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Associations of hospital-treated infections with subsequent dementia: nationwide 30-year analysis

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Infections, which can prompt neuroinflammation, may be a risk factor for dementia[1–5]. More information is needed concerning associations across different infections and different dementias, and from longitudinal studies with long follow-ups. This New Zealand-based population register study tested whether infections antedate dementia across three decades. We identified individuals born between 1929 and 1968 and followed them from 1989 to 2019 (n = 1,742,406, baseline age = 21–60 years). Infection diagnoses were ascertained from public hospital records. Dementia diagnoses were ascertained from public hospital, mortality and pharmaceutical records. Relative to individuals without an infection, those with an infection were at increased risk of dementia (hazard ratio 2.93, 95% confidence interval 2.68–3.20). Associations were evident for dementia diagnoses made up to 25–30 years after infection diagnoses. Associations held after accounting for preexisting physical diseases, mental disorders and socioeconomic deprivation. Associations were evident for viral, bacterial, parasitic and other infections, and for Alzheimer's disease and other dementias, including vascular dementia. Preventing infections might reduce the burden of neurodegenerative conditions.

Prevention and control of infectious diseases through vaccination and antibiotic treatment have lengthened life expectancy[6]. However, many low-income and lower-middle-income countries have limited vaccine coverage[7], and infection prevalence remains high in some industrialized nations[8–10]. In this study, we leveraged nationwide administrative data from New Zealand to investigate the link between infections and dementia.

Common infections have been associated with cognitive impairment in older adults[11,12], and reports also indicate associations with dementia[1–4,13–17]. Several mechanisms have been hypothesized to explain this association[2,3,18–20]. With few exceptions[2–4,13,16], previous studies linking infections and dementia have generally used cross-sectional designs, or longitudinal designs with follow-up periods of less than 10 years; considered only a narrow range of infections; and have not tested associations across different dementia types. Studies that ascertain participants from younger ages and follow them for long periods are necessary to improve our understanding of the temporal relationship between infections and dementia. Furthermore, as dementia has a long pre-diagnosis phase, long follow-ups are necessary to reduce the potential for reverse causation. Measuring a broad range of infections

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Table 1 | Associations between infections and subsequent dementia in the New Zealand population

Birth years and ages	Total *n*	*n* (%) men	Men			Women		
			n (%) with infection	*n* (%) with dementia	HR (95% CI)	*n* (%) with infection	*n* (%) with dementia	HR (95% CI)
Born 1959–1968; aged 21–60 years	603,348	306,375 (50.8)	63,132 (20.6)	369 (0.1)	4.51 (3.63–5.60)	70,059 (23.6)	270 (0.1)	4.12 (3.21–5.29)
Born 1949–1958; aged 31–70 years	511,041	259,482 (50.8)	61,017 (23.5)	1,410 (0.5)	3.14 (2.81–3.50)	50,598 (20.1)	1,056 (0.4)	4.54 (4.01–5.14)
Born 1939–1948; aged 41–80 years	373,419	188,718 (50.5)	60,414 (32.0)	5,121 (2.7)	2.48 (2.34–2.62)	48,810 (26.4)	4,377 (2.4)	3.55 (3.34–3.77)
Born 1929–1938; aged 51–90 years	254,601	127,302 (50.0)	57,252 (45.0)	11,589 (9.1)	2.55 (2.46–2.65)	54,051 (42.5)	13,014 (10.2)	3.14 (3.03–3.25)

Estimates show the associations between individuals' index infection (their first diagnosed infection during the observation period) and subsequent dementia, controlling for birth year and for mental disorders and chronic physical diseases diagnosed before the index infection. Mental disorders included substance use, psychotic, mood, neurotic (that is, anxiety), physiological disturbance, personality, developmental, behavioral and unspecified disorders, as well as self-harm. Physical diseases included coronary heart disease, gout, chronic obstructive pulmonary disease, diabetes, cancer, traumatic brain injury, stroke and myocardial infarction. Counts were randomly rounded to a base of three per the confidentiality rules of Statistics New Zealand. Age ranges indicate ages during the 30-year observation period.

and dementias can also aid in determining the specificity of associations and provide insight into underlying mechanisms, for instance, by identifying whether associations are unique to certain pathogens.

The current study addressed these gaps. We analyzed prospective associations between infections and dementia using population register data on 1.7 million individuals followed for up to 30 years. We tested the hypothesis that hospital-treated infections are associated with an elevated risk of dementia. We tested whether associations are present across different types of infections (viral, bacterial, parasitic and other infections), and for Alzheimer's disease (AD), other dementias (for example, vascular dementia, Parkinson's disease (PD) dementia, frontotemporal dementia) and unspecified dementias. To address the potential for ascertainment bias and reverse causation related to dementia's long pre-diagnosis phase, we also tested whether associations with dementia held across varying follow-up intervals, up to 25–30 years after infection. We tested whether associations held after controlling for preexisting mental disorders and chronic physical diseases because poor mental and physical health may increase the risk for both infection and dementia[21–24]. In addition, we tested whether associations held after controlling for socioeconomic deprivation because both infections and dementias are more common among individuals living in deprived circumstances[8,25–27].

Results

The study population included 1,742,406 individuals (881,877 (50.6%) male, baseline age = 21–60 years). Of these individuals, 254,601 (14.6%) were born between 1929 and 1938, 373,419 (21.4%) between 1939 and 1948, 511,041 (29.3%) between 1949 and 1958, and 603,348 (34.6%) between 1959 and 1968.

During the 30-year period, 465,330 individuals (26.7%) were identified as having an infection and 37,212 (2.1%) were identified as having dementia. Similar percentages of men and women and more older than younger individuals were identified as having an infection and as having dementia (Table 1).

Figure 1 shows the distributions of age-at-first-infection and age-at-first-dementia diagnosis among individuals who received both diagnoses during the observation period. The median age-at-first-dementia diagnosis was 9.3 years later than the median age-at-first-infection diagnosis in the population, with similar degrees of temporal separation in men and women. The time span between median age-at-first-diagnosis for infection and dementia ranged from 8.5 years in the earliest-born, eldest cohort to 13.0 years in the latest-born, youngest cohort.

Associations of infections with dementia

Dementia was overrepresented among individuals with an infection: of individuals diagnosed with an infection, 5.3% (24,696 of 465,330) were also diagnosed with dementia during the observation period, compared with 1.0% of individuals (12,519 of 1,277,076) without an infection (Fig. 2a). Dementia was overrepresented among infection cases in men, women and all age bands (Fig. 2b,c).

A substantial portion of individuals with dementia had an infection history: of individuals diagnosed with dementia, 66.4% (24,696 of 37,212) were also diagnosed with an infection during the observation period, compared with 25.8% of individuals (440,634 of 1,705,194) without dementia.

Individuals with an infection diagnosis were at elevated risk of subsequent dementia; this was the case even after accounting for individuals who received a mental disorder or physical disease diagnosis

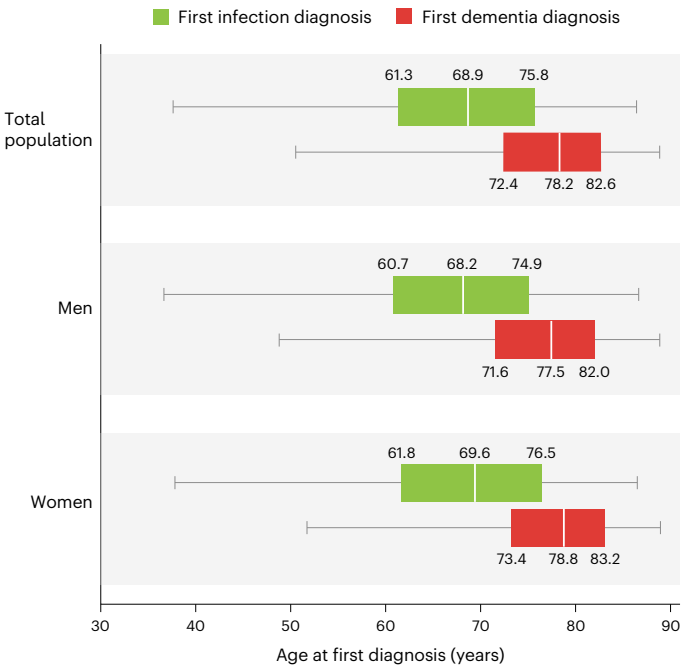

Fig. 1 | Distributions of age-at-first-diagnosis for infection and dementia. Degree of temporal separation between first inpatient hospital diagnoses of infection and dementia. The box plots display the median, first and third quartiles, and bottom first and upper 99th percentiles of the distributions of age-at-first-diagnosis, within the total population, and for men and women. The confidentiality rules of Statistics New Zealand do not permit reporting of minimum and maximum values. Distributions were calculated for individuals who had both an infection and a dementia diagnosis during the observation period (n = 24,696).

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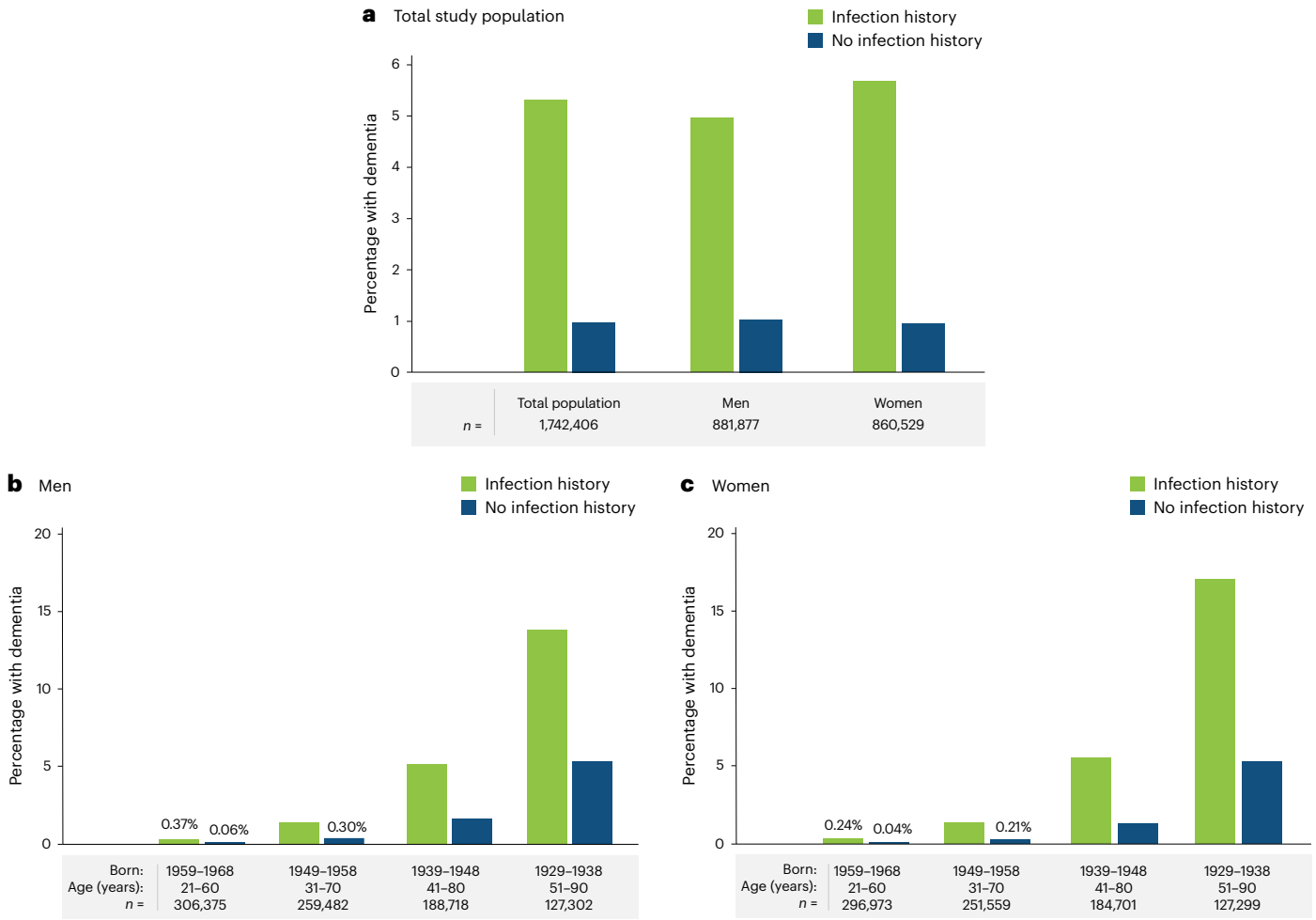

Fig. 2 | Overrepresentation of dementia among individuals with an infection. **a**–**c**, Prevalence of dementia diagnoses was higher among individuals diagnosed with an infection than among those without an infection diagnosis. This was the case in the total study population (**a**), and among men (**b**) and women (**c**) of all ages. Estimates were calculated over the 30-year observation period. Counts were randomly rounded to a base of three per the confidentiality rules of Statistics New Zealand. Therefore, counts do not always sum to totals. Age ranges indicate ages during the 30-year observation period.

before their index infection diagnosis (hazard ratio (HR) = 2.93, 95% confidence interval (CI) = 2.68–3.20). Increased risk was maintained across all follow-up intervals from the index infection, ranging from 0–1 years (HR = 2.64, 95% CI = 2.38–2.94) to 25–30 years (HR = 3.60, 95% CI = 3.08–4.20; Extended Data Fig. 1). Among individuals diagnosed with dementia, those diagnosed with an infection developed dementia, on average, 2.72 years earlier than those without an infection diagnosis (mean time to dementia: infection = 8.75 years, no infection = 11.47 years; Supplementary Results 1). Associations of infection with dementia were observed across sex and age (Table 1). Associations were stronger among more recently-born, younger cohorts. Associations in earlier-born, older cohorts were stronger in women than men (Table 1).

Additionally, in a dose–response pattern, individuals who accumulated more infection-related hospital admissions, across a 20-year exposure period, were more likely to be diagnosed with dementia in the 10-year follow-up period. After accounting for preexisting mental disorders and physical illnesses, the relative risks were 1.55 (95% CI = 1.50–1.60) for one infection-related admission and 2.43 (95% CI = 1.98–2.97) for two or more infection-related admissions, relative to no admission. The increase in risk was modest for the number of infection types: relative risks ranged from 1.53 (95% CI = 1.48–1.59) for one type to 1.76 (95% CI = 1.33–2.32) for four types, relative to no infection diagnosis (Extended Data Fig. 2).

Associations across infection types

Individuals diagnosed with viral, bacterial, parasitic and all other infections were all more likely than those without an infection to be diagnosed with subsequent dementia, even after accounting for their mental disorder and physical disease histories (Fig. 3a and Supplementary Table 1). HRs ranged from 3.19 (95% CI = 2.88–3.53) for other infections to 3.84 (95% CI = 3.37–4.38) for parasitic infections (Fig. 3a).

Associations across dementia types

Individuals diagnosed with infections were more likely than those without an infection to develop different types of dementia, even after accounting for their mental disorder and physical disease histories (Fig. 3b and Supplementary Table 1). Individuals with an infection diagnosis were at elevated risk for AD (HR = 2.28, 95% CI = 2.11–2.48); other dementias (HR = 4.39, 95% CI = 3.83–5.04), including vascular dementia (HR = 4.60, 95% CI = 4.31–4.92; Supplementary Table 2); and unspecified dementias (HR = 2.65, 95% CI = 2.38–2.96; Fig. 3b).

Sensitivity analyses

The dementia ascertainment scheme drew on information gathered from hospital records over 30 years, death records over 29 years and pharmaceutical records available for 9 years. To determine whether findings depended on these information sources, we reestimated associations after removing mortality and pharmaceutical records,

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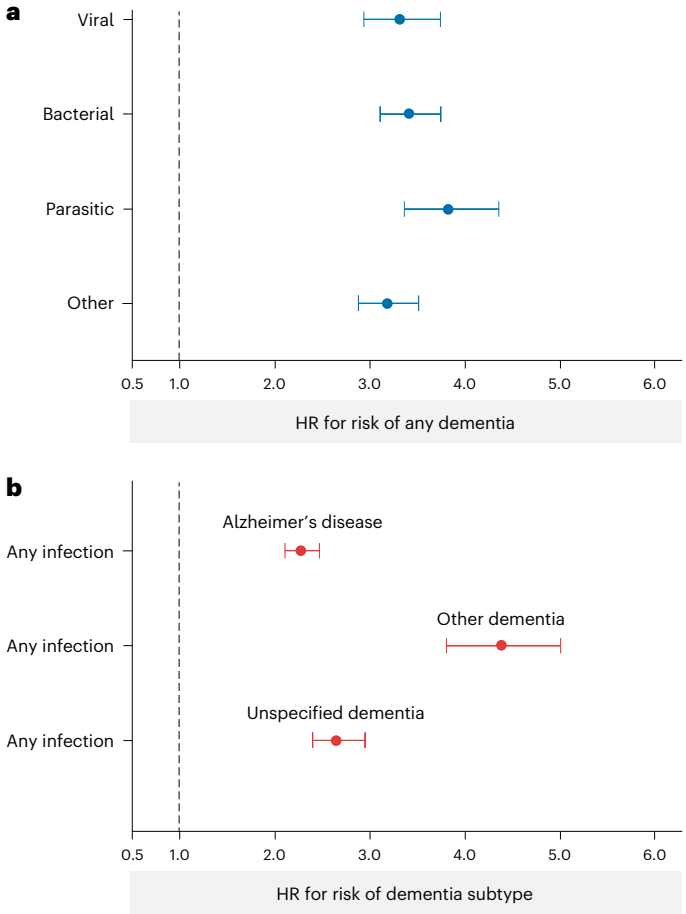

Fig. 3 | Specificity of associations. a,**b**, Infections of different types were associated with subsequent onset of any dementia (**a**); infections were associated with Alzheimer's disease (AD), other dementias (for example, vascular dementia, Parkinson's disease dementia, frontotemporal dementia) and unspecified dementias (**b**). Estimates are shown as HRs. Error bars indicate the 95% CIs. Total population numbers, including infection cases and controls, were 1,316,880 (viral infection), 1,489,080 (bacterial infection), 1,288,707 (parasitic infection) and 1,538,523 (other infection). Total population numbers, including dementia cases and controls, were 1,710,144 (AD), 1,716,513 (other dementia) and 1,727,412 (unspecified dementia). Controls were individuals without any infection diagnosis (**a**) and individuals without any dementia diagnosis (**b**). Due to computational constraints, hazard models could not be estimated in the total population. Total population estimates were derived using meta-analysis to pool associations across four randomly selected 25% subsets of males and females. Associations were estimated within subsets controlled for birth year and for preexisting mental disorder and chronic physical disease diagnoses (Methods). Because anti-dementia drug prescriptions in pharmaceutical records do not permit determination of dementia subtype, diagnoses of AD and other dementias were ascertained using International Classification of Diseases, Tenth Revision (ICD-10) and corresponding International Classification of Diseases, Ninth Revision (ICD-9) codes from public hospital and mortality records; dementias with diagnostic codes of 'unspecified' in hospital or mortality records and those ascertained only through pharmaceutical prescriptions were coded as unspecified. Associations by age and sex are shown in Supplementary Tables 1 and 2.

separately, from the ascertainment scheme. Associations after removing pharmaceutical records were larger (Supplementary Table 3). Associations after removing mortality records were smaller, but robust (Supplementary Table 4).

We evaluated additional sources of potential confounding of the infection–dementia association (Supplementary Table 5). To test whether associations were attributable to socioeconomic differences, we controlled for neighborhood deprivation. Effect sizes were attenuated, but robust (from HR = 2.93, 95% CI = 2.68–3.20 to HR = 2.08, 95% CI = 2.04–2.13). To assess the potential for unmeasured confounding to explain the association, we computed an E-value[28]. The association between infection and dementia (HR = 2.08, 95% CI = 2.04–2.13) could only be explained away by an unmeasured confounder associated with both infection and dementia by a risk ratio of at least 3.58-fold each, above and beyond the measured confounders of mental disorder and physical disease histories and deprivation.

Discussion

In this nationwide health register study of 1.7 million citizens followed for up to 30 years, hospital-treated infections were associated with increased risk for subsequent dementia and younger dementia onset. Associations were evident across viral, bacterial, parasitic and other infections; early-onset and later-onset dementias; AD and other, related dementias; men and women; and all age groups. They also persisted across varying follow-up intervals from the index infection and up to 25–30 years after infection, suggesting that associations were not attributable to ascertainment bias or reverse causation. Associations remained after accounting for preexisting mental disorders and physical diseases, and socioeconomic deprivation.

These results have several implications. First, if associations are causal, preventing infections—at least more severe infections requiring hospital treatment—may reduce dementia risk. We identified associations with multiple infection types, suggesting that preventing any type of infection might benefit cognitive health. It is important to note that these data cannot confirm causality. We established the temporal ordering of infections before dementia, addressed reverse causation and ruled out poor mental and physical health and neighborhood deprivation as alternative explanations for associations. However, there may be other shared risk factors for infections and dementia; for instance, a general vulnerability to both poor body and brain health (including age-related vulnerabilities such as frailty) and low education. Even if infections are not a causal dementia risk factor, our results indicate they are an important early warning sign of risk for cognitive decline and neurodegenerative disease.

Second, the lack of specificity that we observed in associations provides insights into potential underlying mechanisms. It has been proposed that specific infectious agents invade the brain and lead to dementia; studies linking pathogens such as herpes simplex virus, *Helicobacter pylori*, hepatitis C and influenza viruses with dementia support this hypothesis[16,29–31]. However, we detected associations with a broad range of infectious diseases, supporting the proposal that systemic inflammation (or some other general process), rather than specific pathogens, may lead to dementia. This conclusion is bolstered by previous human studies linking different types of infections with dementia[1–4], as well as nonhuman animal studies that identified associations between systemic inflammation and neuroinflammation[32].

The antimicrobial protection hypothesis states that amyloid-β plaques form in response to invading pathogens, then lead to neuroinflammation and AD[20]. Our findings extend beyond this hypothesis in that dementias other than AD (for example, vascular, frontotemporal and PD dementias) were associated with infections. This aligns with work implicating neuroinflammation in the etiology of many dementia types[5], and a recent study demonstrating associations between infections and dementias beyond AD, including vascular dementia[3]. However, different hypotheses concerning factors that link infections with dementia may not be mutually exclusive, and multiple mechanisms may operate. For instance, infections may lead to dementia by increasing vulnerability to health conditions that confer dementia risk, including depression and stroke[22,33,34]. Moreover, neuropathologies such as amyloid-β plaques may be less specific than assumed to AD versus other dementia types[35,36]. Future research should aim to interrogate potential differences in how different types of infections may confer risk for AD versus other dementias, as the findings in this study suggest that all infections matter.

Third, our findings suggest that infections predict dementia more strongly among recently-born, younger adults than earlier-born, older adults. This age-cohort difference in effect size is consistent with previous studies documenting stronger associations with hospital-treated infections for early-onset than late-onset dementias[3,4], suggesting that infections may confer greater risk for early-onset conditions. However, there are alternate explanations for this age-cohort difference. Individuals who have experienced infections—particularly severe infections requiring inpatient hospital treatment—tend to die earlier than individuals without an infection history, and therefore do not contribute dementia cases to the oldest age groups. Older adults also have more opportunity to accumulate dementia causes other than infection. It should be noted that although this age cohort difference holds in relative risk terms, when considering absolute risk differences, we observed larger differences among earlier-born, older cohorts, where baseline dementia risk was also higher (Fig. 2).

Infections may represent a cause of dementia ('infectious origin theory') or accelerate a dementia disease pathology that is already underway ('infectious accelerant theory')[18]. Our study design did not enable us to determine whether individuals had subtle early dementia signs when diagnosed with infection. If they did, this would suggest that the earlier dementia onset observed among adults with infections likely reflects an acceleration of dementia progression. However, we observed associations across 30 years, with increased risk maintained over time; and the mean time-to-dementia diagnosis after individuals' first infection diagnosis was 8.8 years in the study population and 11.0 years in the youngest cohort. Most infection diagnoses in this cohort were received before the typical age of pre-diagnosis dementia onset. More detailed prospective data concerning dementia progression will adjudicate between the infectious origin and infectious accelerant theories, which may not be mutually exclusive.

Our findings should be evaluated against several limitations. First, our results may not generalize to other nations, ancestry groups or healthcare systems. However, associations between infections and dementia have been observed in other countries[1–4,13,15–17,37]. Second, although nationwide data enabled us to ascertain a broad range of infections from inpatient hospital records, inpatient records overlook less severe cases treated in outpatient settings and undetected cases. However, previous studies have identified associations between infections and dementia ascertained in primary care and outpatient treatment data[2,4]. Furthermore, more severe infections are likely to prompt a greater inflammatory response, providing a stronger test of the potential role of infection-induced inflammation in dementia risk. Third, even with a 30-year observation period, we were selectively missing later-diagnosed dementias in the youngest cohort and earlier-diagnosed infections in the oldest cohort. Fourth, our results were limited to public hospital records. However, only about 5% of New Zealand hospitalizations occur in private hospitals, primarily for elective surgeries[8]. Fifth, results might vary with historical changes in diagnostic practices. However, we observed associations between infections and dementia among individuals born up to 39 years apart. Different birth cohorts in New Zealand lived through different diagnosis and treatment regimens because there were historical changes in medical practice to manage infections and dementia during the 1900s. For example, the first antibiotic, penicillin, became available in the 1940s, which markedly changed infectious disease diagnosis and treatment. Thus, early-born cohorts did not have penicillin as a child, but later-born cohorts did. However, our analysis of the association between infections and dementia focused on the link over a 30-year observation window, between 1989 and 2019. As such, all age groups in this study experienced the same conditions of diagnosis and treatment because the medical records used as data in this study began in 1989. Nevertheless, it is possible that early life experiences could have affected medical status in ways unknown to us. Finally, we lacked data on all factors that could have contributed to an association between infection and dementia, such as chronic kidney disease. However, the E-value we computed indicates that unmeasured confounders would have to show associations with infections and dementia on the scale of 3.58 in terms of relative risk, above and beyond the measured confounders that were included in our analyses (for example, mental disorders such as substance use and depression, chronic physical diseases such as coronary heart disease and stroke, and socioeconomic deprivation).

The infections we studied were treated, but still tended to be followed by dementia, pointing to the importance of primary prevention of infections, which is possible by personal hygiene behaviors, immunization, safe food, safe water and safe sex. Results from our study and others[1–4,13,14,16,17] raise the question of whether infections should be considered a key modifiable risk factor for dementia, alongside other established factors such as depression and physical inactivity[22]. Efforts to mitigate infection and dementia are needed in the context of an aging global population and growing concern about the effects of coronavirus disease 2019 on neuroinflammation, cognitive decline and impairment, and risk for neurological disorders[38–41].

Methods

Data were from the New Zealand Integrated Data Infrastructure (IDI), a collection of de-identified, individually linked, whole-population administrative data sources[42,43]. Ethical approval was obtained from the Auckland Health Research Ethics Committee (ref. AH24164). Output data underwent confidentiality review by Statistics New Zealand Tatauranga Aotearoa. Informed consent was not obtained per rule 11(2)(c)(iii) of the New Zealand Health Information Privacy Code[44], which, under certain circumstances, allows for anonymized health data to be used for research without the authorization of the individual concerned. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

Study population

Our study population included all individuals born in New Zealand between 1929 and 1968 who resided in New Zealand for any time between the July 1989 and June 2019 fiscal years (age = 21–90 years, n = 1,742,406). We included as wide an age range as possible while also capturing the period of risk for dementia (including early-onset conditions) during the 30-year period. We divided the population into 10-year age bands (born 1929–1938 (baseline age = 51–60 years), 1939–1948 (41–50 years), 1949–1958 (31–40 years) and 1959–1968 (21–30 years)).

Infections

We collected information about primary and secondary diagnoses of infections and medical conditions arising from infections (for example, infectious mononucleosis) using ICD-9 and corresponding ICD-10 diagnostic codes in public inpatient hospital records. We classified four types of infections: viral, bacterial, parasitic and all other infections (Supplementary Table 6).

AD and related dementias

We collected information about dementia diagnoses using a previously published scheme[23,45]. Dementias were ascertained via primary and secondary ICD-10 and corresponding ICD-9 dementia codes in public inpatient hospital and mortality records maintained by the New Zealand Ministry of Health, and anti-dementia drug prescriptions in pharmaceutical records maintained by the New Zealand Pharmaceutical Management Agency (Supplementary Table 7). Hospital records were available for the 30-year observation period (July 1989–June 2019), mortality records were available for July 1989–December 2018, and pharmaceutical records were available for November 2010–June 2019. (Pharmaceutical data were available from July 2006, but the first dispensing for prescriptions in our dementia ascertainment scheme occurred in November 2010.) We classified

three types of dementia: AD, other dementias (for example, vascular dementia, PD dementia, frontotemporal dementia) and unspecified dementias. Although it is likely that dementia in the community was under-identified through our medical register-based ascertainment scheme, we have shown that cases identified through this scheme are classified accurately, with most also diagnosed in community-based assessments[23] (Supplementary Results 2).

Covariates

Mental disorders. We classified nine broad categories of mental disorders: substance use, psychotic, mood, neurotic (that is, anxiety), physiological disturbance, personality, developmental, behavioral and unspecified disorders. We also obtained data about self-harm (Supplementary Table 8).

Chronic physical diseases. We obtained information about eight physical diseases classified as chronic by the New Zealand Ministry of Health: coronary heart disease, gout, chronic obstructive pulmonary disease, diabetes, cancer, traumatic brain injury, stroke and myocardial infarction (Supplementary Table 9).

Neighborhood deprivation. We assessed neighborhood deprivation using the 2013 New Zealand Deprivation Index (NZDep2013)[46], an area-level measure of deprivation. NZDep2013 assigns census areas a deprivation decile value ranging from 1 (least deprived) to 10 (most deprived) based on socioeconomic indicators from the 2013 New Zealand Census. Neighborhood deprivation information was available from 2000 to the end of the study period (2019). We used deprivation information for individuals' first registered address during the study period.

Statistics and reproducibility

We used Cox proportional hazards models, with infection diagnosis modeled as a time-varying covariate, to estimate associations between individuals' index infection (first diagnosed infection during the observation period) and subsequent dementia, controlling for mental disorders and physical diseases diagnosed before the index infection. Individuals who died from causes other than dementia, out-migrated or reached the end of the observation period without a dementia diagnosis were censored in the analyses. We used generalized linear models to obtain unadjusted and covariate-adjusted estimates (least squares means) of mean time-to-dementia diagnosis among individuals with and without an infection diagnosis.

To address the potential for ascertainment bias, analyses excluded individuals diagnosed with dementia within 1 month of their infection diagnosis. To further address the potential for ascertainment bias as well as reverse causation related to dementia's long pre-diagnosis phase, in addition to estimating associations across the full 30-year observation period, we estimated associations across varying follow-up intervals from the index infection (0–1, 1–5, 5–10, 10–15, 15–20, 20–25 and 25–30 years). For each follow-up interval, we censored cases where dementia occurred before the start of the interval. Follow-up intervals were nonoverlapping, such that the dementia risk estimated for a particular time interval considered only dementia diagnoses made in the specified interval and did not include risk in the previous years. We analyzed associations for all infections together, then separately according to infection type; and for all dementias together, then separately according to dementia type.

Sensitivity analyses tested whether associations were robust to exclusion of pharmaceutical and mortality records from the dementia ascertainment scheme, and to control for neighborhood deprivation. To assess the potential for unmeasured confounding to explain associations, we computed an E-value, which estimates what the risk ratio would need to be for an unmeasured confounder (or set of confounders) to explain away a relationship[28].

Associations were estimated by age band and sex, among men (in four randomly selected 25% subsets of the male population) and among women (in four randomly selected 25% subsets of the female population), controlling for birth year. Due to computational constraints, hazard models could not be estimated in all men and all women, or in the total population. We therefore used fixed-effects meta-analysis to pool associations across the subsets to derive total population estimates, using the metafor package in R[47].

No sample size calculation was performed because the study population consisted of the entire New Zealand population with the birth years and residency characteristics of interest; we did not subsample from these individuals. These birth year and residency characteristics were the starting point for study population construction; no individuals with these characteristics were excluded. There was no randomization. Researchers were not blinded to experimental conditions as this population register analysis consisted of secondary data and participants were not allocated into experimental groups.

Per the confidentiality rules of Statistics New Zealand, reported frequencies and counts were randomly rounded to a base of three. Therefore, counts do not always sum to totals. Analyses were conducted using SAS Enterprise Guide v.8.3 (SAS Institute) and R v.4.1.2 (R Core Team 2021). The statistical code has been archived at GitHub (https://github.com/leahrr-umich/Infection-Dementia.git) and is available upon request from the corresponding author.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The following administrative databases from the IDI were used in the study: publicly funded hospital discharges, pharmaceutical data, mortality data, address notification, person overseas spell, personal details, resident population table, births and deaths. Information about the databases is located at www.stats.govt.nz/integrated-data/integrated-data-infrastructure/data-in-the-idi. The IDI register data used in this article are stored on Statistics New Zealand servers and cannot be shared by the authors. Access to the IDI is by application to Statistics New Zealand. Information about the application process is available at www.stats.govt.nz/integrated-data/apply-to-use-microdata-for-research/.

Code availability

The statistical code has been archived with GitHub at https://github.com/leahrr-umich/Infection-Dementia.git and is available upon request from the corresponding author.

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Author contributions

L.S.R.-R., A.C., T.E.M. and B.J.M. designed the research. All authors performed the research. L.S.R.-R., M.T.I., S.D., L.K. and B.J.M. analyzed the data. L.S.R.-R., M.T.I., L.K., A.C. and T.E.M. wrote the manuscript. All authors reviewed the manuscript drafts, provided critical feedback and approved the final manuscript.

Competing interests

The authors declare no competing interests.

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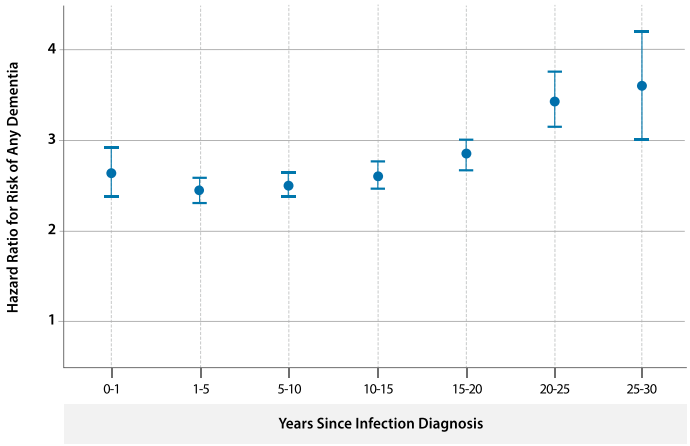

Extended Data Fig. 1 | Associations of infections with dementia across varying follow-up intervals. To address the potential for ascertainment bias as well as reverse-causation related to dementia's long pre-diagnosis phase, we estimated associations across varying follow-up intervals from the index infection (0–1, 1–5, 5–10, 10–15, 15–20, 20–25, and 25–30 years). Increased risk of dementia was observed across varying follow-up intervals from infection, from 0–1 years to 25–30 years. Analyses comprised 1,732,080 individuals; individuals with dementia diagnoses that predated infection diagnoses were excluded. Estimates are hazard ratios. Error bars indicate 95% confidence intervals. Follow-up intervals were non-overlapping, such that dementia risk estimated for a particular time interval considered only dementia diagnoses made in the specified interval, and did not include risk in the prior years.

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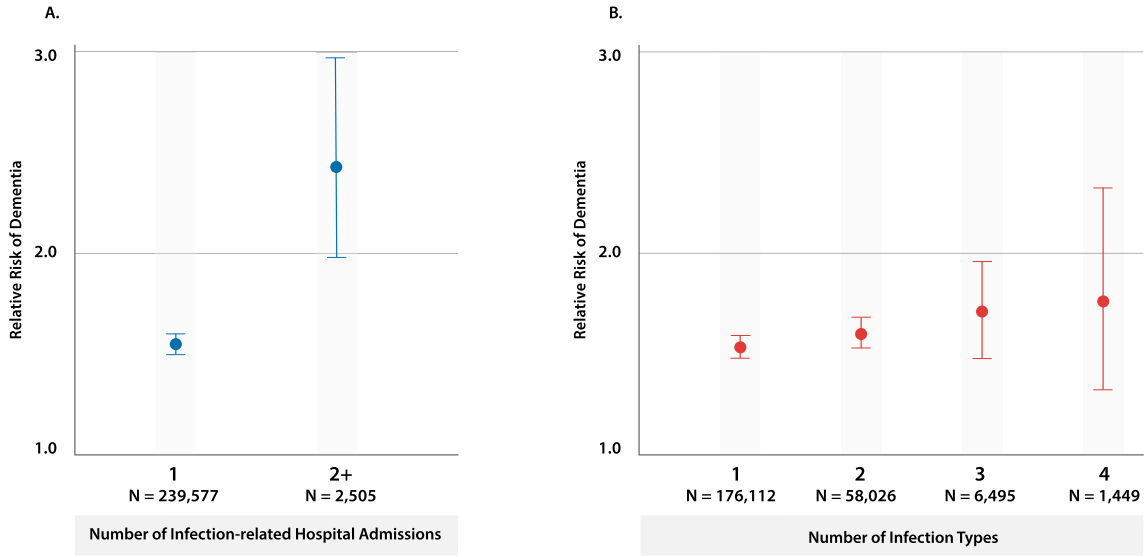

Extended Data Fig. 2 | Tests of a dose-response pattern. In secondary analyses to test for a dose-response pattern, we counted infection-related hospital admissions and infection types across a 20-year exposure period (July 1989-June 2009), and as outcome ascertained dementia diagnoses across a 10-year follow-up period (July 2009-June 2019). We used Poisson regression models with relative risks to estimate the associations between number of infection-related hospital admissions and number of infection diagnoses of different types with subsequent dementia, controlling for mental disorders and physical diseases diagnosed before the index infection. Individuals who accumulated more infection-related hospital admissions (**a**) and more infection diagnoses of different types (**b**), across a 20-year exposure period, were more likely to be diagnosed with dementia in the 10-year follow-up period. Analyses excluded the 169,983 individuals who received a dementia diagnosis, died, or left the country during the exposure period. Error bars indicate 95% confidence intervals.

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Sampling strategy	The study population comprised the entire New Zealand population born between 1929-1968 who resided in the country for any time between the July 1989-June 2019 fiscal years (age = 21-90 years). We divided the population into age-bands (born 1929-38, 1939-48, 1949-58, 1959-68). No sample-size calculation was performed because the study population comprised the entire New Zealand population with the birth years and residency characteristics of interest; we did not subsample from these individuals.
Data collection	Data were from the New Zealand IDI. Output data underwent confidentiality review by Statistics New Zealand Tatauranga Aotearoa. Informed consent was not obtained per rule 11(2)(c)(iii) of the New Zealand Health Information Privacy Code, which, under certain circumstances, allows for anonymized health data to be used for research without the authorization of the individual concerned. Researchers were not blinded to experimental conditions as this population-register analysis comprised secondary data and participants were not allocated into experimental groups.
Timing	Our study population included all individuals born in New Zealand (NZ) between 1929-1968 who resided in NZ for any time between the July 1989-June 2019 fiscal years (age=21-90y, N=1,742,406).
Data exclusions	Our study population included individuals who were born in New Zealand between 1929-1968 and who resided in the country for any time during the July 1989-June 2019 years. These characteristics were the starting point for study-population construction; no individuals with these characteristics were excluded.
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