Population incidence and associated mortality of urinary tract infection in people living with dementia

Journal of Infection 88 (2024) 106167

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Infectious Disease Practice

Population incidence and associated mortality of urinary tract infection in people living with dementia

Helen Lai [a,b], Magdalena Kolanko [a,b], Lucia M. Li [a,b], Megan E. Parkinson [a,c], Niall J. Bourke [b,d], Neil S.N. Graham [a,b], Michael C.B. David [a,b], Emma-Jane Mallas [a,b], Bowen Su [e], Sarah Daniels [a,b], Danielle Wilson [a,b], Mara Golemme [a,b], Claire Norman [a,g], Kirsten Jensen [a,f], Raphaella Jackson [a,f], Martin Tran [a,f], Paul S. Freemont [a,f], David Wingfield [a,b,g], Tim Wilkinson [h], Edward W. Gregg [e,i], Ioanna Tzoulaki [e,j], David J. Sharp [a,b,1], Eyal Soreq [a,*,1]

[a] UK Dementia Research Institute Care Research and Technology Centre (UK DRI CR&T) at Imperial College London and the University of Surrey, Imperial College London, White City Campus, 86 Wood Lane, London W12 0BZ, UK
[b] Department of Brain Sciences, Faculty of Medicine, Imperial College London, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK
[c] Perioperative and Ageing Group, Imperial College London, South Kensington Campus, London SW7 2AZ, UK
[d] Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King's College London, 16 De Crespigny Park, London SE5 8AB, UK
[e] Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, South Kensington Campus, London SW7 2AZ, UK
[f] Section of Structural and Synthetic Biology, Department of Infectious Disease, Imperial College London, School of Medicine, St Mary's Hospital, Praed Street, London W2 1NY, UK
[g] Brook Green Medical Centre, Hammersmith and Fulham GP Partnership, Bute Gardens, London W6 7EG, UK
[h] Centre for Clinical Brain Sciences, University of Edinburgh, 49 Little France Crescent, Edinburgh EH16 4SB, UK
[i] School of Population Health, Royal College of Surgeons of Ireland, University of Medicine and Health Sciences, 123 St Stephen's Green, Dublin 2, Ireland
[j] Biomedical Research Foundation Academy of Athens, 4 Soranou Ephessiou Street, Athens 115 27, Greece

ARTICLE INFO

Article history:
Accepted 20 April 2024
Available online 26 April 2024

Keywords:
Urinary tract infections
Diabetes mellitus
Dementia
Anti-bacterial agents
Therapeutics
Population health
Incidence
Mortality
Comorbidity

SUMMARY

Objectives: Urinary tract infections (UTIs) frequently cause hospitalisation and death in people living with dementia (PLWD). We examine UTI incidence and associated mortality among PLWD relative to matched controls and people with diabetes and investigate whether delayed or withheld treatment further impacts mortality.
Methods: Data were extracted for n = 2,449,814 people aged ≥ 50 in Wales from 2000–2021, with groups matched by age, sex, and multimorbidity. Poisson regression was used to estimate incidences of UTI and mortality. Cox regression was used to study the effects of treatment timing.
Results: UTIs in dementia (HR=2.18, 95 %CI [1.88–2.53], p < .0) and diabetes (1.21[1.01–1.45], p = .035) were associated with high mortality, with the highest risk in individuals with diabetes and dementia (both) (2.83[2.40–3.34], p < .0) compared to matched individuals with neither dementia nor diabetes. 5.4 % of untreated PLWD died within 60 days of GP diagnosis—increasing to 5.9 % in PLWD with diabetes.
Conclusions: Incidences of UTI and associated mortality are high in PLWD, especially in those with diabetes and dementia. Delayed treatment for UTI is further associated with high mortality.

Introduction

Urinary tract infections (UTIs) frequently cause hospitalisation in older adults. They are particularly common in people living with dementia (PLWD)[1,2] where cognitive impairment, catheterisation and co-morbid health conditions can lead to atypical presentation of symptoms.[3,4] Impairments of insight and difficulties with self-reporting symptoms pose challenges for UTI management.[5–8] These challenges are acknowledged in the current guidelines for diagnosing UTI in older adults, however no gold standard measure exists to mitigate the risk of UTI misdiagnosis in this population.[9,10] In addition, PLWD admitted to hospital often experience extended durations of stay, frequent readmissions,[7,11,12] and are at risk of hospital-acquired complications associated with increased mortality.[13] Despite this, studies quantifying UTI

* Correspondence to: Imperial College London, White City Campus, 9/F, Sir Michael Uren Hub, W12 0BZ London, UK.
E-mail address: e.soreq14@imperial.ac.uk (E. Soreq).
[1] Senior authors: David J. Sharp, Eyal Soreq.

https://doi.org/10.1016/j.jinf.2024.106167

incidence and clinical outcomes in PLWD are limited. Understanding the public health burden of UTIs and the impact of co-morbidities on their clinical outcomes are important, as these can potentially be improved through more timely intervention.

While some UTIs resolve spontaneously, untreated or incompletely treated UTIs may rapidly lead to clinical complications such as severe infection and mortality.[14,15] The management of UTIs is made complex by the global emergence of multi-drug-resistant organisms, prompting scrutiny of antibiotic prescription practices.[15] However, population-level studies on the effects of antibiotic timing on UTI management in the general population have shown surprisingly high mortality rates for untreated infections. For example, data from English primary care records show that delayed or withheld antibiotic treatment is associated with increased mortality.[16,17] Given the vulnerability of PLWD to infection, an improved understanding of the clinical effects of delayed treatment in this specific population is important.

To the best of our knowledge, population-level studies of UTI incidence in PLWD have not yet been performed, and it is unknown whether this group has worse outcomes following delayed treatment than patients without dementia. Previous research on emergency admissions suggests that PLWD are twice as likely to be diagnosed with UTI, but this work also highlighted the potential for misdiagnosis in emergency settings.[18] Other studies investigating UTIs in PLWD have been conducted in care homes,[19] where high rates of drug-resistant organisms among residents potentially linked to inappropriate antimicrobial prescription may bias findings and limit generalisability.[20]

In this study, we aimed to 1) establish the overall incidence of UTIs and associated mortality in PLWD using linked primary and secondary care data, and 2) examine the impact of factors that may influence survival following UTI, including the timing of antibiotic treatment. We used Welsh electronic health records spanning more than twenty years to investigate the incidence rates of UTI in PLWD, diabetes, and co-morbid dementia and diabetes. Incidence was compared to controls with no history of either condition. Diabetes is a well-established risk factor for UTIs due to associated immunocompromise, urinary glucose, and bladder dysfunction.[21–25] In general, diabetes alone does not cause cognitive impairment, and so provides a comparator group that have an increased risk of UTI but without major cognitive problems. The inclusion of people with both dementia and diabetes enables us to additionally observe effects of age-related co-morbidity. Within demographically-matched populations, we further investigate overall survival following UTI and the effects of antibiotic treatment timing on clinical outcome, extending previous analyses.[16,17] We hypothesised that PLWD with and without diabetes are at increased risk of UTI and mortality within 60 days following diagnosis, and that delayed or withheld treatment leads to increased mortality following UTI in PLWD.

Materials and methods

Study design and study population

Data sources

Data from this retrospective cohort study were obtained through the Secure Anonymised Information Linkage (SAIL) Databank,[26] and includes the following sources: Welsh Demographic Service Dataset (WDSD), comprising sex, week of birth, date of death, and the Welsh Index for Multiple Deprivation (WIMD), a composite measure of eight domains of deprivation within geographical areas, including housing, education, and access to services.[27] The Welsh Longitudinal General Practice (WLGP) contains information from primary care including diagnoses and prescriptions,[28] and the Patient Episode Dataset for Wales (PEDW) comprises inpatient diagnoses. Data spanned the study period from 1st January 2000 to 31st December 2021.

Population

We investigated adults aged ≥ 50 within the SAIL data sources (Fig. 1) (Supplementary Fig. 1A). Participants entered the study on 1st January 2000 or on the date they turned 50, whichever was sooner, and exited the study on 31st December 2021, when they turned 101, or when a date of death was recorded. Dementia and diabetes were identified using diagnostic codes (Supplementary Table 1). Validation studies of UK primary care data have been demonstrated to identify dementia and diabetes with high accuracy.[29,30] Individuals were classified into four groups: those with prior diagnoses of dementia and diabetes, dementia only, diabetes only, and controls (no prior diagnoses of either condition).

Identification and extraction of UTI-related clinical information

Clinical data on UTIs and antibiotic treatment within 60 days of recorded UTIs in SAIL were extracted. The codes used were based on published literature,[16,17,31–33] verified using the Read Clinical Terminology Browser[34] and the World Health Organisation ICD-10 browser,[35] and reviewed by experienced clinicians (Supplementary Table 1).

UTIs

We included codes relating to lower and upper UTIs, and recurrent or catheter-associated UTIs, but excluded asymptomatic bacteriuria and suspected or pregnancy-related UTIs (Supplementary Table 1).

Group assignment

Individuals experiencing one or more UTI episodes were categorised into up to three groups during their respective follow-up periods: first, the control group, prior to any morbidity diagnosis; second, one of the morbidity groups (dementia or diabetes) if a relevant diagnostic code for either condition was identified; and

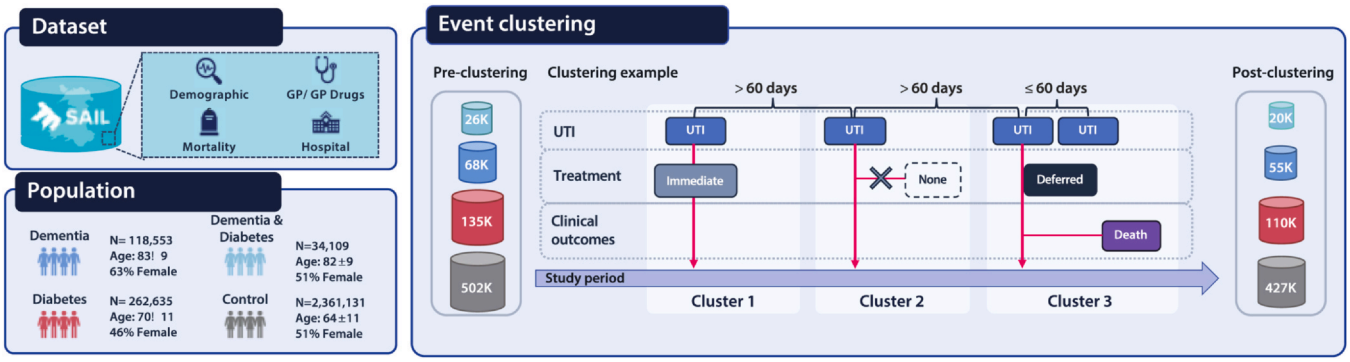

Fig. 1. Experimental Design. From the initial study sample, UTI events were identified and clustered temporally, resulting in 20 K events in people with both dementia and diabetes, 55 K events in people with dementia, 110 K in people with diabetes, and 427 K in controls.

finally, the co-morbid group, if diagnostic codes for both conditions were identified.

UTI episodes within the groups were mutually exclusive while the individuals were not. For instance, where an individual experienced multiple UTIs, one occurring after a diagnosis of dementia but before a diagnosis of diabetes, and another occurring after diagnoses of both, the two UTIs were included in their respective groups (dementia, dementia & diabetes), whereas the individual was counted in both groups.

Treatment type and timing

Analyses of treatment type and timing within this study were restricted to UTIs occurring within primary care as hospital prescription data were not available. Antibiotics were identified according to the NHS Wales Primary Care Antimicrobial Guidelines (section: UTI).[36] Codes were included for tablets, capsules, and suspensions, but injections and infusions were excluded due to the low frequency of these prescriptions in a community setting.

Clinical outcomes

All-cause mortality within 60 days following UTI was examined as the clinical outcome of this study.

Health conditions

Diagnostic codes relating to common health conditions were extracted and used to match the morbidity groups by their respective profiles of multimorbidity. The following conditions were included: mental health (anxiety and depression), cancer, respiratory (chronic obstructive pulmonary disease (COPD) and asthma), cardiovascular (congestive heart failure, hypertension, hypertensive heart disease, and ischaemic heart disease), liver (alcoholic and non-alcoholic), renal (chronic kidney disease), cerebrovascular, smoking, and catheterisation.

Data processing and statistical analysis

Data analytics were performed using Python version 3.9 software[37] with the following packages: data processing (pyodbc, numpy, pandas, scipy), machine learning (scikit-learn), statistics (lifelines, statsmodels, pingouin) and visualisation (matplotlib).

Temporal clustering of UTI codes

To account for repeated diagnostic coding within the same health episode, extracted UTI codes were temporally clustered based on previous literature[16,17] (Fig. 1). Clustering was done individually on a rolling basis, and codes recorded within 60 days were assumed to be part of the same cluster. For instance, if five consecutive UTI codes occurring 40 days apart were recorded for an individual, the entire sequence was considered one cluster. A sixth code occurring after seventy days was considered part of a new cluster. The clinical outcome of mortality in 60 days following the final code was then examined within each cluster.

UTI incidence

Age and sex-specific incidence rates were calculated using a generalised linear model (GLM) with a Poisson distribution, implemented in the statsmodels package. Age bands were mean-centred to facilitate interpretation and improve model stability. The aggregated table summed the total number of UTIs, deaths within 60 days following UTI, and the follow-up period for each age band across all conditions of interest. The formula for the GLM was extended to include interactions between condition, sex, and mean-centred age bands. It was adjusted for an offset term, the natural logarithm of the total follow-up time in years.

Propensity score

Propensity scores[38] were calculated to match individuals in the smallest (minority) group of co-morbid dementia and diabetes to their counterparts in the three larger (majority) groups (controls, diabetes, and dementia). Continuous variables (e.g. age) were standardised to have a mean of zero and a standard deviation of one, while categorical variables (e.g. sex, health conditions) were transformed into dummy variables. The specific matching variables are described further in their respective sections (2.2.5–2.2.7). A logistic regression model was then trained using these features, and the propensity score was computed as the model's logit (log-odds) output.

Optimal pair matching

The linear sum assignment (Hungarian matching) algorithm[39] was employed to minimise the overall "distance" between the propensity scores of individuals in the minority group and those in the majority groups and identify best-matched pairs.

Incidence matching

To assess the variation in UTI incidence across different morbidity groups, optimal pair matching was used to identify the most suitable matches between individuals in the minority group and those in the three majority groups. This matching process was conducted iteratively per individual over the 22-year study period, matching for factors of age, sex, year of UTI occurrence, and health conditions (defined in section 2.1.8). This generated a "year of matching" index (Supplementary Table 2), and the dataset was constructed to include all subsequent years of follow-up for the identified optimal pairings (Supplementary Table 3) (Supplementary Fig. 1B). This resulted in 1:1 matched episodes with dementia, 1:2 matched episodes with diabetes, and 1:4 matched controls. (Supplementary Figs. 2 and 3).

Survival matching – service

Optimal pair matching was again used to compare survival following UTI episodes across morbidity groups. Optimal pairings were identified between UTI episodes in the minority group and their counterparts in the majority groups. In addition to the variables of age, sex, year of UTI occurrence, and health conditions, groups were also matched by service to ensure comparable proportions of GP and hospital events. This yielded 1:3 matched episodes with dementia, 1:5 matched episodes with diabetes, and 1:10 matched controls. (Supplementary Table 4).

Survival matching – treatment

As inpatient prescription data were not available, a final matching was conducted after subsetting the data to UTIs diagnosed and managed within primary care. The groups were then matched by age, sex, year of UTI occurrence, and health conditions (Supplementary Table 5).

Overall survival following UTI

Cox proportional hazard models were implemented to estimate survival probability within sixty days following a UTI among the matched groups (section 2.2.6). Events were right-censored. The exposures examined included morbidity diagnosis (dementia, diabetes, dementia & diabetes, controls) and source of UTI diagnosis (primary or secondary care). Covariates included age and sex. We then conducted three sensitivity analyses to examine the effects of temporal variation, UTI diagnosis, and time since diagnosis as a proxy of dementia severity.

Effects of antibiotic and treatment timing on survival in matched groups

We used two models to examine the respective effects of antibiotic treatment type and treatment timing on 60-day survival after UTI across the matched morbidity groups (section 2.2.7). Using Cox regression, we first analysed the effects of the most frequently prescribed antibiotics within this cohort (trimethoprim, nitrofurantoin, cefalexin, other) relative to no treatment within one week.

For treatment timing, UTIs were grouped into three categories: immediate (IMM), including all UTIs treated on the same day as diagnosis; deferred (1 W), including UTIs treated within one week following the diagnosis date, and no evidence (NE), indicating no evidence of treatment within one week of UTI diagnosis.

A final Cox regression model was then implemented to examine the effect of morbidity and treatment timing on survival across the matched morbidity groups. Age and sex were again included as covariates across the three models to account for the natural distribution of the variables within the matched groups.

Results

Cohort description

The study population comprised 2,449,814 million adults aged 50–101 and registered in Wales between 1st January 2000 and 31st December 2021, totalling 31,777,282 person-years of follow-up over the 22-year study period (Table 1). Four groups were identified: Those with no prior diagnoses of dementia or diabetes (Controls, n = 2,361,131, mean age=63.7 ± 11.2, follow-up=29,113,388 person-years); diabetes (n = 262,635, age=69.9 ± 10.9, 2,176,149 person-years); dementia (n = 118,553, age=82.6 ± 9.3, 390,689 person-years); and co-morbid dementia and diabetes (n = 34,109, age=81.5 ± 8.9, 97,027 person-years) (Fig. 1) (Table 1) (Supplementary Fig. 1A).

Within the study population, 730,670 diagnostic codes for UTI were identified in 331,617 individuals (Table 2). Following temporal clustering, this was reduced to 612,453 UTI episodes. As expected, there were more females (68.5 %) than males with recorded UTIs. They also experienced more UTI events over the follow-up period (2.0 ± 1.8) compared to males (1.6 ± 1.3), accounting for 72.3 % of the total UTI episodes. Both groups had similar average follow-up periods (F: 15.8 ± 6.1 person-years; M: 15.7 ± 5.9) and age distributions (F: 71.3 ± 11.2; M: 71.3 ± 9.9).

Among those with UTIs, the control group was the largest, with 427,174 UTI episodes across 242,793 individuals (71.6 % female, mean ± SD age: 71.5 ± 12.5). The diabetes group followed, with 110,045 episodes across 61,340 individuals (59.0 % female, age: 74.6 ± 10.8). The dementia group was the oldest, comprising 55,043 episodes across 38,068 individuals (68.6 % female, age: 84.0 ± 8.3 years). Finally, the smallest group of dementia & diabetes had 20,191 episodes across 12,894 individuals (60.2 % females, age: 82.1 ± 8.3).

Groups were matched to the smallest group of individuals with co-morbid dementia and diabetes, with 1.6 mean UTI episodes. Matched controls comprised n = 99,926 individuals aged 80.7 ± 9.6, with 1.4 mean UTI episodes. Matched people with diabetes included n = 41,499, aged 79.1 ± 9.0, with 1.6 mean UTI episodes. The matched dementia group had 30,195 individuals, aged 83.7 ± 8.0, with 1.4 mean UTI episodes. (see Supplementary Table 3 and Supplementary Figs. 2 and 3).

Incidence of UTI in dementia and diabetes

Using Poisson regression models, we calculated the incidence rate of UTI episodes across the matched groups (Fig. 2 A). After adjusting for age and gender, the incidence rate in the control group served as the reference at 24 per 1000 person-years ($p < 0.0001$). In individuals with diabetes, the adjusted incidence was 48 per 1000 person-years (IRR = 2.1, 95 % CI [1.9–2.3], $p < 0.001$). For PLWD, the incidence was 68 per 1000 person-years (IRR=3.0, 95 % CI [2.7–3.4], $p < 0.001$), and for PLWD with co-morbid diabetes, it was 130 per 1000 person-years (IRR=5.7, 95 % CI [5.0–6.4], $p < 0.001$). Interestingly, males had a lower overall incidence compared to females (IRR=17 per 1000 person-years, IRR=0.54, 95 % CI [0.46–0.64], $p < 0.001$). However, a significant interaction effect was observed in both the dementia and co-morbid groups, with higher incidence rates in males (IRR=1.69, 95 % CI [1.4–2.04], $p < 0.001$; IRR=1.66, 95 % CI [1.39–1.98], $p < 0.001$) (Supplementary Tables 6 and 7).

Table 1
Demographics for all individuals within the study sample.

	Controls	Diabetes	Dementia	Dementia & Diabetes	Total
Study sample					
n	2,361,131	262,635	118,553	34,109	2,449,814
n Females (%)	1,211,184 (51.3 %)	120,199 (45.8 %)	74,181 (62.6 %)	18,602 (54.5 %)	1,254,318 (51.2 %)
Follow-up (years)	29,113,430	2,176,150	390,689	97,027	31,777,282
Mean follow-up	12.3 ± 7.3	8.3 ± 6.2	3.3 ± 3.7	2.8 ± 3.4	13.0 ± 7.2
Deaths	523,221 (22.2 %)	107,146 (40.8 %)	90,458 (76.3 %)	26,902 (78.9 %)	747,727 (30.5 %)
Age Bands (years)					
50-54	1,443,577 (61.1 %)	60,396 (23.0 %)	3488 (2.9 %)	851 (2.5 %)	1,485,644 (60.6 %)
55-59	1,290,564 (54.7 %)	75,286 (28.7 %)	4341 (3.7 %)	1178 (3.5 %)	1,343,406 (54.8 %)
60-64	1,122,566 (47.5 %)	89,892 (34.2 %)	5796 (4.9 %)	1750 (5.1 %)	1,187,138 (48.5 %)
65-69	971,808 (41.2 %)	101,604 (38.7 %)	8978 (7.6 %)	2907 (8.5 %)	1,048,165 (42.8 %)
70-74	827,054 (35.0 %)	105,652 (40.2 %)	16,274 (13.7 %)	5276 (15.5 %)	911,946 (37.2 %)
75-79	654,410 (27.7 %)	93,752 (35.7 %)	28,322 (23.9 %)	9051 (26.5 %)	738,083 (30.1 %)
80-84	474,133 (20.1 %)	70,925 (27.0 %)	41,541 (35.0 %)	12,110 (35.5 %)	548,931 (22.4 %)
85-89	303,551 (12.9 %)	41,753 (15.9 %)	44,011 (37.1 %)	11,298 (33.1 %)	360,239 (14.7 %)
90-94	157,739 (6.7 %)	17,004 (6.5 %)	28,864 (24.3 %)	6200 (18.2 %)	189,451 (7.7 %)
95-99	66,192 (2.8 %)	4594 (1.7 %)	9922 (8.4 %)	1704 (5.0 %)	77,441 (3.2 %)
Welsh Index of Multiple Deprivation (WIMD)					
1 (Most deprived)	414,280 (17.5 %)	60,553 (23.1 %)	22,000 (18.6 %)	7512 (22.0 %)	436,047 (17.8 %)
2	445,470 (18.9 %)	57,470 (21.9 %)	24,518 (20.7 %)	7434 (21.8 %)	465,186 (19.0 %)
3	492,555 (20.9 %)	51,898 (19.8 %)	22,930 (19.3 %)	6653 (19.5 %)	509,678 (20.8 %)
4	496,495 (21.0 %)	47,166 (18.0 %)	23,681 (20.0 %)	6452 (18.9 %)	511,875 (20.9 %)
5 (Least deprived)	461,277 (19.5 %)	43,239 (16.5 %)	24,578 (20.7 %)	5885 (17.3 %)	475,254 (19.4 %)
Not available	51,054 (2.2 %)	2309 (0.9 %)	846 (0.7 %)	173 (0.5 %)	51,774 (2.1 %)
Health conditions (%)					
UTI	239,452 (10.1 %)	60,880 (23.2 %)	37,799 (31.9 %)	12,835 (37.6 %)	327,699 (13.4 %)
Cancer	472,055 (20.0 %)	65,875 (25.1 %)	12,399 (10.5 %)	3350 (9.8 %)	491,474 (20.1 %)
Cardiovascular	583,776 (24.7 %)	54,649 (20.8 %)	12,796 (10.8 %)	2360 (6.9 %)	602,056 (24.6 %)
Liver	44,159 (1.9 %)	12,390 (4.7 %)	2001 (1.7 %)	834 (2.4 %)	47,510 (1.9 %)
Mental Health	214,617 (9.1 %)	29,288 (11.2 %)	10,683 (9.0 %)	2849 (8.4 %)	224,772 (9.2 %)
Renal	63,115 (2.7 %)	27,782 (10.6 %)	6576 (5.5 %)	3490 (10.2 %)	72,636 (3.0 %)
Smoking	311,313 (13.2 %)	39,395 (15.0 %)	9123 (7.7 %)	2397 (7.0 %)	324,491 (13.2 %)
Catheterisation	54,584 (2.3 %)	13,752 (5.2 %)	5129 (4.3 %)	1973 (5.8 %)	58,523 (2.4 %)

Table 2
Demographics for individuals with UTI in the study sample.

	Controls	Dementia	Diabetes	Dementia & Diabetes	Total
Study sample					
N	242,793	38,068	61,340	12,894	331,617
N Females	173,914 (71.6 %)	26,124 (68.6 %)	36,204 (59.0 %)	7760 (60.2 %)	227,131 (68.5 %)
Age	71.5 ± 12.5	84.0 ± 8.3	74.6 ± 10.8	82.1 ± 8.3	73.4 ± 12.5
UTI					
Codes	501,761	68,286	134,792	25,831	730,670
episodes	427,174	55,043	110,045	20,191	612,453
Mean episode	1.8 ± 1.6	1.4 ± 0.9	1.8 ± 1.5	1.6 ± 1.1	1.8 ± 1.7
Mortality within 60 days	21,825 (5.1 %)	8647 (15.7 %)	8899 (8.1 %)	3203 (15.9 %)	42,574 (7.0 %)
Welsh Index of Multiple Deprivation (WIMD)					
1 (Most deprived)	45,807 (10.7 %)	7171 (13.0 %)	14,438 (13.1 %)	2859 (14.2 %)	65,247 (10.7 %)
2	48,555 (11.4 %)	8062 (14.6 %)	13,687 (12.4 %)	2867 (14.2 %)	68,189 (11.1 %)
3	48,586 (11.4 %)	7092 (12.9 %)	11,937 (10.8 %)	2457 (12.2 %)	65,684 (10.7 %)
4	47,612 (11.1 %)	7499 (13.6 %)	10,997 (10.0 %)	2373 (11.8 %)	64,031 (10.5 %)
5 (Least deprived)	50,334 (11.8 %)	8056 (14.6 %)	9862 (9.0 %)	2298 (11.4 %)	66,003 (10.8 %)
Not available	1899 (0.4 %)	188 (0.3 %)	419 (0.4 %)	40 (0.2 %)	2463 (0.4 %)
Health conditions (%)					
Cancer	180,649 (42.3 %)	25,179 (45.7 %)	52,343 (47.6 %)	9818 (48.6 %)	267,989 (43.8 %)
Cardiovascular	291,717 (68.3 %)	42,527 (77.3 %)	98,564 (89.6 %)	18,413 (91.2 %)	451,221 (73.7 %)
Liver	9020 (2.1 %)	1616 (2.9 %)	5395 (4.9 %)	1076 (5.3 %)	17,107 (2.8 %)
Mental Health	102,276 (23.9 %)	15,442 (28.1 %)	29,804 (27.1 %)	6576 (32.6 %)	154,098 (25.2 %)
Renal	13,681 (3.2 %)	3688 (6.7 %)	12,246 (11.1 %)	3130 (15.5 %)	32,745 (5.3 %)
Smoking	139,507 (32.7 %)	16,561 (30.1 %)	43,193 (39.3 %)	7648 (37.9 %)	206,909 (33.8 %)
Catheterisation	26,567 (6.2 %)	5441 (9.9 %)	11,864 (10.8 %)	2924 (14.5 %)	46,796 (7.6 %)

High mortality rates in dementia following UTI

We then examined the incidence of mortality within 60 days following UTI across the morbidity groups. After adjusting for age and gender, the incidence rate in the control group served as the reference at 2 per 1000 person-years ($p < 0.001$). In individuals with diabetes, the adjusted incidence was 6 per 1000 person-years (IRR=3.32, 95 % CI [1.99–5.53], $p < 0.001$). For PLWD, the incidence was 9 per 1000 person-years (IRR=6.31, 95 % CI [3.82–10.44], $p < 0.001$), and for PLWD with co-morbid diabetes, it was 16 per 1000 person-years (IRR=10.17, 95 % CI [6.23–16.61], $p < 0.001$). (Fig. 2B) (Supplementary Tables 8 and 9).

Next, we used Cox regression to compare the effects of diagnosis within primary versus secondary care and quantify the overall survival rates within 60 days following UTI. Hospital diagnoses were associated with higher odds of death, over four-fold higher than those made in primary care (HR=4.29, 95 % CI [4.09–4.52], $p < 0.005$, Supplementary Table 10) (Fig. 3A). Dementia was associated with lower 60-day survival than controls across primary and secondary care (Dementia: HR=1.34 [1.31–1.38], $p < 0.005$), and the lowest 60-day survival was observed in the co-morbid group (HR=1.43 [1.37–1.48], $p < 0.005$). This was consistent across primary (Fig. 3B) and secondary care (Fig. 3C) diagnoses, where only 96.2 % and 84.5 % of people within the co-morbid group survived for 60 days after a UTI diagnosis, respectively.

Temporal sensitivity analysis

To assess whether hazard ratios were affected by temporal variability, the UTI episodes were divided into two distinct time frames, with the addition of 'period' as a covariate in the Cox regression survival analysis. When comparing 2014–2022 to 2000–2013, the HR was 1.00, suggesting no significant change in mortality risk across the two periods ($p = 0.83$) (Supplementary Table 11).

Diagnosis sensitivity analysis

To examine the stability of comorbidity effects across clinical classifications, common UTI diagnostic codes accounting for 99 % of all UTI

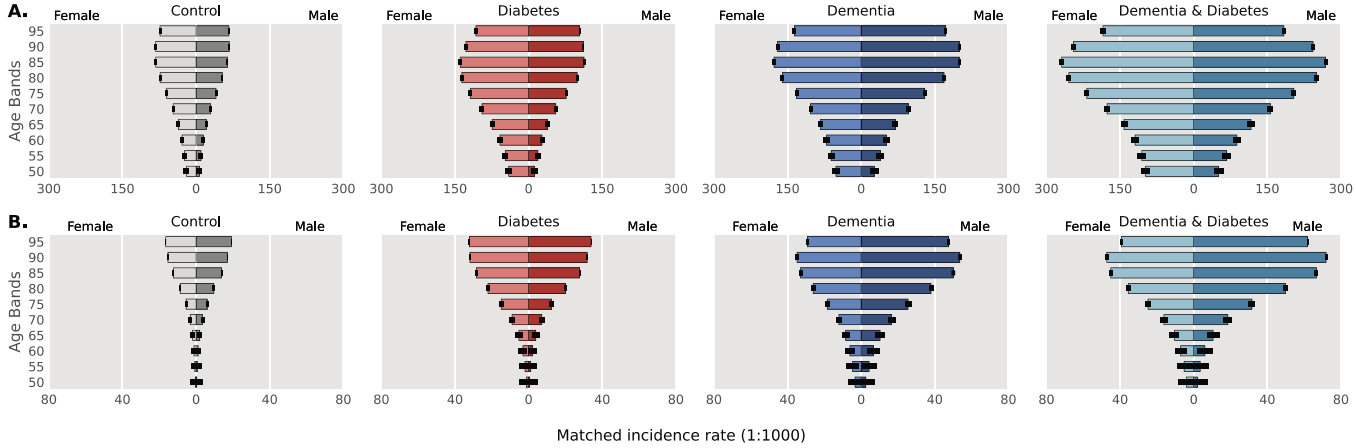

Fig. 2. Incidence rates of A) UTI and B) death within 60 days of UTI. From left to right, the panels correspond to results across the four groups: controls, diabetes, dementia, and co-morbid dementia and diabetes. Each plot is mirrored along the x-axis, with incidence in females depicted on the left and in males on the right. Y-axes are shared throughout the plots and depict effect of increasing age bands.

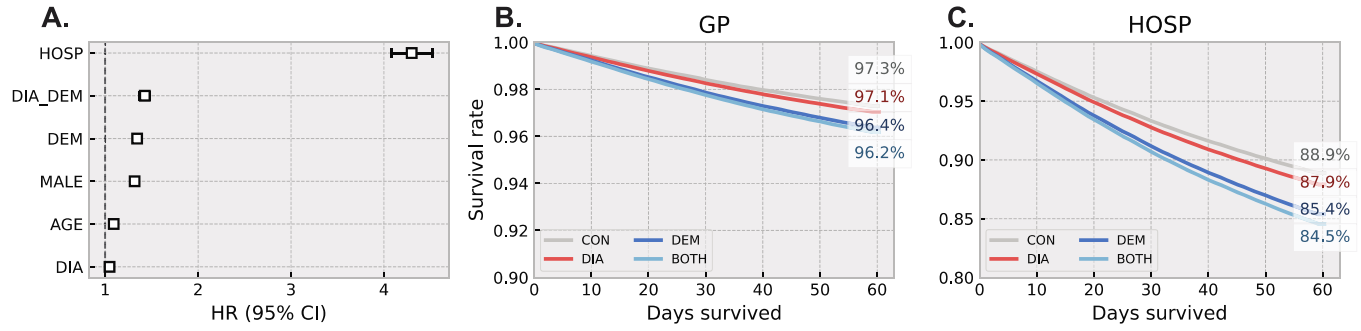

Fig. 3. Cox regression results and survival curves for overall mortality within 60 days following UTI across matched samples. A: Hazard ratios for impact of examined factors on death within 60 days of UTI (referent groups as follows: secondary care (HOSP) compared to primary care (GP); diabetes & dementia (DIA_DEM), diabetes (DIA), and dementia (DEM) compared to controls (CON); male compared to female); B: 60-day survival following UTI diagnosis made at a primary care (GP) level across the morbidity groups; C: 60-day survival following UTI diagnosis made at a secondary care (hospital) level across the morbidity groups.

episodes were stratified by UTI type into lower and upper UTI and compared against recurrent UTI (Supplementary Table 1). As expected, the results indicated that both lower and upper UTIs were associated with higher risk of 60-day mortality compared to chronic UTI; upper UTIs were associated with double the risk (HR=2.00), while lower UTIs showed a 38 % higher risk (HR=1.38) (Supplementary Table 12).

Time since diagnosis sensitivity analysis

We then examined the effect of time since dementia diagnosis as a proxy for dementia severity, as information about dementia staging was not available. Time since diagnosis was binned evenly into three groups, approximately ≤1, 1–3, and 3–10 years post-diagnosis. The group with the longest time since diagnosis was associated with significantly higher risk of 60-day mortality (HR=1.08 [1.03,1.15], p < 0.00), with no significant differences between the other two groups (Supplementary Table 13).

High rates of mortality with delayed treatment for diabetes and dementia

In primary care data, we then quantified the effect of antibiotic treatment type and treatment timing on survival following UTI. Propensity sampling resulted in 31,171 UTI events in n = 24,336 matched individuals. The proportions of prescribed antibiotics changed considerably from 2000 to 2022, particularly from 2018 (Fig. 4A).

Across all UTIs diagnosed and treated within primary care, nitrofurantoin, trimethoprim, and cefalexin were the most prescribed,

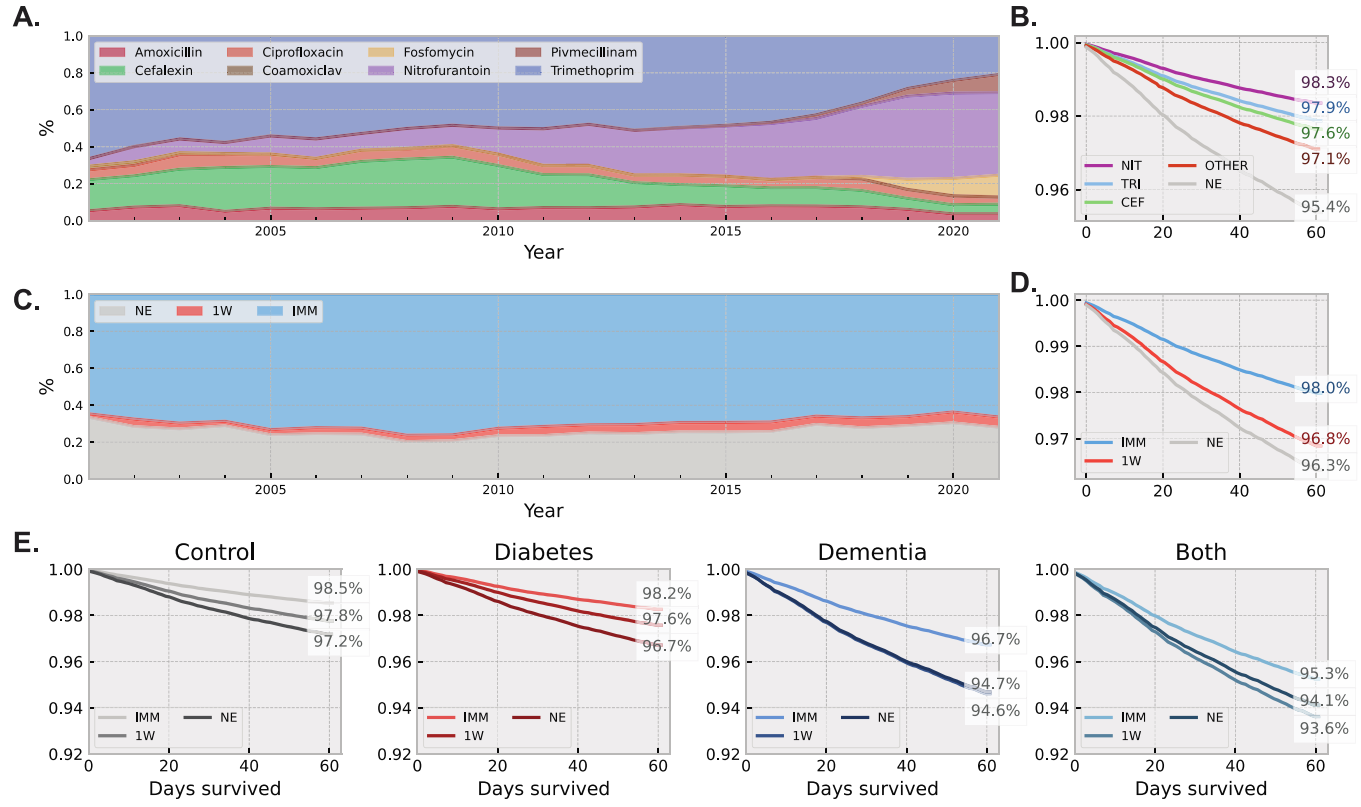

Fig. 4. Effects of antibiotic treatment type and treatment timing on 60-day survival rate following UTI within the propensity-matched groups. A: Proportion of antibiotics prescribed for UTIs within the study sample over the study period; B: effects of antibiotic prescribing on survival across all morbidity groups (NIT: nitrofurantoin, TRI: Trimethoprim, CEF: Cefalexin, OTHER: any other recorded antibiotics, NE: no evidence of treatment within a week). C: Treatment timing over the study period, depicting changes in proportions of people treated immediately (IMM), deferred within a week (1W), and withheld/no evidence of treatment within a week (NE). D: Effects of treatment timing on survival across all morbidity groups. E: Combined effects of morbidity and treatment timing on survival within 60 days following UTI.

accounting for 84.0 % of total antibiotic prescriptions. All three were associated with higher 60-day survival compared to no treatment within a week (nitrofurantoin: HR=0.35, [95 % CI 0.29–0.43], p < 0.005; trimethoprim: HR=0.46 [0.39–0.53], p < 0.005; cefalexin: HR=0.50 [0.41–0.62], p < 0.005). (Supplementary Table 14) (Fig. 4B).

Treatment timing also significantly influenced survival. The proportions of individuals receiving immediate, deferred, and no treatment within one week remained relatively stable throughout the study period (See Fig. 4C; for group-specific proportions see Table 2). Deferred and withheld treatment were associated with higher risk of 60-day mortality compared to immediate treatment (1 W: HR=1.57 [95 % CI 1.22–2.02], p < 0.001; NE: HR=1.85 [95 % CI 1.63–2.09], p < 0.001) (Fig. 4D; Supplementary Table 15). Extending this analysis to include the effect of morbidity, co-morbid dementia and diabetes were associated the highest mortality risk, almost three-fold that of controls (HR=2.83, [95 % CI 2.40–3.34], p < 0.001). Dementia alone was associated with the second-highest mortality risk, two times higher than controls (HR=2.18 [1.88–2.53], p < 0.001), followed by diabetes (HR=1.21 [1.01–1.45], p = .035) (Fig. 4E; Supplementary Table 16). The difference in survival rates between immediate and delayed treatment became more pronounced across the morbidity groups, increasing from 0.7 % in controls and 0.6 % in diabetes to 2.0 % in dementia and 1.7 % in the co-morbid group. A similar trend was observed when comparing survival rates between immediate and withheld treatment, with 1.3% in controls and 1.5 % in the diabetes group, increasing to 2.1 % in the dementia group.

Discussion

Urinary tract infections (UTIs) are a significant health problem for people living with dementia (PLWD). Using linked primary and secondary care data, we show for the first time the incidence and clinical outcomes of UTI in this group. The incidence of UTI diagnosis is 93 % higher in PLWD than in matched diabetics, and 201 % higher than that of controls without either condition. Mortality rates within two months of UTI are also high in PLWD, particularly when diagnosed in the hospital. UTIs diagnosed in primary care with no record of treatment within 24 h have lower survival, emphasising the importance of timely identification and intervention. The influence of co-morbidity was marked, with dementia and diabetes associated with higher rates of UTI and mortality following UTI regardless of treatment timing.

High incidence of UTI diagnosis in PLWD is expected, as patients with dementia are more susceptible to UTIs for several reasons. Dementia is often associated with problems with self-care,[40–42] including dehydration and neglect of personal hygiene that can directly increase the risk of UTI.[43–45] Autonomic dysfunction is common in some types of dementia, such as dementia with Lewy Bodies (DLB) and Parkinson's Disease Dementia (PDD), impacting on bladder control, resulting in urinary incontinence and increasing bacterial colonisation.[46–49] PLWD experiencing frequent hospitalisation are at especially high risk of healthcare-associated UTIs, such as those resulting from indwelling urethral catheter use,[50,51] and are overall vulnerable to complications.[52] Finally, those residing in care homes are at further risk of pathogen transmission within and between facilities.[53,54]

Mortality rates were strikingly high following UTI in PLWD, particularly in the presence of co-morbidity with diabetes. In PLWD, death rates were five times higher than that of matched controls, and almost nine times higher than controls in those with dementia and diabetes. There are a range of possible reasons for this. UTIs often present atypically in older age and in PLWD, complicating the diagnostic process.[55–57] PLWD often lack insight into their health and may not recognise or report symptoms when they emerge,[58] resulting in delayed treatment and increased infection severity. Other studies have also indicated that UTI may be overdiagnosed within older adults, potentially leading to delays in the identification of other serious health conditions.[18,59] Finally, multi-morbidity and frailty are common[60] and can increase the impact of infection.[61–64] We show a striking effect of diabetes on the incidence and clinical effect of UTI in PLWD. Diabetes is known to increase UTI risk due to factors such as high urinary glucose levels and impaired kidney and bladder function.[65,66] As expected,[67–69] we found that the incidence of UTI in people with diabetes alone was twice that of controls. This general effect of diabetes may interact with the presence of cognitive impairment, adversely affecting medication compliance or diabetes monitoring, contributing to poor glycaemic control and exacerbating the effects of UTI.[70,71] In general, cognitive impairment may impact the ability of PLWD to manage comorbid health conditions, ultimately increasing the risk of mortality from potentially preventable conditions like infection.[72,73]

As in previous studies, we found that delayed and withheld treatment were generally associated with higher 60-day mortality across older adults within the study population.[16,17] This effect was particularly marked in PLWD. Survival rates following GP-diagnosed UTIs in PLWD were 96.7 % when treated immediately, decreasing by 2.1 % to 94.6 % when untreated within a week. In PLWD with diabetes, survival rates were just 95.3 % for UTIs treated immediately, decreasing by 1.2 % to 94.1 % when the UTI was untreated. The decision to prescribe antibiotics is not always straightforward, especially in light of increasing antimicrobial resistance.[74,75] In this study, the majority of PLWD received immediate antibiotic treatment following a UTI diagnosis, consistent with previous findings in the literature.[76] Our data highlight that prompt intervention is likely to be important in this vulnerable group, potentially reflecting not only the impact of treatment, but also the efficiency and availability of broader healthcare provision.

The high rates of mortality associated with UTIs in PLWD suggest the need to improve current approaches to UTI diagnosis and treatment. Rapid, reliable, and accurate diagnosis is required to enable timely and appropriate intervention. Current guidelines for the diagnosis of UTI are reliant on subjective symptom reporting, which may not be appropriate for PLWD. The recent emergence of portable point-of-care diagnostics may allow UTI testing that can be deployed at home, limiting delays associated with sample processing and analysis in the laboratory.[77,78] Better understanding of the underlying mechanisms and risk factors for UTIs in this population will further allow the implementation of targeted prevention and treatment strategies, limiting the potential for inappropriate prescribing and antibiotic misuse.

One of the strengths of this study is the very large sample size and substantial follow-up period, allowing us to investigate representative changes in incidence over time. Additionally, this allowed us to conduct demographic matching on an individual level, reducing potential for confounding. However, the study also has limitations. Our data lacked clinical factors such as frailty and severity of cognitive impairment, which may have influenced the likelihood of UTI diagnosis and are independently associated with mortality risk. Next, we did not have information about how the coded UTIs were diagnosed. While we excluded a substantial proportion of codes for suspected UTI in our analysis to improve confidence, we were unable to validate the identified infections against pathology data. The non-specific presentation of illnesses in older adults with dementia often results in the misdiagnosis of infections such as UTI, leading to potential delays in the identification and management of serious or life limiting health conditions. Relatedly, we are not aware of the clinical context in which the treatment plan is devised, for instance if patients were under palliative care. We acknowledge that in some circumstances antibiotic treatment may not be deemed appropriate for PLWD approaching the end of their life.[79] We also did not account for polypharmacy and the influence of

other (non-antibiotic) interventions such as the management of pain or blood pressure, or the review of recurrent prescriptions such as prophylactic treatments, all of which may have exerted effects on survival. Finally, we did not examine effects of ethnicity due to limited heterogeneity within the sample. Findings from this study could be extended within more diverse populations and consider effects of residence (i.e., long-term care facilities) to test generalisability.

In conclusion, our study suggests that individuals with dementia, especially those with co-morbid diabetes, suffered a disproportionate incidence of UTI diagnosis over the last twenty years. The associated mortality observed subsequent to diagnosis potentially reflects the impact of diagnostic uncertainty as well as delays in diagnosis and intervention. Our findings highlight the importance of preventive measures, early and accurate detection, and appropriate treatment of UTIs in cognitively impaired populations.

Ethical approval

The project protocol and access to the study data was reviewed and approved by the SAIL Information Governance Review Panel (IGRP). Individual patient consent was not required for the use of anonymised electronic health records.

Funding

This work is supported by Imperial College London and the UK Dementia Research Institute [award number: DRI-CORE2020-CRT] which receives its funding from UK DRI Ltd, funded by the UK Medical Research Council, Alzheimer's Society and Alzheimer's Research UK. The work was also supported by the Imperial College London NIHR Biomedical Research Centre. The funding sources were not involved in the study design, or in the preparation and submission of the article for publication.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106167.

References

1. Natalwala A, Potluri R, Uppal H, Heun R. *Reasons for hospital admissions in dementia patients in Birmingham, UK, during 2002–2007. DEM* 2008;**26**(6):499–505.
2. Gungabissoon U, Perera G, Galwey NW, Stewart R. *Potentially avoidable causes of hospitalisation in people with dementia: contemporaneous associations by stage of dementia in a South London clinical cohort. BMJ Open* 2022;**12**(4):e055447.
3. Rowe TA, Juthani-Mehta M. *Urinary tract infection in older adults. Aging Health* 2013;**9**(5):519–28.
4. Nicolle LE. *Urinary tract infections in the elderly. Clin Geriatr Med* 2009;**25**(3):423–36.
5. Rodriguez-Mañas L. *Urinary tract infections in the elderly: a review of disease characteristics and current treatment options. Drugs Context* 2020;**9**. 2020-4–13.
6. Nicolle L. *Symptomatic urinary tract infection or asymptomatic bacteriuria? Improving care for the elderly. Clin Microbiol Infect* 2019;**25**(7):779–81.
7. Shepherd H, Livingston G, Chan J, Sommerlad A. *Hospitalisation rates and predictors in people with dementia: a systematic review and meta-analysis. BMC Med* 2019;**17**(1):130.
8. Detweiler K, Mayers D, Fletcher SG. *Bacteruria and urinary tract infections in the elderly. Urol Clin* 2015;**42**(4):561–8.
9. Overview. Urinary tract infections in adults. Quality standards. NICE [Internet]. NICE; 2015 [cited 2024 Jan 31]. Available from: ⟨https://www.nice.org.uk/guidance/qs90⟩.
10. Bilsen MP, Lambregts M, Conroy S. *Guideline commentary on updated NICE guidelines for urinary tract infections. Age Ageing* 2023;**52**(3):afad013.
11. Rao A, Suliman A, Vuik S, Aylin P, Darzi A. *Outcomes of dementia: systematic review and meta-analysis of hospital administrative database studies. Arch Gerontol Geriatr* 2016;**66**:198–204.
12. Tropea J, LoGiudice D, Liew D, Gorelik A, Brand C. *Poorer outcomes and greater healthcare costs for hospitalised older people with dementia and delirium: a retrospective cohort study. Int J Geriatr Psychiatry* 2017;**32**(5):539–47.
13. Fox A, MacAndrew M, Ramis MA. *Health outcomes of patients with dementia in acute care settings—a systematic review. Int J Older People Nurs* 2020;**15**(3):e12315.
14. Barber AE, Norton JP, Spivak AM, Mulvey MA. *Urinary tract infections: current and emerging management strategies. Clin Infect Dis* 2013;**57**(5):719–24.
15. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. *Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol* 2015;**13**(5):269–84.
16. Shallcross L, Rockenschaub P, Blackburn R, Nazareth I, Freemantle N, Hayward A. *Antibiotic prescribing for lower UTI in elderly patients in primary care and risk of bloodstream infection: a cohort study using electronic health records in England. PLOS Med* 2020;**17**(9):e1003336.
17. Gharbi M, Drysdale JH, Lishman H, Goudie R, Molokhia M, Johnson AP, et al. *Antibiotic management of urinary tract infection in elderly patients in primary care and its association with bloodstream infections and all cause mortality: population based cohort study. BMJ* 2019;**364**:l525.
18. Yourman LC, Kent TJ, Israni JS, Ko KJ, Lesser A. *Association of dementia diagnosis with urinary tract infection in the emergency department. J Am Coll Emerg Physicians Open* 2020;**1**(6):1291–6.
19. Dufour AB, Shaffer ML, D'Agata EMC, Habtemariam D, Mitchell SL. *Survival after suspected urinary tract infection in individuals with advanced dementia. J Am Geriatr Soc* 2015;**63**(12):2472–7.
20. Mitchell SL, Shaffer ML, Loeb MB, Givens JL, Habtemariam D, Kiely DK, et al. *Infection management and multidrug-resistant organisms in nursing home residents with advanced dementia. JAMA Intern Med* 2014;**174**(10):1660–7.
21. Ronald A, Ludwig E. *Urinary tract infections in adults with diabetes. Int J Antimicrob Agents* 2001;**17**(4):287–92.
22. Stapleton A. *Urinary tract infections in patients with diabetes. Am J Med* 2002;**113**(1, Supplement 1):80–4.
23. Chen SL, Jackson SL, Boyko EJ. *Diabetes mellitus and urinary tract infection: epidemiology, pathogenesis and proposed studies in animal models. J Urol* 2009;**182**(6, Supplement):S51–6.
24. Nitzan O, Elias M, Chazan B, Saliba W. *Urinary tract infections in patients with type 2 diabetes mellitus: review of prevalence, diagnosis, and management. Diabetes Metab Syndr Obes* 2015;**8**:129–36.
25. Gomez CS, Kanagarajah P, Gousse AE. *Bladder dysfunction in patients with diabetes. Curr Urol Rep* 2011;**12**(6):419–26.
26. Lyons RA, Jones KH, John G, Brooks CJ, Verplancke JP, Ford DV, et al. *The SAIL databank: linking multiple health and social care datasets. BMC Med Inform Decis Mak* 2009;**9**(1):3.
27. WIMD - Home Page [Internet]. [cited 2024 Jan 15]. Available from: ⟨https://wimd.gov.wales/⟩.
28. Health Data Research Innovation Gateway. Health Data Research Innovation Gateway. Welsh Longitudinal Practice Dataset (WLGP) - Welsh Primary Care (SAIL). Available from: ⟨https://web.www.healthdatagateway.org/dataset/33fc3ffd-aa4c-4a16-a32f-0c900aaea3d2⟩.
29. Wilkinson T, Ly A, Schnier C, Rannikmäe K, Bush K, Brayne C, et al. *Identifying dementia cases with routinely collected health data: a systematic review. Alzheimer's Dement* 2018;**14**(8)):1038–51.
30. Eastwood SV, Mathur R, Atkinson M, Brophy S, Sudlow C, Flaig R, et al. *Algorithms for the capture and adjudication of prevalent and incident diabetes in UK biobank. PLOS ONE* 2016;**11**(9):e0162388.
31. Schnier C, Wilkinson T, Akbari A, Orton C, Sleegers K, Gallacher J, et al. The secure anonymised information linkage databank dementia e-cohort (SAIL-DeC). Int J Popul Data Sci; 5(1): p. 1121.
32. Crellin E, Mansfield KE, Leyrat C, Nitsch D, Douglas IJ, Root A, et al. *Clinical code list - read codes - urinary tract infection [internet].* London, United Kingdom: London School of Hygiene & Tropical Medicine; 2017. [cited 2022 Nov 17]. ⟨https://datacompass.lshtm.ac.uk/id/eprint/470/⟩.
33. Palin V, Mölter A, Belmonte M, Ashcroft DM, White A, Welfare W, et al. *Antibiotic prescribing for common infections in UK general practice: variability and drivers. J Antimicrob Chemother* 2019;**74**(8):2440–50.
34. NHS Digital. NHS Digital. [cited 2023 Apr 20]. Read codes. Available from: ⟨https://digital.nhs.uk/services/terminology-and-classifications/read-codes⟩.
35. World Health Organisation. International statistical classification of diseases and related health problems 10th revision - ICD-10 Version; 2019 [Internet]. [cited 2022 Nov 17]. Available from: ⟨https://icd.who.int/browse10/2019/en⟩.
36. All Wales Medicine Strategy Group. Primary care antimicrobial guidelines [Internet]. NHS Wales; 2022 [cited 2022 Oct 24] p. 1–60. Available from: ⟨https://awttc.nhs.wales/medicines-optimisation-and-safety/medicines-optimisation-guidance-resources-and-data/prescribing-guidance/primary-care-antimicrobial-guidelines/⟩.
37. Python.org [Internet]. [cited 2023 Feb 24]. Python Release Python 3.9.0. Available from: ⟨https://www.python.org/downloads/release/python-390/⟩.
38. Rosenbaum PR, Rubin DB. *The central role of the propensity score in observational studies for causal effects. Biometrika* 1983;**70**(1):41–55.
39. Kuhn HW. *The Hungarian method for the assignment problem. Nav Res Logist Q* 1955;**2**(1–2):83–97.
40. Prizer LP, Zimmerman S. *Progressive support for activities of daily living for persons living with dementia. Gerontologist* 2018;**58**(suppl_1):S74–87.
41. Giebel CM, Sutcliffe C, Challis D. *Activities of daily living and quality of life across different stages of dementia: a UK study. Aging Ment Health* 2015;**19**(1):63–71.
42. Amella EJ. *Feeding and hydration issues for older adults with dementia. Nurs Clin* 2004;**39**(3):607–23.

43. Toot S, Devine M, Akporobaro A, Orrell M. *Causes of hospital admission for people with dementia: a systematic review and meta-analysis. J Am Med Dir Assoc* 2013;**14**(7):463–70.
44. Eriksson I, Gustafson Y, Fagerström L, Olofsson B. *Prevalence and factors associated with urinary tract infections (UTIs) in very old women. Arch Gerontol Geriatr* 2010;**50**(2):132–5.
45. El-Sharkawy AM, Virdee A, Wahab A, Humes DJ, Sahota O, Devonald MAJ, et al. *Dehydration and clinical outcome in hospitalised older adults: a cohort study. Eur Geriatr Med* 2017;**8**(1):22–9.
46. Na HR, Cho ST. *Relationship between lower urinary tract dysfunction and dementia. Dement Neurocognitive Disord* 2020;**19**(3):77–85.
47. Sakakibara R, Uchiyama T, Yamanishi T, Kishi M. *Dementia and lower urinary dysfunction: with a reference to anticholinergic use in elderly population. Int J Urol* 2008;**15**(9):778–88.
48. Thaisetthawatkul P, Boeve BF, Benarroch EE, Sandroni P, Ferman TJ, Petersen R, et al. *Autonomic dysfunction in dementia with Lewy bodies. Neurology* 2004;**62**(10):1804–9.
49. Okunoye O, Kojima G, Marston L, Walters K, Schrag A. *Factors associated with hospitalisation among people with Parkinson's disease – a systematic review and meta-analysis. Park Relat Disord* 2020;**71**:66–72.
50. Meddings J, Saint S, Krein SL, Gaies E, Reichert H, Hickner A, et al. *Systematic review of interventions to reduce urinary tract infection in nursing home residents. J Hosp Med* 2017;**12**(5):356–68.
51. Nicolle LE. *Catheter associated urinary tract infections. Antimicrob Resist Infect Control* 2014;**3**(1):23.
52. Bail K, Berry H, Grealish L, Draper B, Karmel R, Gibson D, et al. *Potentially preventable complications of urinary tract infections, pressure areas, pneumonia, and delirium in hospitalised dementia patients: retrospective cohort study. BMJ Open* 2013;**3**(6):e002770.
53. D'Agata EMC, Habtemariam D, Mitchell S. *Multidrug-resistant gram-negative bacteria: inter- and intradissemination among nursing homes of residents with advanced dementia. Infect Control Hosp Epidemiol* 2015;**36**(8):930–5.
54. Lasseter G, Charlett A, Lewis D, Donald I, Howell-Jones R, McNulty CAM. *Staphylococcus aureus carriage in care homes: identification of risk factors, including the role of dementia. Epidemiol Infect* 2010;**138**(5):686–96.
55. Matthews SJ, Lancaster JW. *Urinary tract infections in the elderly population. Am J Geriatr Pharmacother* 2011;**9**(5):286–309.
56. Limpawattana P, Phungoen P, Mitsungnern T, Laosuangkoon W, Tansangworn N. *Atypical presentations of older adults at the emergency department and associated factors. Arch Gerontol Geriatr* 2016;**62**:97–102.
57. Komagamine J, Yabuki T, Noritomi D, Okabe T. *Prevalence of and factors associated with atypical presentation in bacteremic urinary tract infection. Sci Rep* 2022;**12**(1):5197.
58. Liu KY, Howard R, Banerjee S, Comas-Herrera A, Goddard J, Knapp M, et al. *Dementia wellbeing and COVID-19: review and expert consensus on current research and knowledge gaps. Int J Geriatr Psychiatry* 2021;**36**(11):1597–639.
59. Kistler CE, Wretman CJ, Zimmerman S, Enyioha C, Ward K, Farel CE, et al. *Overdiagnosis of urinary tract infections by nursing home clinicians versus a clinical guideline. J Am Geriatr Soc* 2022;**70**(4):1070–81.
60. Browne J, Edwards DA, Rhodes KM, Brimicombe DJ, Payne RA. *Association of comorbidity and health service usage among patients with dementia in the UK: a population-based study. BMJ Open* 2017;**7**(3):e012546.
61. Wallace LMK, Theou O, Darvesh S, Bennett DA, Buchman AS, Andrew MK, et al. *Neuropathologic burden and the degree of frailty in relation to global cognition and dementia. Neurology* 2020;**95**(24):e3269–79.
62. Kulmala J, Nykänen I, Mänty M, Hartikainen S. *Association between frailty and dementia: a population-based study. Gerontology* 2013;**60**(1):16–21.
63. Kojima G, Taniguchi Y, Iliffe S, Walters K. *Frailty as a predictor of alzheimer disease, vascular dementia, and all dementia among community-dwelling older people: a systematic review and meta-analysis. J Am Med Dir Assoc* 2016;**17**(10):881–8.
64. Petermann-Rocha F, Lyall DM, Gray SR, Esteban-Cornejo I, Quinn TJ, Ho FK, et al. *Associations between physical frailty and dementia incidence: a prospective study from UK Biobank. Lancet Healthy Longev* 2020;**1**(2):e58–68.
65. de Lastours V, Foxman B. *Urinary tract infection in diabetes: epidemiologic considerations. Curr Infect Dis Rep* 2014;**16**(1):389.
66. Wilke T, Boettger B, Berg B, Groth A, Mueller S, Botteman M, et al. *Epidemiology of urinary tract infections in type 2 diabetes mellitus patients: an analysis based on a large sample of 456,586 German T2DM patients. J Diabetes Complicat* 2015;**29**(8):1015–23.
67. Hirji I, Guo Z, Andersson SW, Hammar N, Gomez-Caminero A. *Incidence of urinary tract infection among patients with type 2 diabetes in the UK General Practice Research Database (GPRD). J Diabetes Complicat* 2012;**26**(6):513–6.
68. Boyko EJ, Fihn SD, Scholes D, Abraham L, Monsey B. *Risk of urinary tract infection and asymptomatic bacteriuria among diabetic and nondiabetic postmenopausal women. Am J Epidemiol* 2005;**161**(6):557–64.
69. Muller LMAJ, Gorter KJ, Hak E, Goudzwaard WL, Schellevis FG, Hoepelman AIM, et al. *Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin Infect Dis* 2005;**41**(3):281–8.
70. Santos T, Lovell J, Shiell K, Johnson M, Ibrahim JE. *The impact of cognitive impairment in dementia on self-care domains in diabetes: a systematic search and narrative review. Diabetes/Metab Res Rev* 2018;**34**(6):e3013.
71. Thorpe CT, Thorpe JM, Kind AJH, Bartels CM, Everett CM, Smith MA. *Receipt of monitoring of diabetes mellitus in older adults with comorbid dementia. J Am Geriatr Soc* 2012;**60**(4):644–51.
72. Gungabissoon U, Broadbent M, Perera G, Ashworth M, Galwey N, Stewart R. *The impact of dementia on diabetes control: an evaluation of HbA1c trajectories and care outcomes in linked primary and specialist care data. J Am Med Dir Assoc* 2022;**23**(9):1555–1563.e4.
73. Hopkins R, Shaver K, Weinstock RS. *Management of adults with diabetes and cognitive problems. Diabetes Spectr* 2016;**29**(4):224–37.
74. Hartman EAR, Groen WG, Heltveit-Olsen SR, Lindbæk M, Høye S, Sundvall PD, et al. *Decisions on antibiotic prescribing for suspected urinary tract infections in frail older adults: a qualitative study in four European countries. Age Ageing* 2022;**51**(6):afac134.
75. van Buul LW, van der Steen JT, Doncker SM, Achterberg WP, Schellevis FG, Veenhuizen RB, et al. *Factors influencing antibiotic prescribing in long-term care facilities: a qualitative in-depth study. BMC Geriatr* 2014;**14**(1):136.
76. van der Maaden T, Hendriks SA, de Vet HCW, Zomerhuis MT, Smalbrugge M, Jansma EP, et al. *Antibiotic use and associated factors in patients with dementia: a systematic review. Drugs Aging* 2015;**32**(1):43–56.
77. Santos M, Mariz M, Tiago I, Martins J, Alarico S, Ferreira P. *A review on urinary tract infections diagnostic methods: laboratory-based and point-of-care approaches. J Pharm Biomed Anal* 2022;**219**:114889.
78. Davenport M, Mach KE, Shortliffe LMD, Banaei N, Wang TH, Liao JC. *New and developing diagnostic technologies for urinary tract infections. Nat Rev Urol* 2017;**14**(5):296–310.
79. Fairweather J, Cooper L, Sneddon J, Seaton RA. *Antimicrobial use at the end of life: a scoping review. BMJ Support Palliat Care* 2020. bmjspcare-2020-002558.