2.36 [1.05, 5.27] | 2.43 [1.09, 5.44] |
| Past | 91 (0.20) | 1.53 [1.23, 1.89] | 1.19 [1.05, 5.27] | 1.21 [0.97, 1.51] |
| Temazepam | | | | |
| Non-use | 1065 (0.14) | 1.00 | 1.00 | 1.00 |
| Use | 52 (0.21) | 1.56 [1.18, 2.06] | 1.09 [0.82, 1.46] | 1.11 [0.83, 1.49] |
| Temazepam timing* | | | | |
| Current | 5 (0.97) | 7.26 [3.02, 17.48] | 5.15 [2.13, 12.45] | 5.19 [2.15, 12.57] |
| Recent | 1 (0.16) | 1.15 [0.16, 8.14] | 0.83 [0.12, 5.89] | 0.85 [0.12, 6.05] |
| Past | 46 (4.20) | 1.45 [1.08, 1.94] | 1.01 [0.75, 1.338] | 1.03 [0.76, 1.40] |
| Lorazepam | | | | |
| Non-use | 1105 (0.14) | 1.00 | 1.00 | 1.00 |
| Use | 12 (0.40) | 2.95 [1.67, 5.20] | 2.02 [1.14, 3.59] | 2.08 [1.17, 3.70] |
| Lorazepam timing[†]* | | | | |
| Current | 2 (2.47) | — | | — |
| Recent | 0 (0.00) | — | | — |
| Past | 10 (0.36) | — | | — |
| Zopiclone | | | | |
| Non-use | 1063 (0.14) | 1.00 | 1.00 | 1.00 |
| Use | 54 (0.21) | 1.55 [1.18, 2.04] | 1.16 [0.87, 1.54] | 1.18 [0.89, 1.56] |
| Zopiclone timing* | | | | |
| Current | 3 (0.34) | 2.56 [0.82, 7.94] | 1.95 [0.63, 6.07] | 1.97 [0.63, 6.12] |
| Recent | 2 (0.20) | 1.49 [0.37, 5.98] | 1.13 [0.28, 4.52] | 1.16 [0.29, 4.65] |
| Past | 49 (0.21) | 1.52 [1.14, 2.02] | 1.13 [0.84, 1.52] | 1.15 [0.85, 1.55] |

ILI, influenza-like illness; CI, confidence interval; HR, hazard ratio.
Model 1 adjusted for age, sex, Charlson's co-morbidity index score, insomnia and other sleeping disorders, alcohol consumption, current smoking, body mass index and Index of Multiple Deprivation; Model 2: Model 1 covariates, sex, anxiety, stress, depression, psychosis, opioids, steroids, statins, antibiotics, antivirals and flu vaccination. Statistically significant results are highlighted in bold. Drug non-users are the comparison group.
*The reference group is the non-user category of the respective drug.
[†]The effect of drug timing was not calculated due to insufficient numbers of respective drug use within the categories.

Benzodiazepine and zopiclone use was noted in 60 282 (7.5%) and 25 578 (3.18%) study patients, respectively. Study patients prescribed benzodiazepines were more likely to be adults, female, users of other drugs and have co-morbid diseases as compared with non-users of benzodiazepines (Table 1).

In the ILI-related pneumonia analyses, covariates that met the inclusion criteria for Model 1 (as defined in the previous section) were age, deprivation, current smoking, alcohol use, sleep disorders, Charlson's co-morbidity index score and body mass index. Model 1 in the ILI-related mortality analyses included age, Charlson's co-morbidity index score, anxiety, sleeping disorders, opioids, alcohol consumption, current smoking, body mass index, statins, antivirals and influenza vaccination (Tables 1, S1 and S2).

*The association between benzodiazepines/zopiclone and influenza-like illness-related pneumonia*

The adjusted cumulative hazard rate curves indicate increased pneumonia risk with benzodiazepine use (Figure 1). Table 2 presents HRs for the association between study drugs and occurrence of pneumonia within 30 days following ILI diagnosis. Benzodiazepine use at any time before ILI diagnosis was

associated with a 35% increase in the risk of developing ILI-related pneumonia compared with not using benzodiazepines (adjusted HR 1.35; 95%CI [1.12, 1.63]). A heightened increase in the occurrence of ILI-related pneumonia was observed with current benzodiazepine use (adjusted HR 4.24; 95%CI [2.27, 7.95]). ILI-related pneumonia was observed among both short-term and long-term users of benzodiazepines (short-term use: adjusted HR 1.28, 95%CI [1.05, 1.56]; long-term use: adjusted HR 3.14, 95% CI [1.76, 5.60]). Similar statistically significant increases in ILI-related pneumonia were found within the assessed individual benzodiazepines (diazepam, temazepam and lorazepam). The observed increase in the occurrence of ILI-related pneumonia with zopiclone use lacked statistical significance (adjusted HR 1.18; 95%CI [0.89, 1.56]).

### The association between benzodiazepines/zopiclone and influenza-like illness-related mortality

Similar to observations for ILI-related pneumonia, the adjusted cumulative hazard rate curves for ILI-related death showed increased death hazard with benzodiazepine use (Figure 2). Benzodiazepine use at any time prior to ILI diagnosis was associated with a 63% increase in ILI-related death (adjusted HR 1.63; 95%CI [1.37, 1.93]). The observed effect was strengthened with an approximately 20-fold increase in mortality with current use of benzodiazepines (adjusted HR

20.69; 95%CI [15.54, 27.54]). The increase in 30-day mortality was also observed among current users of individual benzodiazepines as well as zopiclone (Table 3).

### Sensitivity analyses

Low numbers of patients with ILI-related pneumonia/mortality (outcomes of interest) were observed across the various exposure categories. For instance, only 6 and 12 subjects with recent exposure to benzodiazepines experienced ILI-related pneumonia and ILI-related death, respectively (Tables 2 and 3). Simulation studies suggest that there should be a minimum number of around 10 outcome events per variable included in a regression model for statistically significant associations.[24,25] To fulfil this criteria, current and recent categories of benzodiazepine use were combined, for one of the sensitivity analyses, so that >10 events would be present per category in the regression model. Cox regression analysis results for the recoded benzodiazepine use variable (prescription of benzodiazepines within 90 days prior to the diagnosis of ILI compared with benzodiazepines non-use) show statistically significant increased risk of ILI-related pneumonia and mortality (ILI-related pneumonia results: adjusted HR 2.84, 95%CI [1.73, 4.69]; ILI-related mortality results: adjusted HR 10.78, 95%CI [8.30, 14.01]).
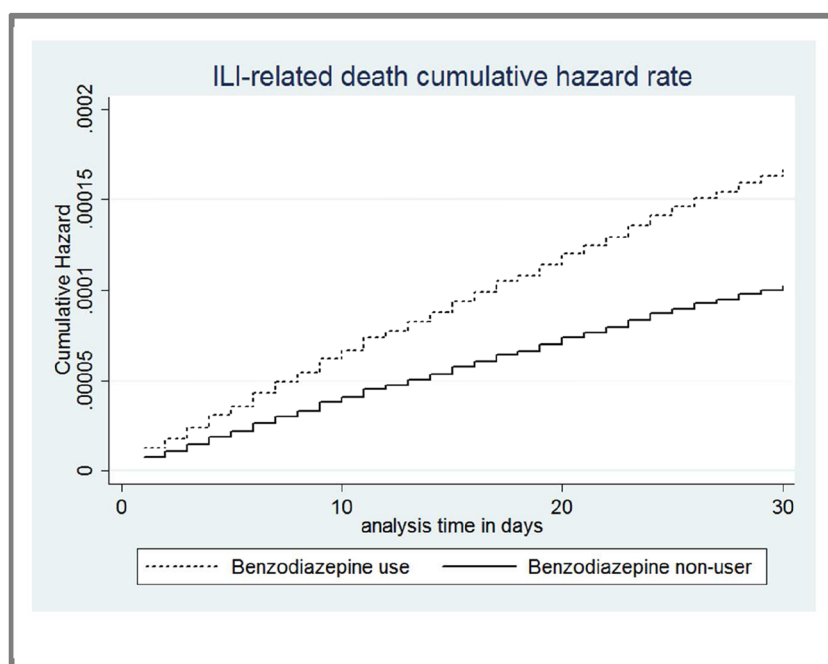


Figure 2. Influenza-like illness (ILI)-related death adjusted cumulative hazard rate during 30 days of follow-up period

The sensitivity analysis for the association between any time benzodiazepine use and ILI-related pneumonia among study subjects aged 18 years and older produced HRs similar to the original estimates (sensitivity analysis results: adjusted HR 1.34, 95%CI [1.11, 1.62], $p = 0.003$; original results: adjusted HR 1.35, 95%CI [1.12, 1.63], $p = 0.002$). Likewise, the results for the sensitivity analysis of ILI-related mortality were similar to the primary calculations (sensitivity analysis results: adjusted HR 1.81, 95%CI [1.52, 2.15], $p < 0.001$; original results: adjusted HR 1.98, 95%CI [1.67, 2.36], $p < 0.001$).

Stratified analyses according to patient age groups showed increased occurrence of ILI-related death with exposure to benzodiazepines in most age groups:

<25 years (HR 31.50; 95%CI [7.41, 133.84]), 25–44 years (HR 2.87; 95%CI [1.30, 6.35]) and ≥65 years (HR 1.62; 95%CI [1.35, 1.95]). In patients aged between 45 and 64 years, the association between benzodiazepine and ILI-death lacked statistical significance (HR 0.97; 95%CI [0.54, 1.72]). On the other hand, the increased occurrence of ILI-related pneumonia with exposure to benzodiazepines was only observed among patients aged less than 65 years (<25 years: HR 2.60, 95%CI [1.31, 5.14]; 25–44 years: HR 1.31, 95%CI [0.93, 1.84]; 45–64 years: HR 1.77, 95%CI [1.26, 2.49]; ≥65 years: HR 0.95, 95%CI [0.68, 1.34]).

A subgroup analysis for the ILI-related death outcome that excluded 1117 patients with severe ILI (patients

Table 3. Association between benzodiazepine/zopiclone use and ILI-related mortality in all ages ($n = 804\,051$)

| Drug | ILI-related death Yes ($n = 707$) | Unadjusted model HR [95%CI] | Adjusted model HR [95%CI] | |
|---|---|---|---|---|
| | | | Model 1 | Model 2 |
| **Benzodiazepines** | | | | |
| Non-use | 521 (0.07) | 1.00 | 1.00 | 1.00 |
| Use | 186 (0.31) | 4.42 [3.74, 5.22] | 1.60 [1.35, 1.89] | 1.63 [1.37, 1.93] |
| **Benzodiazepines** | | | | |
| Current | 55 (3.84) | 57.43 [43.50, 75.83] | 20.63 [15.53, 27.42] | 20.69 [15.54, 27.54] |
| Recent | 12 (0.60) | 8.64 [4.87, 15.31] | 3.41 [1.92, 6.06] | 3.38 [1.90, 6.01] |
| Past | 119 (0.21) | 2.99 [2.45, 3.65] | 1.09 [0.89, 1.33] | 1.11 [0.91, 1.34] |
| **Benzodiazepines duration** | | | | |
| Short-term use | 142 (0.24) | 3.47 [2.89, 4.18] | 1.31 [1.09, 1.58] | 1.34 [1.11, 1.61] |
| Long-term use | 44 (2.48) | 36.34 [26.72, 49.44] | 5.57 [4.07, 7.60] | 5.58 [4.09, 7.63] |
| **Diazepam** | | | | |
| Non-use | 600 (0.08) | 1.00 | 1.00 | 1.00 |
| Use | 107 (0.23) | 2.88 [2.34, 3.54] | 1.12 [0.91, 1.38] | 1.15 [0.93, 1.41] |
| **Diazepam timing** | | | | |
| Current | 23 (2.41) | 31.32 [20.65, 47.51] | x11.85 [7.76, 18.08] | 12.36 [8.09, 18.90] |
| Recent | 5 (0.33) | 4.18 [1.73, 10.09] | 1.91 [0.79, 4.61] | 1.95 [0.80, 4.71] |
| Past | 79 (0.18) | 2.24 [1.77, 2.83] | 0.88 [0.69, 1.11] | 0.90 [0.71, 1.14] |
| **Temazepam** | | | | |
| Non-use | 621 (0.08) | 1.00 | 1.00 | 1.00 |
| Use | 86 (0.35) | 4.42 [3.53, 5.54] | 1.36 [1.08, 1.72] | 1.38 [1.09, 1.75] |
| **Temazepam timing** | | | | |
| Current | 24 (4.64) | 61.12 [40.66, 91.90] | 20.10 [13.27, 30.42] | 19.56 [12.85, 29.78] |
| Recent | 4 (0.62) | 7.86 [2.94–21.01] | 2.41 [0.90–6.48] | 2.30 [0.86–6.20] |
| Past | 58 (0.25) | 3.13 [2.39, 4.09] | 0.97 [0.73, 1.27] | 0.98 [0.75, 1.30] |
| **Lorazepam** | | | | |
| Non-use | 676 (0.08) | 1.00 | 1.00 | 1.00 |
| Use | 31 (1.05) | 12.46 [8.69, 17.85] | 3.30 [2.30, 4.75] | 3.37 [2.34, 4.85] |
| **Lorazepam timing** | | | | |
| Current | 9 (11.11) | 149.05 [77.21, 287.10] | 35.11 [18.12, 68.05] | 34.82 [17.95, 67.55] |
| Recent | 7 (6.03) | 74.61 [35.43, 157.11] | 16.77 [7.93, 35.45] | 15.70 [7.39, 33.35] |
| Past | 15 (0.54) | 6.43 [3.85, 10.72] | 1.72 [1.03, 2.88] | 1.76 [1.05, 2.95] |
| **Zopiclone** | | | | |
| Non-use | 631 (0.08) | 1.00 | | 1.00 |
| Use | 76 (0.30) | 3.68 [2.90, 4.67] | 1.46 [1.14, 1.86] | 1.48 [1.16, 1.89] |
| **Zopiclone timing** | | | | |
| Current | 20 (2.28) | 29.32 [18.77, 45.76] | 10.81 [6.90, 16.93] | 10.86 [6.93, 17.02] |
| Recent | 7 (0.71) | 8.86 [4.21, 18.67] | 3.61 [1.70, 7.63] | 3.61 [1.70, 7.64] |
| Past | 49 (0.21) | 2.56 [1.91, 3.42] | 1.01 [0.75, 1.36] | 1.02 [0.76, 1.38] |

ILI, influenza-like illness; CI, confidence interval; HR, hazard ratio.
Drug non-users are the comparison group. Model 1 adjusted for age, Charlson's co-morbidity index score, anxiety, sleeping disorders, opioids, alcohol consumption, current smoking, body mass index, statins, antivirals and flu vaccination. Model 2 adjusted for all model variables plus sex, stress, depression, psychosis, multiple deprivation, steroids and antibiotics. Statistically significant results are highlighted in bold.

diagnosed with pneumonia within 30 days following ILI) from the main alnalysis model (anytime benzodiazepine use) yielded comparable results with the original ones (subgroup analysis results: adjusted HR 1.68, 95%CI [1.40, 2.01], $p < 0.001$; original results: adjusted HR 1.63, 95%CI [1.37, 1.93], $p < 0.001$).

## DISCUSSION

### Summary of main findings

Results from this study indicate that benzodiazepine use is associated with increased occurrence of both ILI-related pneumonia and mortality. The increased risk is present with long-term as well as short-term use of benzodiazepines. This effect is also present across the individual benzodiazepines assessed, namely, diazepam, temazepam and lorazepam. Zopiclone, the non-benzodiazepine hypnotic with the same mechanism of action as benzodiazepines, was also found to be associated with increased ILI-related mortality but not pneumonia.

### Strengths and limitations

Given almost all ILI cases are managed in the community, using general practice data allowed access to a large sample of ILI patients ($n = 804\,051$) as well as to a wide range of data pertaining to patient prescription and medical history. As these were cohort data, temporal biases relating to timing of exposure were minimised. This study also adjusted for a wide range of potential confounders. Confounding by co-morbidity was controlled for using a robust measure, Charlson's co-morbidity index, designed specifically to predict mortality given a set of co-morbid diseases.[26] This co-morbidity measure has also been validated for use in morbidity studies.[27] In addition, other illnesses identified in literature as confounders of the relationship between benzodiazepines and disease outcomes were controlled for. These include insomnia and sleep disorders, depression, psychosis, anxiety and stress.[15,17] Furthermore, other drugs that could be concurrently prescribed with benzodiazepines (e.g. opioids and corticosteroids) and lifestyle factors (e.g. smoking and alcohol consumption) were controlled for.

A possible limitation of this study may be an overestimation of exposure to study drugs (hence underestimation of drug effect) given prescription data, which do not guarantee drug compliance, were used to determine exposure status. While this could lead to misclassification bias, the effects are likely to be non-differential and at most would bias results towards the null. Nevertheless, the observed associations still remained when chronic benzodiazepine use as indicated by repeat prescriptions was assessed (Tables 2 and 3).

There is also a validity issue of the analysed clinically diagnosed pneumonia given the absence of radiological confirmation. However, chest X rays, although advised in making a diagnosis of pneumonia, according to the British Thoracic Society guidelines, are not necessary for the majority of patients with pneumonia managed in primary care.[28]

As in any other observational study that uses secondary data, some residual confounding is inevitable in our results as a consequence of factors that might have been inadequately assessed.[29] However, considering the minimal impact of the major confounders for which we did control, we think it unlikely that confounding explains the high secondary infection rate and mortality that we found associated with benzodiazepines.

A plausible explanation of our observation may be derived from the recent reports of the immunomodulatory effects of benzodiazepines. Sanders et al. have shown in laboratory studies that activation of $GABA_A$ receptors located on immune cells impairs the host innate immune defence mechanisms in a dose-dependent manner.[5,9] The higher point estimates with current exposure to benzodiazepines and long-term use are consistent with the preclinical data and add weight to the biological plausibility of our findings.[9] Furthermore, the preclinical studies show that the impairments that occur with anxiolytic doses in mice are consistent with community use of the drugs.[15] All clinically available benzodiazepines are non-specific, targeting any Gamma2 subunit-containing $GABA_A$ receptor.[30,31] Intriguingly, Sanders et al. found that anxiolytic doses of benzodiazepines that lacked activity at Alpha1-Gamma2-containing $GABA_A$ receptors did not impair immune responses.[5] Our data suggest that alternatives to non-specific benzodiazepines should be investigated. It is possible that more selective drugs could be developed that would have an improved immune side effect profile.

### Comparison with existing literature

The findings from the current study are in line with results from a similar epidemiological study by Obiora et al.[15] This also observed a statistically significant but weaker association between current benzodiazepine use and increased pneumonia-related mortality

(adjusted HR 1.35). It is interesting to note that the effect of benzodiazepines on ILI-related pneumonia lacked statistical significance in patients aged ≥65 years (HR 0.95; 95%CI [0.68, 1.34]). Such a finding however is not unique to our study as previous pneumonia studies have also failed to establish a statistically significant effect of benzodiazepines on pneumonia risk among the elderly.[32,33] A possible explanation may be the presence of high co-morbidity burden in older adults. In a recent study of the impact of benzodiazepines on asthma outcomes[34] and in the paper of Obiora et al.,[15] an interaction with co-morbidity was observed, with the effect of benzodiazepines being larger in patients with lower co-morbidity burden. The effect of co-morbidity on the benzodiazepine-associated change in risk of pneumonia may be explained by the influence of cumulative disease processes outweighing the effects of the drug. Another explanation is that inflammation from co-morbid diseases influences the expression of the $GABA_A$ receptor, the suggested immune target for benzodiazepines.[5,9] Sanders et al.[5] observed that certain inflammatory cytokines and stimuli reduce $GABA_A$ receptor expression on alveolar macrophage. Thus, a reduction in expression of the receptor target, by co-morbid inflammation, would be expected to result in a reduction of detrimental effects of benzodiazepines on immune response to infection.

The association between benzodiazepine use and increased secondary infection observed in this study is also supported by findings from animal and clinical studies; for instance, treatment with diazepam at anxiolytic doses increased susceptibility to streptococcal pneumonia superinfection in influenza-infected C57BL/6 mice.[5] Similarly, in critically ill patients, increased risk of secondary infection was reported in sedation with benzodiazepine midazolam relative to dexmedetomidine.[19] However, in this latter study, higher doses of benzodiazepines were used for sedation, thus limiting the generalisability of their findings to studies assessing benzodiazepine use in the community.[15,32] Increased infection risk has also been found with the use of non-benzodiazepine GABAergic hypnotics, including zopiclone, in a meta-analysis of data from randomised controlled trials.[14] Although the current study observed an increased occurrence of ILI-related pneumonia with zopiclone use, this association failed to achieve statistical significance. A possible explanation may be the lack of statistical power as low numbers of patients were exposed to zopiclone in this study (Table 2).

Mortality estimates for use of benzodiazepines and zopiclone at any point in time prior to ILI diagnosis observed in this study are comparable with findings from some previous studies.[35–38] However, the present estimates of current benzodiazepine/zopiclone use are higher than those reported in the available literature.[17,18] The higher mortality point estimates also persisted in the sensitivity analysis that combined current and recent benzodiazepine exposure into a single category to boost numbers of exposed patients with the outcome of interest (ILI-related mortality sensitivity analysis results: adjusted HR 10.78, 95%CI [8.30, 14.01]; original results: adjusted HR 20.69, 95%CI [15.54, 27.54]). A plausible explanation for the differences in mortality estimates observed in the present study compared with previous studies could be the different study populations utilised. Unlike previous studies undertaken in the general population,[17,18,35] the present study assessed the effects of benzodiazepines in a cohort of patients with underlying ILI diagnosis, and results from animal models of infection have reported increased susceptibility to underlying infection with benzodiazepine use.[5,6]

## CONCLUSION

This study shows statistically significant associations between benzodiazepine use and increased occurrence of ILI-related pneumonia and mortality. In light of the existing evidence, this study adds weight to previously expressed concerns regarding the safety of benzodiazepines with respect to respiratory infection risk and mortality.

## CONFLICTS OF INTEREST

KEY POINTS

- An increased likelihood of influenza-like illness-related pneumonia and mortality was found with benzodiazepine use.
- A similar increase in the occurrence of influenza-like illness-related deaths was found with zopiclone use.
- These findings suggest a cautionary approach to prescribing benzodiazepine in people known to be at increased risk of pneumonia or mortality.

## ETHICS STATEMENT

This is database research which which was approved by ISAC MHRA as stated in the first paragraph of the method's section.

## ACKNOWLEDGEMENTS

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web site.

Appendix 1: Patient selection flow chart
Table S1: Association between potential confounders and outcomes of interest (ILI-related pneumonia and mortality [$n = 804\,051$]).
Table S2: Association between benzodiazepines and study outcomes adjusted for individual confounders
Table S3: Charlson's co-morbidity index weighting score