

THE LANCET

Healthy Longevity

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Supplementary appendix

Supplementary Appendix 1: Search strategy

a) MEDLINE (OVID) search strategy

1. Pneumonia/ or pneumonia, bacterial/
2. Pneumonia.ti,ab
3. Lower respiratory tract infection*.ti,ab
4. (LRTI or LRTIS).ti,ab.
5. Exp urinary tract infections/
6. (Urinary adj5 infection*).ti,ab.
7. (UTI or UTIS).ti,ab
8. exp Cystitis/
9. (bacteriuria or pyuria or cystitis or pyelonephritis or cellulitis).ti,ab.
10. exp cellulitis/
11. (Skin and soft tissue infection).mp.
12. exp sepsis/
13. (septic* or sepsis or septic?emia or systematic inflammatory response syndrome or blood stream infection or py?emia).ti,ab.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. Exp dementia/
16. Exp prion diseases/
17. (huntington* or kluber-bucy or prion disease or Creutzfeldt-jakob or primary progressive aphasia).ti,ab
18. (Dement* or Alzheimer*).ti,ab
19. (Lewy*adj2 bod*).ti,ab.
20. Cognitive dysfunction/
21. (Mild cognitive impairment or MCI).ti,ab
22. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)).ti,ab.
23. Cognitive function.ti,ab.
24. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23

25. cohort studies/ or longitudinal study/ or follow-up study/ or prospective study/ or retrospective study/
or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.
26. Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or ((case* adj5 control*) or (case
adj3 comparison*) or control group*).ti,ab.
27. Incidence/ or incidence.ti,ab,kw.
28. (hazard ratio or HR or odds ratio or relative risk or RR).ti,ab.
29. 25 or 26 or 27 or 28
30. 14 and 24 and 29

b) Embase (OVID) search strategy

1. Bacterial pneumonia/ or Pneumonia/
2. Pneumonia.ti,ab
3. Lower respiratory tract infection*.ti,ab
4. (LRTI or LRTIS).ti,ab.
5. Exp Urinary tract infections/
6. exp Bacteriuria/
7. exp Pyuria/
8. (Urinary adj5 infection*).ti,ab.
9. (UTI or UTIS).ti,ab
10. Exp cystitis/
11. (bacteriuria or pyuria or cystitis or pyelonephritis or cellulitis).ti,ab.
12. exp cellulitis/
13. (Skin and soft tissue infection).mp.
14. exp sepsis/
15. (septic* or sepsis or septic?emia or systematic inflammatory response syndrome or blood stream infection or py?emia).ti,ab.
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. Exp dementia
18. Exp Creutzfeldt-jakob disease
19. (huntington* or kluver-bucy or prion disease or Creutzfeldt-jakob or primary progressive aphasia).ti,ab
20. Dement*.ti,ab.
21. Exp mild cognitive impairment/
22. (Mild cognitive impairment or MCI)ti,ab
23. ((cognit* or memory or cerebr* or mental*) adj3 (declin* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder*)),ti,ab.
24. Cognitive function.ti,ab.
25. Alzheimer*.ti,ab
26. (Lewy*adj2 bod*).ti,ab.
27. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28. cohort analysis/ or longitudinal study/ or follow-up/ or prospective study/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.

29. Case control study/ or Control Group/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.

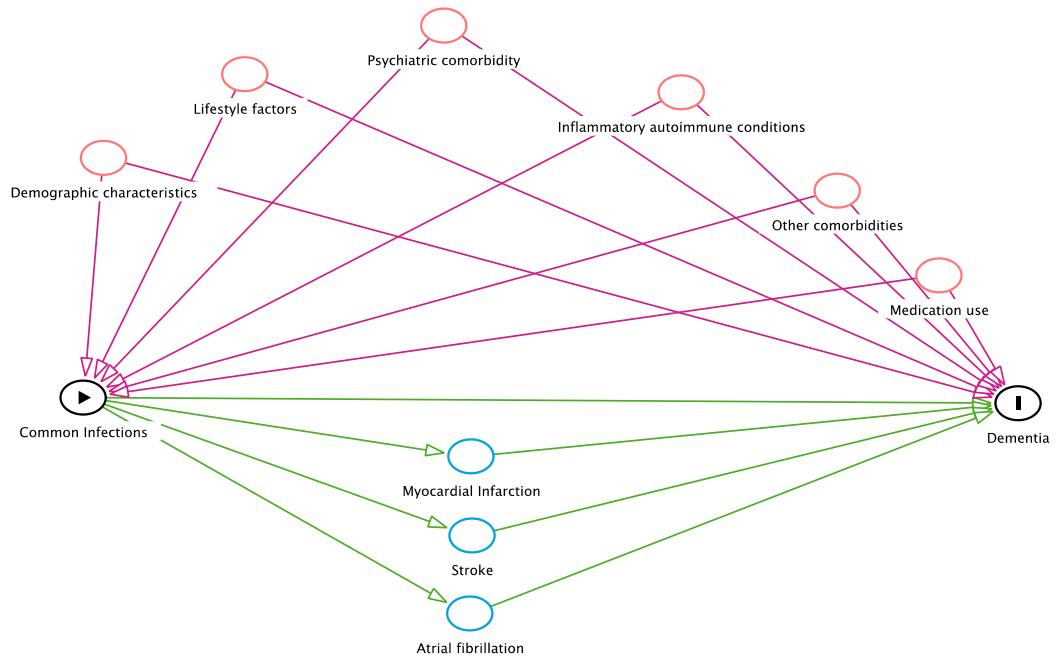
30. Incidence/ or incidence.ti,ab,kw.

31. (hazard ratio or HR or odds ratio or relative risk or RR).ti,ab.

32. 28 or 29 or 30 or 31

33. 16 and 27 and 32

Supplementary Appendix 2: Directed acyclic graph depicting the possible confounders and effect modifiers in the association between common infections and dementia.



Legend:

- exposure
- outcome
- ancestor of outcome
- ancestor of exposure and outcome
- biasing path
- causal path

Supplementary Appendix 3: Variable definitions

Infections

First ever infection

Infections were identified using primary care data from the Clinical Practice Research Datalink (CPRD) and secondary care data from Hospital Episode Statistics (HES). In order to confirm a diagnosis of infections and capture more serious infections, urinary tract infections (UTIs) and skin and soft tissue infections (SSTIs) were defined using a Read code and a prescription for antibiotics on the same date as a diagnosis of infection. Sepsis, pneumonia and other lower respiratory tract infections (LRTIs) were not defined using a prescription for antibiotics as these infections can also be caused by viruses. Infections identified in HES were not linked with a prescription for antibiotics as medication data is not available in HES and hospitalised infections are likely to be more serious than those diagnosed in the community.

To avoid misclassification of dementia, we excluded the first 3 months after an infection. That is, when an individual was diagnosed with an infection, they exited the study for 3 months and re-entered after the 3-month exit period.

Type and clinical setting of infection

For instances in which an individual was diagnosed with two different types of infections on the same date, a hierarchical approach was used based on the infection type and data source. If two different infections were diagnosed on the same date in CPRD and HES, the infection recorded in HES was used as the primary diagnosis. Then, if sepsis was diagnosed on the same date as another infection, sepsis was the primary diagnosis. If pneumonia and other lower respiratory tract infections were diagnosed on the same date, then the pneumonia diagnosis was taken. If two infections were diagnosed in hospital and GP records, the infection diagnosed in hospital was taken.

Frequency of infections

Individuals who were diagnosed with subsequent infections during the 3-month exit period remained out of the study 3 months from subsequent infection diagnosis.

Covariates

Socioeconomic deprivation

We linked CPRD to patient-level Index of Multiple Deprivation 2015 (IMD 2015). The IMD 2015 is a measure of relative deprivation for small areas across England based on seven domains which can be divided into groups ranking from least to most deprived.(1) Socioeconomic deprivation was defined using patient-level Index of Multiple Deprivation (IMD) which includes only English GP practices. Socioeconomic deprivation was categorised into quintiles; 1 least deprived and 5 most deprived.(1)

Ethnicity

Ethnicity was categorised as follows: White, South Asian, Black and Mixed/Other. Using CPRD, we used the most commonly recorded ethnicity, then we used the most recent ethnicity where several ethnicities were recorded. When ethnicity in CPRD was missing, we then used ethnicity recorded in HES. The algorithm we used for ethnicity in CPRD and HES has been previously described.(2)

BMI and smoking status

We derived BMI at entry into the study from the CPRD additional details file and defined using methods previously described.(3) We excluded records when an individual was under 16 years, during pregnancy or records under 20kg. BMI was calculated using weight records with height recorded on the same date. However, if a height record on the same date as weight record was not available, we used an older height record. If not available, we used a future height record. The following cut-off points by the World Health Organisation (WHO) were used to define BMI; underweight (<18.5), normal weight (18.5-24.9), overweight (25.0-29.9), obese (30.0>). Smoking status was defined in CPRD, using Read codes and data from the additional details file. Smoking and BMI status were assigned using the nearest record in the period of -1 year to +1 month from start of follow up, if available (best). If not available, the second option was to use the nearest record in the period +1month to +1 year after start of follow up. If not available, the third option was to take the nearest record before -1 year from start of follow up and if not available the least best option was to take any nearest record after +1 year from start of follow up.

Depression and anxiety

Depression and anxiety were also defined in CPRD and HES. In CPRD, we included individuals with:

- 1) a diagnostic or symptomatic Read code for depression or anxiety and
- 2) a prescription for antidepressants or medications indicated for treatment of anxiety in the British National Formulary (BNF) within 90 days of clinical code.

Depression and anxiety were defined as above due to the changes in diagnosing depression in the UK primary care given that in 2006 GPs switched from using diagnostic to symptomatic codes (4). Additionally, from 2004 antidepressants were no longer routinely prescribed for mild depression, therefore to increase the likelihood of capturing those with more severe depression, we defined depression with a clinical code and prescription for antidepressants (5). Given that depression and anxiety have overlapping clinical codes and medication, we combined the variables for depression and anxiety together. In HES, we used ICD-10 codes alone as individuals diagnosed in hospital are more likely to be severe than those in diagnosed in primary care.

Diabetes

We defined diabetes using diagnoses for diabetes mellitus (type 1, type 2 and unspecified) and codes for diabetes complications. To define diabetes, we used Read codes in CPRD and ICD-10 codes in HES. Codes for gestational diabetes, secondary diabetes such as “diabetes mellitus induced by steroids” and diabetes care codes were excluded.

Polypharmacy

We defined polypharmacy as the concurrent use of 5 or more medications using BNF chapters. We excluded vaccines and devices that do not administer medication. Medication use was captured in the 12 months prior to baseline.

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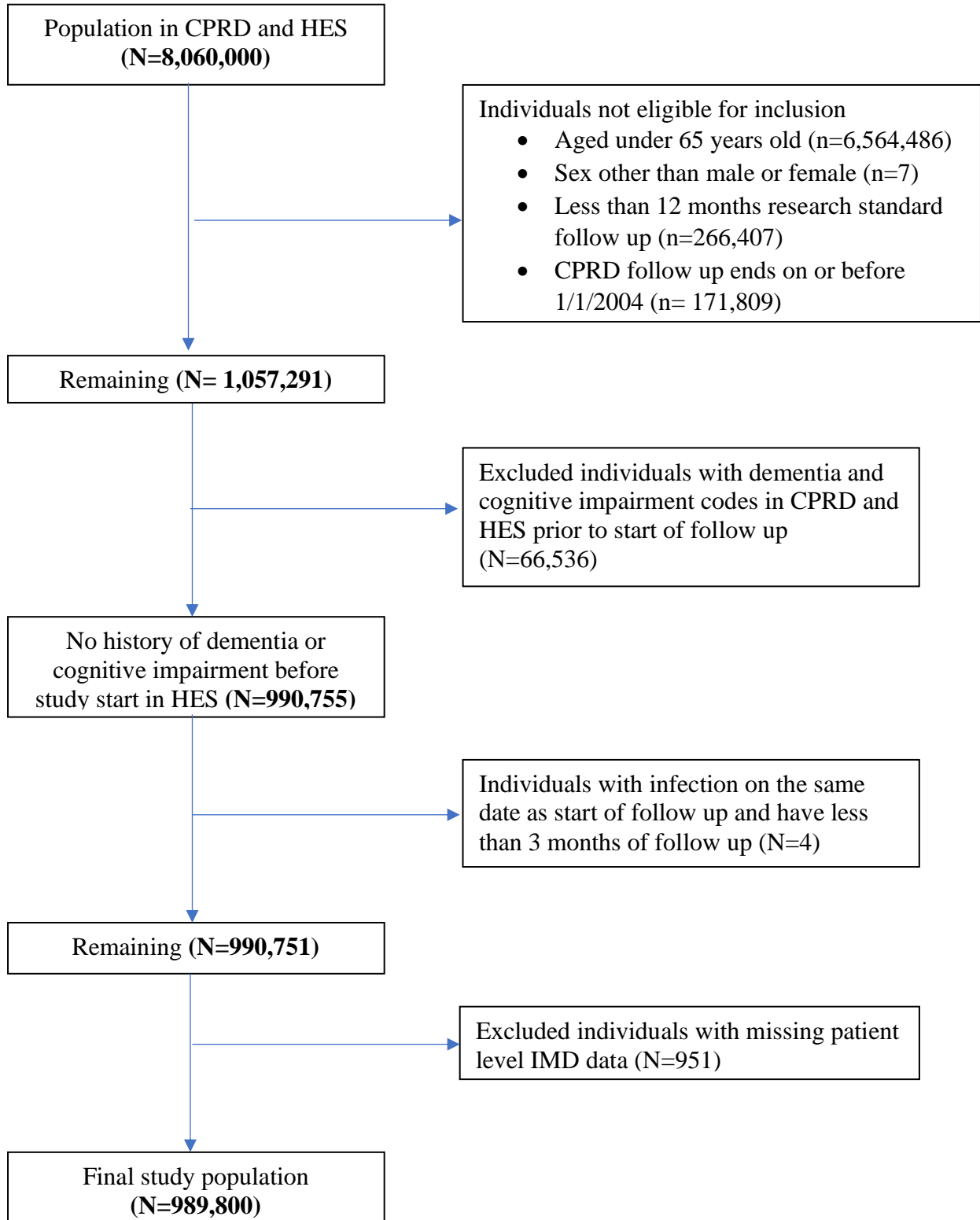
1. Department for Communities and Local Government. English indices of deprivation 2015 : Department for Communities and Local Government,; 2016 [cited Department for Communities and Local Government, . Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/579151/English_Indices_of_Deprivation_2015_-_Frequently_Asked_Questions_Dec_2016.pdf.
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Supplementary Table 1: Sensitivity analyses

Sensitivity analysis	Justification
Primary analyses repeated excluding individuals with secondary dementia causally related to other conditions.	Infections are unlikely to be causally associated with this type of dementia
Primary analyses repeated defining all infections in CPRD with a diagnostic code and prescription for antibiotics	To improve the accuracy of our infection definition
Primary analysis repeated excluding individuals diagnosed with infections from two different sites (e.g. skin and soft tissue infections and pneumonia) on the same date	To avoid any potential biases introduced from including these infections.
We excluded codes relating to symptoms of cognitive impairment from analysis of infections and cognitive impairment	To improve the accuracy of our definition of cognitive impairment

Supplementary Figures

Supplementary Figure 1: Flowchart of study population



Supplementary Table 2. Age-specific incidence rates of dementia during person-time with and without prior common infections.

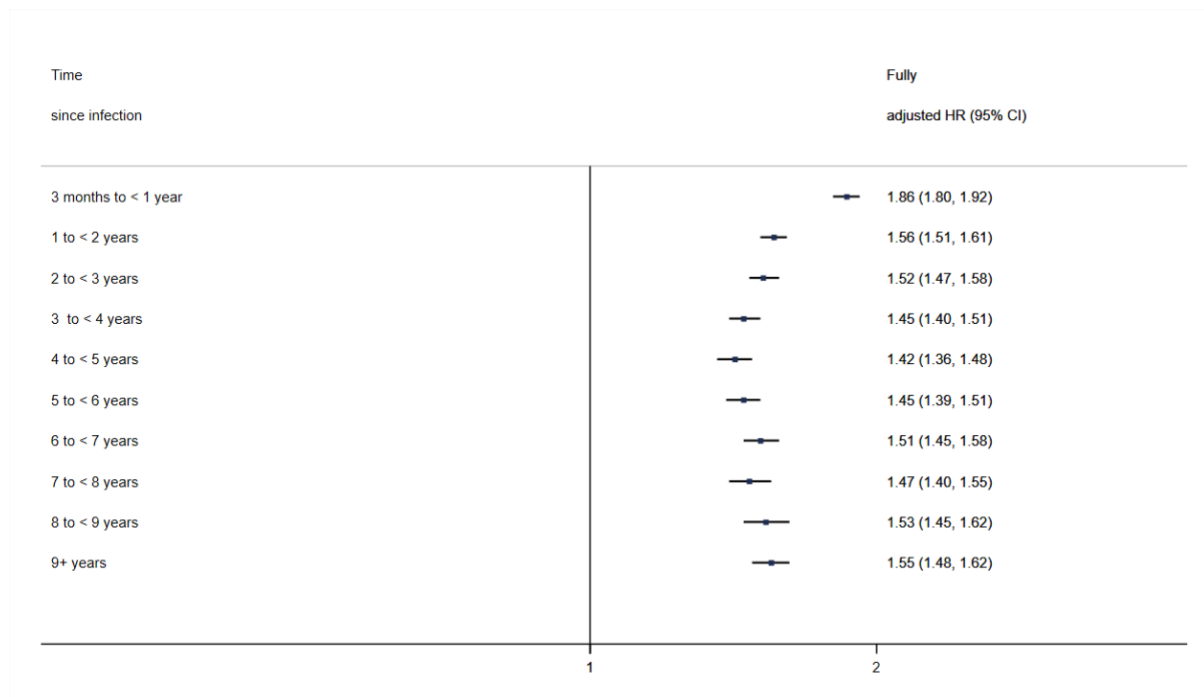
Age group (years)	Person-years	Total number of incident dementia diagnoses	Rate (per 1000-person years)	Lower (95% CI)	Upper (95% CI)
No infections					
65-69	1395965	1263	0.90	0.86	0.96
70-74	935486	2523	2.70	2.59	2.80
75-79	693243	4684	6.76	6.57	6.95
80-84	481002	6697	13.92	13.59	14.26
85-89	258807	6079	23.49	22.91	24.09
90+	130528	4068	31.17	30.22	32.14
Total	3895032	25314	6.50	6.42	6.58
Any infections					
65-69	260196	544	2.09	1.92	2.27
70-74	426037	2104	4.94	4.73	5.15
75-79	408733	4681	11.45	11.13	11.79
80-84	331452	7749	23.38	22.86	23.91
85-89	212080	8865	41.80	40.94	42.68
90+	116458	7545	64.79	63.34	66.27
Total	1754956	31488	17.94	17.75	18.14

Supplementary Table 3. Crude rate and hazard ratios for the association of common infections and dementia, additionally adjusted for potential mediators and BMI

Infection	Total number of incident dementia diagnoses	Person-years at risk	Crude incidence rate (95% CI)	*Fully adjusted HR	**Additionally adjusted for potential mediators HR	***Additionally adjusted for BMI HR
No infection	25314	3895032	6.50 (6.42-6.58)	1.00	1.00	1.00
Any Infection	31488	1754956	17.94 (17.75-18.14)	1.53 (1.50-1.55)	1.65 (1.62-1.68)	1.53 (1.50-1.56)
Sepsis	427	16814	25.40 (23.10-27.92)	2.08 (1.89-2.29)	2.32 (2.11-2.56)	2.07 (1.87-2.29)
Pneumonia	1247	47836	26.07 (24.66-27.56)	1.88 (1.77-1.99)	2.11 (2.00-2.24)	1.88 (1.77-2.00)
Other LRTI	13429	910432	14.75 (14.50-15.00)	1.34 (1.31-1.37)	1.46 (1.42-1.49)	1.35 (1.32-1.38)
UTI	10513	481341	21.84 (21.43-22.26)	1.73 (1.69-1.78)	1.86 (1.82-1.91)	1.73 (1.68-1.77)
SSTI	5535	291603	18.98 (18.49-19.49)	1.54 (1.49-1.58)	1.67 (1.62-1.72)	1.57 (1.52-1.62)

HR, hazard ratio; LRTIs, lower respiratory tract infections (excluding pneumonia); UTI; urinary tract infection, SSTIs, skin and soft tissue infection
 *Age as underlying time scale. * Adjusted for age, sex, patient level IMD, calendar period, ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy. **Additionally adjusted for atrial fibrillation, myocardial infarction and stroke. ***Fully adjusted model additionally adjusted for BMI

Supplementary Figure 2. Forest plot depicting adjusted hazard ratios of the association between common infections and dementia, stratified according to time since infection (non-overlapping time periods)



HR, hazard ratio. Adjusted for age, sex, patient level IMD, calendar period, ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy.

Supplementary Table 4. Crude rate and hazard ratios for the association of common infections and dementia in people with and without diabetes

Infection	Total number of incident dementia diagnoses	Total person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
Individuals without diabetes						
No infection	22610	3523440	6.42 (6.33-6.50)	1.00	1.00	1.00
Any Infection	27141	1543709	17.58 (17.37-17.79)	1.75 (1.72-1.78)	1.61 (1.58-1.64)	1.50 (1.47-1.53)
Individuals with diabetes						
No infection	2704	371592	7.28 (7.01-7.56)	1.00	1.00	1.00
Any Infection	4347	211247	20.58 (19.98-21.20)	1.94 (1.85-2.04)	1.74 (1.66-1.83)	1.70 (1.61-1.79)

HR, hazard ratio; Age as the underlying time scale. ** Adjusted for age, sex, ethnicity, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy. Likelihood ratio test for interaction comparing models with and without interaction term between infections and diabetes, p=0.00014.

Supplementary Table 5. Crude rate and hazard ratios for the association of common infections and cognitive impairment, stratified by type of infection

Infection	Total number of incident cognitive impairment events	Total person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
No infection	34730	3855389	9.01 (8.91-9.10)	1.00	1.00	1.00
Any Infection	32608	1679805	19.41 (19.20-19.62)	1.57 (1.55-1.60)	1.45 (1.42-1.47)	1.29 (1.27-1.32)
Sepsis	340	15763	21.57 (19.39-23.99)	1.74 (1.56-1.93)	1.57 (1.41-1.75)	1.39 (1.25-1.55)
Pneumonia	1110	44972	24.68 (23.27-26.18)	1.83 (1.72-1.94)	1.65 (1.56-1.75)	1.45 (1.36-1.54)
Other LRTI	15527	875906	17.73 (17.45-18.01)	1.50 (1.47-1.53)	1.38 (1.35-1.41)	1.22 (1.20-1.25)
UTI	9627	457755	21.03 (20.61-21.46)	1.63 (1.60-1.67)	1.51 (1.48-1.55)	1.36 (1.33-1.40)
SSTI	5787	279042	20.74 (20.21-21.28)	1.61 (1.56-1.65)	1.48 (1.43-1.52)	1.34 (1.30-1.38)

HR, hazard ratio; LRTIs, lower respiratory tract infections (excluding pneumonia); UTI; urinary tract infection, SSTI, skin and soft tissue infection
 *Age as the underlying time scale. ** Adjusted for age, sex, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy.

Supplementary Table 6: Crude rate and hazard ratios for the association of common infections and dementia, stratified by dementia subtype

Infection	Total number of incident dementia diagnoses	Person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
Alzheimer's Disease						
No infection	7137	3895032	1.83 (1.79-1.88)	1.00	1.00	1.00
Any Infection	6424	1754956	3.66 (3.57-3.75)	1.33 (1.29-1.38)	1.12 (1.08-1.16)	1.09 (1.05-1.13)
Sepsis	54	16814	3.21 (2.46-4.19)	1.16 (0.89-1.52)	0.99 (0.75-1.29)	0.98 (0.75-1.28)
Pneumonia	203	47836	4.24 (3.70-4.87)	1.40 (1.21-1.61)	1.19 (1.04-1.37)	1.15 (1.00-1.33)
Other LRTI	2956	910432	3.25 (3.13-3.37)	1.25 (1.20-1.30)	1.07 (1.02-1.12)	1.03 (0.99-1.08)
UTI	2050	481341	4.26 (4.08-4.45)	1.47 (1.40-1.55)	1.21 (1.15-1.27)	1.17 (1.11-1.23)
SSTI	1126	291603	3.86 (3.64-4.09)	1.34 (1.26-1.43)	1.13 (1.06-1.21)	1.09 (1.02-1.17)
Vascular Dementia						
No infection	5040	3895032	1.29 (1.26-1.33)	1.00	1.00	1.00
Any Infection	7132	1754956	4.06 (3.97-4.16)	2.06 (1.98-2.13)	1.88 (1.81-1.95)	1.69 (1.62-1.76)
Sepsis	119	16814	7.08 (5.91-8.47)	3.54 (2.96-4.25)	3.16 (2.63-3.79)	2.74 (2.28-3.29)
Pneumonia	295	47836	6.17 (5.50-6.91)	2.79 (2.48-3.13)	2.46 (2.19-2.77)	2.08 (1.85-2.35)
Other LRTI	3136	910432	3.44 (3.33-3.57)	1.85 (1.77-1.94)	1.68 (1.60-1.75)	1.50 (1.43-1.58)
UTI	2262	481341	4.70 (4.51-4.90)	2.24 (2.14-2.36)	2.11 (2.01-2.22)	1.89 (1.79-1.99)
SSTI	1242	291603	4.26 (4.03-4.50)	2.05 (1.92-2.18)	1.87 (1.76-1.99)	1.69 (1.59-1.80)
Unspecified Dementia						
No infection	12210	3895032	3.13 (3.08-3.19)	1.00	1.00	1.00
Any Infection	16956	1754956	9.66 (9.52-9.81)	1.92 (1.88-1.97)	1.84 (1.80-1.89)	1.72 (1.67-1.76)
Sepsis	247	16814	14.69 (12.97-16.64)	2.86 (2.52-3.24)	2.79 (2.46-3.17)	2.51 (2.21-2.85)
Pneumonia	716	47836	14.97 (13.91-16.11)	2.55 (2.36-2.75)	2.46 (2.28-2.65)	2.22 (2.05-2.39)
Other LRTI	6909	910432	7.59 (7.41-7.77)	1.64 (1.59-1.69)	1.57 (1.53-1.62)	1.46 (1.41-1.51)
UTI	5861	481341	12.18 (11.87-12.49)	2.25 (2.18-2.33)	2.14 (2.07-2.21)	1.99 (1.92-2.05)
SSTI	3009	291603	10.32(9.96-10.69)	1.93 (1.85-2.00)	1.86 (1.79-1.94)	1.74 (1.67-1.81)

HR, hazard ratio; LRTIs, lower respiratory tract infections (excluding pneumonia); UTI; urinary tract infection, SSTIs, skin and soft tissue infection
 *Age as underlying time scale. ** Adjusted for age, sex, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy

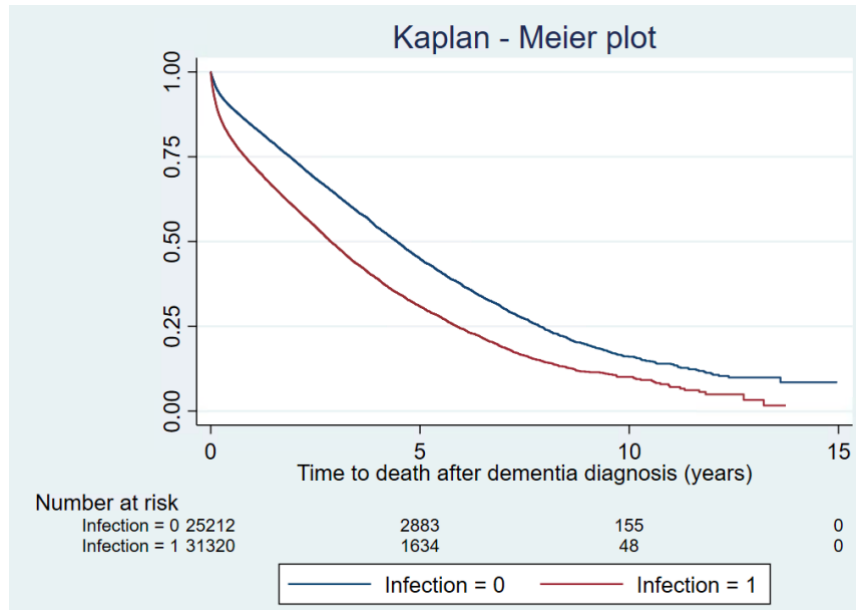
Supplementary Table 7: Crude rate and hazard ratios for the association of common infections and dementia, stratified by sex

Infection	Total number of incident dementia diagnoses	Person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
Female						
No infection	15427	2043935	7.55 (7.43-7.67)	1.00	1.00	1.00
Any infection	20658	1065696	19.38 (19.12-19.65)	1.75 (1.71-1.79)	1.61 (1.58-1.65)	1.51 (1.48-1.55)
Sepsis	219	7641	28.66 (25.11-32.72)	2.51 (2.20-2.87)	2.30 (2.01-2.63)	2.11 (1.84-2.42)
Pneumonia	650	21756	29.88 (27.67-32.26)	2.20 (2.03-2.38)	1.99 (1.84-2.16)	1.81 (1.67-1.96)
Other LRTI	7979	495893	16.09 (15.74-16.45)	1.55 (1.51-1.59)	1.42 (1.38-1.46)	1.33 (1.29-1.37)
UTI	8124	373232	21.77 (21.30-22.25)	1.94 (1.89-1.99)	1.80 (1.75-1.85)	1.68 (1.64-1.73)
SSTI	3469	162895	21.30 (20.60-22.02)	1.73 (1.66-1.79)	1.59 (1.53-1.65)	1.51 (1.45-1.57)
Male						
No infection	9887	1851097	5.34 (5.24-5.45)	1.00	1.00	1.00
Any infection	10830	689261	15.71 (15.42-16.01)	1.83 (1.78-1.88)	1.69 (1.64-1.74)	1.56 (1.51-1.60)
Sepsis	208	9173	22.67 (19.79-25.98)	2.53 (2.21-2.91)	2.30 (2.01-2.64)	2.08 (1.81-2.39)
Pneumonia	597	26080	22.89 (21.13-24.80)	2.42 (2.23-2.63)	2.20 (2.03-2.39)	1.98 (1.82-2.15)
Other LRTI	5450	414539	13.15 (12.80-13.50)	1.61 (1.56-1.67)	1.49 (1.44-1.54)	1.37 (1.33-1.42)
UTI	2389	108109	22.10 (21.23-23.00)	2.25 (2.15-2.36)	2.09 (2.00-2.19)	1.90 (1.81-1.99)
SSTI	2066	128708	16.05 (15.37-16.76)	1.88 (1.79-1.97)	1.73 (1.64-1.81)	1.58 (1.51-1.66)

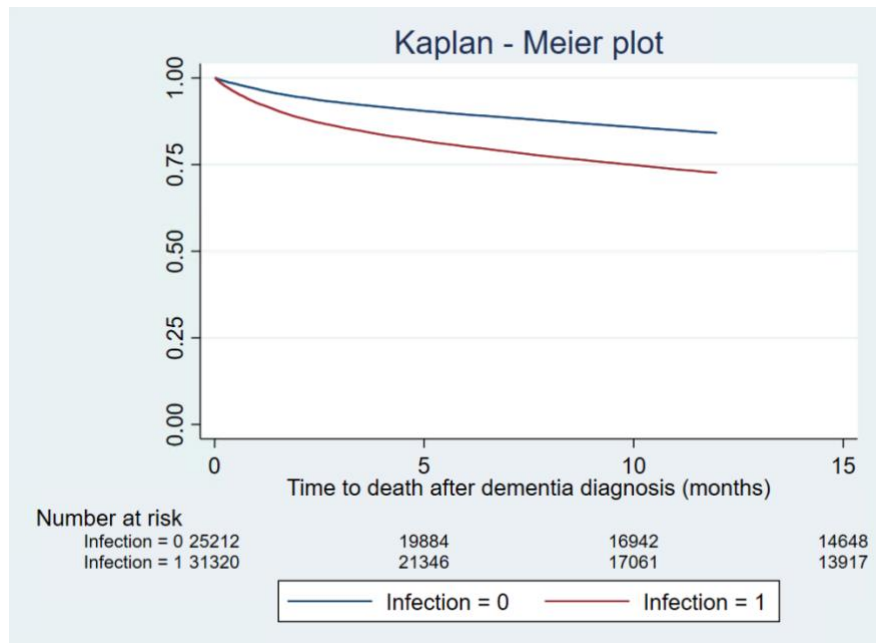
HR, hazard ratio; LRTIs, lower respiratory tract infections (excluding pneumonia); UTI; urinary tract infection, SSTIs, skin and soft tissue infection

*Age as underlying time scale. ** Adjusted for age, sex, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy.

Supplementary Figure 3: Kaplan-Meier survival curve depicting the time to death after a dementia diagnosis in years



Supplementary Figure 4: Kaplan-Meier survival curve depicting the time to death 12 months after dementia diagnosis



Supplementary Table 8: Crude rate and hazard ratios for the association of common infections and dementia, stratified by age

Infection	Total number of incident dementia diagnoses	Total person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
65-79						
No infection	8470	3024694	2.80 (2.74-2.86)	1.00	1.00	1.00
Any Infection	7329	1094966	6.69 (6.54-6.85)	1.72 (1.67-1.78)	1.60 (1.55-1.66)	1.43 (1.38-1.48)
80-89						
No infection	12776	739810	17.27 (16.97-17.57)	1.00	1.00	1.00
Any infection	16614	543532	30.57 (30.11-31.04)	1.72 (1.68-1.76)	1.57 (1.53-1.60)	1.49 (1.46-1.53)
90 years and older						
No infection	4068	130528	31.17 (30.22-32.14)	1.00	1.00	1.00
Any infection	7545	116458	64.79 (63.34-66.27)	2.07 (1.99-2.15)	1.89 (1.82-1.97)	1.76 (1.69-1.84)

*Age as underlying time scale. ** Adjusted for age, sex, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy.

Supplementary Table 9: Crude rate and hazard ratios for the association of common infections and dementia, stratified by age (<90 and 90> years)

Infection	Total number of incident dementia diagnoses	Total person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
<90 years old						
No infection	21246	3764504	5.64 (5.57-5.72)	1.00	1.00	1.00
Any Infection	23943	1638498	14.61 (14.43-14.80)	1.72 (1.69-1.75)	1.58 (1.55-1.61)	1.47 (1.44-1.50)
90 years and older						
No infection	4068	130528	31.17 (30.22-32.14)	1.00	1.00	1.00
Any infection	7545	116458	64.79 (63.34-66.27)	2.07 (1.99-2.15)	1.89 (1.82-1.97)	1.76 (1.69-1.84)

*Age as underlying time scale. ** Adjusted for age, sex, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy.

Supplementary Table 10: Crude rate and hazard ratios for the association of common infections and dementia, with interaction between age and non-proportional covariates (sex, ethnicity, patient-level IMD, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, chronic kidney disease, hypertension, traumatic brain injury, benzodiazepines and polypharmacy)

Infection	Total number of incident dementia diagnoses	Total person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
No infection	25314	3895032	6.50 (6.42-6.58)	1.00	1.00	1.00
Any Infection	31488	1754956	17.94 (17.75-18.14)	1.78 (1.75-1.81)	1.64 (1.61-1.66)	1.52 (1.49-1.55)

*Age as underlying time scale. ** Adjusted for age, sex, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy.

Supplementary Table 11: Crude rate and hazard ratios for the association of common infections and dementia, excluding dementia related to other diseases

Infection	Total number of incident dementia diagnoses	Person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
No infection	24387	3890864	6.27 (6.19-6.35)	1.00	1.00	1.00
Any Infection	30512	1751183	17.42 (17.23-17.62)	1.78 (1.75-1.81)	1.63 (1.61-1.66)	1.52 (1.50-1.55)
Sepsis	420	16789	25.02 (22.74-27.53)	2.52 (2.29-2.78)	2.32 (2.10-2.55)	2.11 (1.91-2.32)
Pneumonia	1214	47753	25.42 (24.03-26.89)	2.28 (2.15-2.41)	2.08 (1.96-2.20)	1.87 (1.77-1.99)
Other LRTI	13001	908633	14.31 (14.06-14.56)	1.57 (1.54-1.60)	1.44 (1.41-1.47)	1.34 (1.31-1.37)
UTI	10173	480182	21.19 (20.78-21.60)	2.03 (1.99-2.08)	1.85 (1.81-1.90)	1.71 (1.67-1.76)
SSTI	5377	290917	18.48 (18.00-18.98)	1.78 (1.73-1.84)	1.64 (1.59-1.69)	1.53 (1.48-1.58)

HR, hazard ratio; LRTIs, lower respiratory tract infections (excluding pneumonia); UTI; urinary tract infection, SSTIs, skin and soft tissue infection
 *Age as underlying time scale. ** Adjusted for age, sex, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy.

Supplementary Table 12: Crude rate and hazard ratios for the association of common infections and dementia, according to definition of infections

Infection	Total number of incident dementia diagnoses	Person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
All infections in CPRD treated with antibiotics						
No infection	27548	4003253	6.88 (6.80-6.96)	1.00	1.00	1.00
Any infection	29503	1653011	17.85 (17.65-18.05)	1.71 (1.69-1.74)	1.57 (1.55-1.60)	1.47 (1.44-1.50)
Sepsis	372	13620	27.31 (24.67-30.23)	2.53 (2.28-2.80)	2.32 (2.09-2.57)	2.13 (1.92-2.36)
Pneumonia	1109	41212	26.91 (25.37-28.54)	2.23 (2.10-2.37)	2.03 (1.91-2.16)	1.84 (1.73-1.95)
Other LRTIs	11635	818240	14.22 (13.96-14.48)	1.48 (1.45-1.52)	1.36 (1.33-1.39)	1.27 (1.24-1.30)
UTI	10511	481330	21.84 (21.42-22.26)	1.96 (1.91-2.00)	1.79 (1.75-1.84)	1.67 (1.63-1.71)
SSTI	5535	291627	18.98 (18.49-19.49)	1.71 (1.66-1.76)	1.58 (1.53-1.63)	1.48 (1.44-1.52)
Excluding multiple infection diagnoses						
No infection	25314	3875552	6.53 (6.45-6.61)	1.00	1.00	1.00
Any infection	31151	1748025	17.82 (17.62-18.02)	1.75 (1.72-1.78)	1.61 (1.58-1.64)	1.50 (1.47-1.53)

HR, hazard ratio; LRTIs, lower respiratory tract infections (excluding pneumonia); UTI; urinary tract infection, SSTIs, skin and soft tissue infection
 *Age as underlying time scale. ** Adjusted for age, sex, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy.

Supplementary Table 13: Crude rate and hazard ratios for the association of common infections and cognitive impairment, excluding codes related to symptoms of cognitive impairment

Infection	Total number of incident cognitive impairment diagnoses	Person-years at risk	Crude incidence rate (95% CI)	*Age-adjusted HR (95% CI)	**Age, sex, IMD and calendar period adjusted HR (95% CI)	***Fully adjusted HR (95% CI)
No infection	5297	3102598	1.71 (1.66-1.75)	1.00	1.00	1.00
Any Infection	7243	1471353	4.92 (4.81-5.04)	1.93 (1.86-2.00)	1.74 (1.68-1.81)	1.62 (1.56-1.68)
Sepsis	97	14809	6.55 (5.37-7.99)	2.40 (1.96-2.93)	2.04 (1.67-2.50)	1.86 (1.52-2.27)
Pneumonia	316	41986	7.53 (6.74-8.40)	2.43 (2.17-2.72)	2.08 (1.85-2.33)	1.87 (1.67-2.10)
Other LRTI	3191	821156	3.89 (3.75-4.02)	1.50 (1.44-1.57)	1.33 (1.27-1.39)	1.21 (1.16-1.27)
UTI	2240	425612	5.26 (5.05-5.49)	1.82 (1.73-1.91)	1.68 (1.60-1.77)	1.57 (1.49-1.65)
SSTI	1332	258961	5.14 (4.87-5.43)	1.78 (1.68-1.89)	1.58 (1.49-1.68)	1.48 (1.40-1.58)

HR, hazard ratio; LRTIs, lower respiratory tract infections (excluding pneumonia); UTI; urinary tract infection, SSTIs, skin and soft tissue infection
 *Age as underlying time scale. ** Adjusted for age, sex, patient level IMD and calendar period *** additionally adjusted for ethnicity, smoking status, heavy alcohol consumption, anxiety and depression, severe mental illness, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, psoriasis, asthma, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, diabetes mellitus, heart failure, hypertension, obstructive sleep apnoea, stroke, traumatic brain injury, benzodiazepines, proton pump inhibitors, systemic corticosteroids and polypharmacy.