The role of frailty and comorbidities in severe infections and the risk of dementia: a prospective, multicohort, observational study

Pyry N Sipilä, Jaana Pentti, Philipp Frank, Michael R Duggan, Keenan A Walker, Timo E Strandberg, Joni V Lindbohm, Mika Kivimäki

Summary

Background Severe infections have been linked to an increased risk of dementia, but whether this association reflects pre-existing conditions that predispose individuals to infections and dementia remains unclear. We assessed whether the association between severe infections and dementia risk is explained by pre-existing frailty, comorbidities, or other age-related physical diseases.

Methods This prospective, multicohort, observational study included participants without severe infections or dementia (between Dec 19, 2006, and Oct 1, 2010, from the UK Biobank study and between Oct 8, 2002, and Nov 30, 2004, from the Whitehall II prospective cohort study). The primary analysis was conducted in the UK Biobank cohort. Frailty was assessed at baseline using the widely used phenotypic Fried Frailty Scale and comorbidities were assessed using the Charlson Comorbidity Index and 78 age-related diseases. Incident severe (hospital-treated) infections were identified from linked hospital discharge diagnoses. Follow-up included a 5-year exposure period from baseline, a 2-year washout period; and a final period extending to the end of follow-up. Incident dementia occurring after the exposure and washout periods was ascertained from hospital records and death certificates until 2022 (Oct 31 in England, Sept 30 in Scotland, and May 31 in Wales). Participants with a record of dementia during the exposure period or subsequent washout period were excluded. We repeated the main analyses in the Whitehall II study and conducted several supplementary analyses with follow-up until March 1, 2023.

Findings We included 449 223 participants without severe infection or dementia from the UK Biobank study and 6106 from the Whitehall II study. Most participants were White (424 405 [94·5%] in UK Biobank and 5616 [92·0%] in the Whitehall II study). In UK Biobank, the mean age of participants was 56·5 years (SD 8·1), of whom 245 139 (54·6%) were female and 204 084 (45·4%) were male. Of 435 957 participants with dementia follow-up, 23 860 (5·5%) had a record of severe infection during the 5-year exposure period. After a 2-year washout period, the remaining follow-up for dementia occurred for a mean of 6·5 years (SD 1·2). 6756 participants developed incident dementia, corresponding to an incidence of 2·37 (95% CI 2·31–2·43) per 1000 person-years. Adjustment for frailty resulted in no statistically significant attenuation of the infection and dementia association (adjusted hazard ratio [HR] 1·54 [95% CI 1·43–1·67] for presence *vs* absence of severe infections before adjustment for frailty and 1·49 [1·37–1·61] after adjustment). The association was also evident within a subgroup of non-frail participants (1·34 [1·18–1·53]). Pre-frail and frail participants had a higher corresponding adjusted HR (1·62 [1·47–1·79]). In the Whitehall II study, the mean age of participants was 60·6 years (SD 6·0), of whom 1772 (29·0%) of 6106 were female and 4334 (71·0%) were male. Of 5824 participants available for dementia follow-up, 237 (4·1%) had a record of infection during the 5-year exposure period. After a 2-year washout period, the remaining mean follow-up for dementia was 11·3 years (SD 2·9). 545 incident cases of dementia were recorded (incidence 8·3 per 1000 person-years). Findings in the Whitehall II study, using an alternative proteomic measure of frailty and cognitive decline as a surrogate outcome, were consistent but less precise.

Interpretation Frailty, comorbidities, and other age-related diseases were associated with a higher risk of dementia but did not account for the elevated dementia risk observed after severe infections. Interventional research to test whether targeting infections lowers dementia incidence is needed.

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Introduction

Individuals with severe infections that require hospital treatment have a higher risk of dementia later in life than those without infections;[1–4] whereas milder infections treated in primary care are not consistently associated with dementia risk.[2,5] Specificity regarding the types of infection

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Department of Public Health (P N Sipilä MD, J Pentti MSc, J V Lindbohm MD, Prof M Kivimäki FMedSci) **and Department of Medicine** (Prof T E Strandberg MD), **Clinicum, University of Helsinki, Helsinki, Finland; Department of Public Health, University of Turku, Turku, Finland** (J Pentti); **UCL Brain Sciences, University College London, London, UK** (P Frank PhD, J V Lindbohm, Prof M Kivimäki); **Laboratory of Behavioral Neuroscience, National Institute on Aging, Baltimore, MD, USA** (M R Duggan PhD, K A Walker PhD); **Department of Internal Medicine and Rehabilitation, Helsinki University Hospital, Helsinki, Finland** (Prof T E Strandberg); **Center for Life Course Health Research, University of Oulu, Oulu, Finland** (Prof T E Strandberg); **Broad Institute of MIT and Harvard University, Klarman Cell Observatory, Cambridge, MA, USA** (J V Lindbohm)

Correspondence to: Dr Pyry N Sipilä, Department of Public Health, Clinicum, University of Helsinki, 00014 Helsinki, Finland **pyry.sipila@helsinki.fi**

Research in context

Evidence before this study

Severe infections are linked to a higher risk of dementia, but whether this association is due to pre-existing long-term conditions (such as frailty or comorbidities) that predispose individuals to severe infections and dementia, remains unknown. We searched PubMed without language restrictions from inception to Sept 23, 2025, using the terms (infectio*[Title] OR pneumonia[Title] OR sepsis[Title] OR cystitis[Title] OR pyelonephritis[Title] OR gastroenteritis[Title]) AND (frailty[Title/Abstract] OR comorbid*[Title/Abstract]) AND (dementia[Title] OR Alzheimer*[Title]). Ten studies examined whether the association between infections and dementia could be explained by frailty or comorbidity. Of those, only one assessed frailty, suggesting that pneumonia might be associated with a higher risk of dementia regardless of frailty status, but the estimates were imprecise.

Added value of this study

Severe infections in participants in the UK Biobank study were associated with higher dementia risk (irrespective of pre-existing conditions) in non-frail and pre-frail or frail individuals and those with and without comorbidities and age-related diseases. The association with dementia was evident for bacterial and viral infections and a range of clinically important diagnoses, such as pneumonia, lower respiratory tract infections, and urinary tract infections. The findings were consistent using data from the British Whitehall II study, although estimates were less precise.

Implications of all the available evidence

Two prospective cohort studies suggest that the increased risk of dementia in individuals with severe infections is unlikely to be driven by pre-existing frailty, comorbidities, or age-related physical diseases. The associations varied slightly by type of infection. Severe infections might accelerate neurodegenerative processes irrespective of pre-existing frailty and age-related conditions, but further mechanistic studies and interventional research targeting infection-related pathways are needed to test this hypothesis and inform dementia prevention strategies.

is low, suggesting that multiple pathogens might contribute to neurodegeneration.[1–4]

The pathways linking severe infections to dementia remain poorly understood. The association is commonly assumed to reflect infection-related mechanisms that adversely affect the central nervous system, including systemic inflammation, microglia priming, neuroimmune dysfunction, and thromboinflammation.[6] An alternative but less studied explanation is that the association is artefactual, arising from confounding by shared risk factors that predispose individuals to severe infections and neurodegenerative disease, such as frailty and comorbid age-related diseases. Frailty is a biological syndrome characterised by multisystem dysfunction, reduced physiological reserve, and increased vulnerability to stressors[7] and is associated with higher risk of severe infections and dementia.[8,9] Similarly, age-related diseases (including many of those captured by the Charlson Comorbidity Index [CCI])[10] have been linked to increased risk of both outcomes.[11–13] However, only a few studies have directly examined whether such pre-existing long-term conditions account for the excess dementia risk observed after severe infections.[2,14,15]

See Online for appendix

To examine this alternative explanation and extend our previous work,[1] we aimed to use two independent prospective cohort studies to assess whether the association between severe infections and dementia risk is explained by pre-existing frailty, comorbidities, or other age-related physical diseases. We further assessed whether this association was restricted to individuals with these conditions (ie, the alternative explanation) or was also present in those without these conditions, which would be expected if severe infections contribute to dementia risk.

Methods

Study design and participants

This prospective, multicohort, observational study included participants without severe infections or dementia (before or at baseline between Dec 19, 2006, and Oct 1, 2010, from the UK Biobank study and between Oct 8, 2002, and Nov 30, 2004, from the Whitehall II prospective cohort study). Patients whose frailty status could not be determined at baseline were excluded from the main analysis but were included in multiple imputation sensitivity analyses. All participants in these studies provided written informed consent and those who later withdrew consent were excluded. The National Health Service (NHS) Research Ethics Service approved the UK Biobank study (11/NW/0382). Ethics approval for the Whitehall II study was obtained from the University College London Medical School Committee (85/0938) and the London–Harrow and Scotland A Research Ethics Committees. Study profiles describing participant selection and cohort information are provided in the appendix (pp 3–4, 18).

Procedures

Frailty was assessed at baseline using the widely used phenotypic Fried Frailty Scale.[7] The scale consists of five characteristics of frailty: shrinking (unintentional weight loss), weakness (low grip strength), poor endurance and energy (exhaustion), slowness (slow walking speed), and low physical activity. Each characteristic is scored 1 or 0 (present or absent), which yields a scale range of 0–5 (0 indicates non-frail [robust], 1–2 indicates pre-frail, and $\geq$3 indicates frail).

In the UK Biobank, frailty components were based on self-reported characteristics defined as shrinking (weight

loss in the previous year), weakness (measured low grip strength), poor endurance and energy (tiredness or low energy more than half the days in the past 2 weeks), slowness (slow usual walking pace), and low physical activity (light activity no more than once per week; appendix p 19).[16] This adapted frailty scale has been validated and shows robust associations with all-cause mortality.[16]

In the Whitehall II study, frailty components were based on self-reported characteristics defined as shrinking (measured weight loss between phases 5 and 7 [baseline of our study], around 5 years apart), poor endurance and energy (feeling that everything was an effort or difficulty in get[ting] going on at least 3 days in the past week), slowness (measured walking speed), and low physical activity (consuming <383 kcal per week for men or <270 kcal per week for women in moderate-to-vigorous activity); data on weakness were not available; appendix p 20). All components of this adapted scale have been validated against risk of admission to hospital.[17]

To assess frailty using an alternative indicator, we used a Proteomic Frailty Index validated in 2025 based on the log-transformed abundance of 25 plasma proteins (appendix p 21).[18] Plasma ethylenediaminetetraacetic acid samples collected in 1997–99 in the Whitehall II study were stored at –80°C. Protein concentrations were measured using SomaScan assays (SomaLogic, Boulder, CO, USA; versions 4.0 and 4.1). All samples underwent standard normalisation, calibration, quality control, and harmonisation across assay versions, as previously described.[19]

The Proteomic Frailty Index has been validated against physical frailty measures in the Atherosclerosis Risk in Communities and Baltimore Longitudinal Study of Aging cohorts and has shown robust associations with age-related clinical measures (eg, glucose and cognitive scores), age-related chronic conditions (eg, diabetes, heart disease, and dementia), and mortality.[18]

Comorbidities were assessed at baseline based on ICD-10 codes retrieved from primary and secondary diagnoses of hospital records from Hospital Episode Statistics for England (HES), Scottish Morbidity Record (SMR), and Patient Episode Database for Wales (PEDW). The CCI was computed using an algorithm for ICD-10 codes.[20] We also considered diseases previously associated with hallmarks of cellular ageing;[21,22] from the 83 hallmark-related diseases available from hospitalisation records,[22] we excluded dementia and all four categories of infections (bacterial infections, viral infections, lower respiratory tract infections, and sepsis), resulting in 78 age-related diseases (appendix pp 23–29).

Participants were linked to national health registries (HES, SMR, and PEDW) for ascertainment of infectious exposures from hospital discharge diagnoses. We used 931 codes[23] from ICD-10 to capture infections that were recorded as a primary or secondary reason for hospital in-patient admission (appendix pp 30–51). We considered bacterial and viral infections separately and several clinically important groups of infections (such as pneumonia, lower respiratory tract infections, urinary tract infections, gastrointestinal infections, skin and subcutaneous tissue infections, and sepsis; appendix pp 52–69).

In UK Biobank, we used linked records from the HES, SMR, PEDW, and death registries to retrieve diagnoses of incident dementia from hospital discharge records and causes of death. The first record with a dementia diagnosis, whether primary or secondary, was taken to signify the date of incident dementia. Follow-up occurred until 2022 (Oct 31 in England, Sept 30 in Scotland, and May 31 in Wales), the latest available dates at the time of data extraction and analysis. A diagnosis of all-cause dementia was defined using the ICD-10 codes (F00–F03, F05.1, G30, G31.0, G31.1, and G31.8).[1] In the Whitehall II study, all-cause dementia cases were identified from HES inpatient and outpatient records, Mental Health Service records, and death records. Follow-up ended on March 1, 2023, which was the latest available date.

Covariates included established risk factors such as sex, education, area deprivation, marital status, smoking, alcohol consumption, BMI, hypertension, diabetes, depression, history of coronary heart disease, history of stroke, and additionally apolipoprotein E (*APOE*) genotype (in the UK Biobank sensitivity analyses) and were assessed at baseline in both studies (appendix p 22).

We conducted two supplementary analyses using data from the cognitive testing battery in the Whitehall II study. First, cognitive function assessment at phase 7 (2002–04 at baseline of the present analysis) was included as an additional baseline covariate to account for pre-existing differences in cognitive performance between participants who subsequently developed severe infections and dementia and those who did not. Second, as an alternative surrogate outcome for dementia, we examined cognitive decline using repeated measurements of cognitive function obtained at phase 7 (2002–04), 9 (2007–09), 11 (2012–13), and 12 (2015–16).

At each phase, four cognitive domains were assessed: memory (20-word free recall test in 2 min), executive function (10 min Alice Heim 4-I test comprising 65 verbal and mathematical reasoning items of increasing difficulty), phonemic fluency (number of words generated beginning with letter S in 1 min), and semantic fluency (number of animals named in 1 min).[24] Domain specific scores were individually standardised to baseline values and then combined into a global cognitive score, which was standardised to baseline values. Cognitive decline (yes *vs* no) was defined using three alternative thresholds (declines of 1·0, 1·5, and 2·0 SDs in standardised cognitive score per 10 years since baseline).

Statistical analysis

Participants with no history of severe infections at baseline were included in the analysis. After confirming that proportional hazards assumptions were not violated using Schoenfeld residuals and log–log plots, we examined associations of baseline frailty and comorbidities with

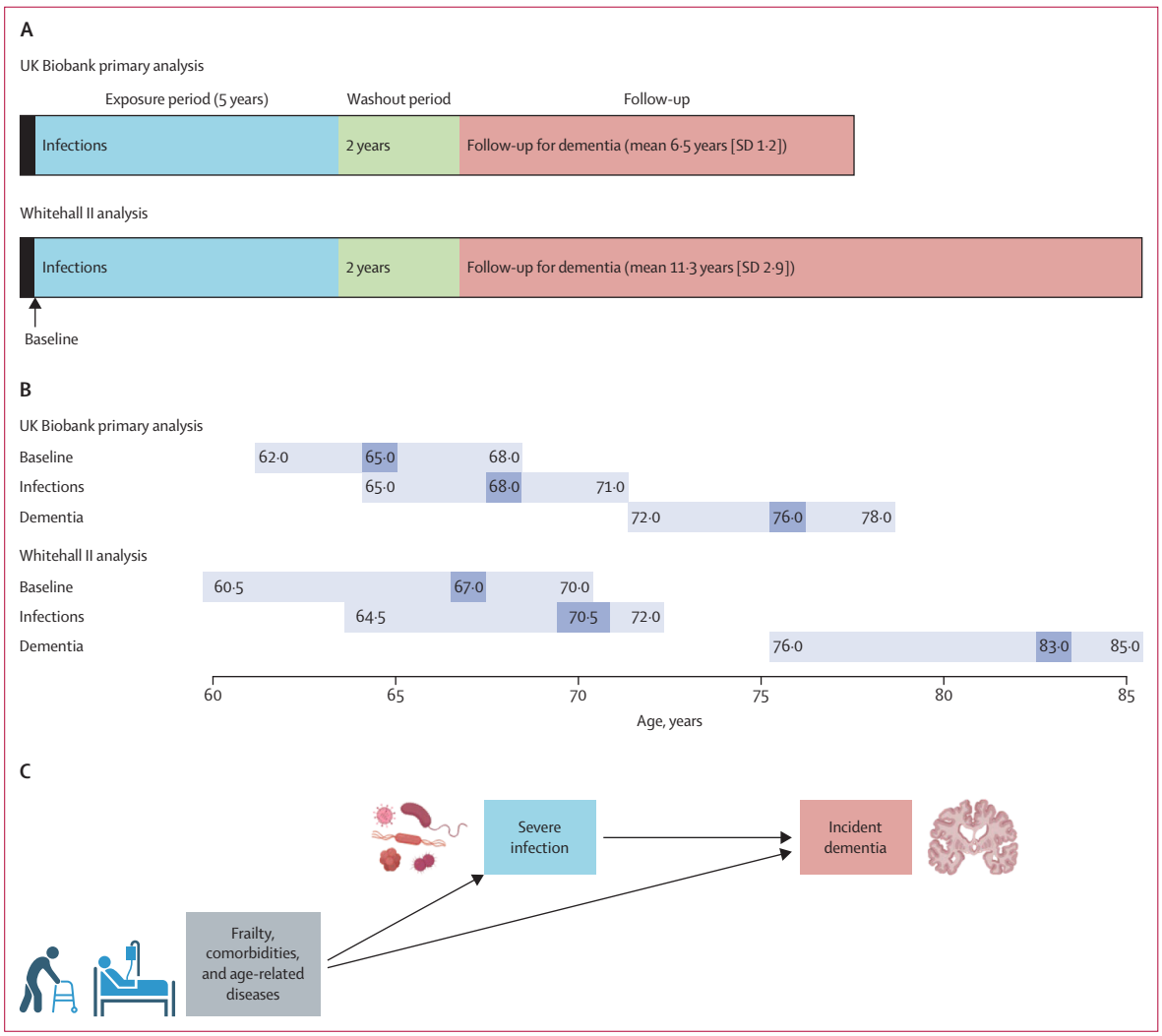

Figure 1: **Overview of the study**
(A) Study design based on the UK Biobank and Whitehall II cohort studies. Frailty, CCI, age-related diseases, and covariates were measured at baseline (2006–10 in UK Biobank and in 2002–04 in Whitehall II). Exposure to severe (hospital-treated) infectious diseases (ie, any infection, bacterial infections, viral infections, pneumonia, lower respiratory tract infections, urinary tract infections, gastrointestinal infections, skin or subcutaneous tissue infections, and sepsis) was assessed for 5 years after baseline, with a 2-year washout period and followed up for incident dementia. (B) Median age (IQR) at baseline and follow-up in those with severe infection and dementia. (C) Study analyses. Figure created with BioRender.com.

incident severe infections and dementia during follow-up using Cox proportional hazards models.

We assessed whether pre-existing frailty, comorbidities, and age-related diseases confounded the associations between subsequent severe infections and dementia risk (appendix p 3). Follow-up was structured into a 5-year exposure period from baseline to capture severe infections; a subsequent 2-year washout period to separate infection ascertainment from dementia diagnosis; and a final period extending to the end of follow-up to record incident dementia cases after the washout period (figure 1A). All newly diagnosed severe infections occurring during the exposure period were recorded. To minimise bias from prevalent dementia or delayed diagnosis, participants with a record of dementia during the exposure period or subsequent washout period were excluded. The included participants were censored at death, loss to follow-up, or end of hospital records.

Using Cox proportional hazards models, we estimated hazard ratios (HRs) for dementia associated with the presence versus absence of severe infection during the exposure period, before and after adjustment for baseline frailty, comorbidities, and age-related diseases. As no standard exposure window exists for incident severe infections, a 5-year exposure period was chosen to balance sufficient exposure accrual with adequate dementia follow-up. To assess sensitivity, analyses were repeated using alternative exposure periods of 3 and 7 years.

All Cox models were adjusted for age (using time since birth as time scale), sex (male and female; using stratification to allow variations in the shape of the baseline hazard function), and country of baseline assessment (stratification by England, Scotland, and Wales; base model). Multiply adjusted models were additionally adjusted for education (low, intermediate, or high), area deprivation (1st [least deprived], 2nd, 3rd, 4th, or 5th quintile [most deprived]), marital status (married or cohabiting *vs* other), smoking (never, former, or current), alcohol consumption (never, former, special occasions, 1–3 times per month, 1–7 days per week [moderate defined as <22 drinks per week for men or <15 drinks per week for women, intermediate defined as 22–27 drinks per week for men or 15–21 drinks per week for women, and heavy defined as >28 drinks per week for men or >22 drinks per week for women]), BMI (<18·50 kg/m^2, 18·50–24·99 kg/m^2, 25·00–29·99 kg/m^2, or ≥30·00 kg/m^2), hypertension, diabetes, history of coronary heart disease, and history of stroke. In a prespecified sensitivity analysis, the models were additionally adjusted for *APOE* genotype (if available; zero *vs* one or two ε4 alleles). Models adjusted for the CCI were not adjusted for diabetes, coronary heart disease, and stroke because these are already included in the index. Similarly, models adjusted for age-related diseases were not adjusted for hypertension, diabetes, coronary heart disease, and stroke because these are already included within age-related diseases.

We examined multiply adjusted associations between severe infections and incident dementia in the total UK Biobank cohort and separately by baseline frailty, comorbidity, and age-related disease. We also compared effect estimates between non-frail participants without comorbidities and age-related diseases with those who were pre-frail, frail, had at least one comorbidity, or with age-related disease. Differences between HRs were tested using the χ^2 test. To address survival bias, we conducted a post-hoc Fine and Gray competing risk analysis with dementia and death as outcomes. In additional post-hoc sensitivity analyses, we ascertained dementia diagnoses only from hospital records; handled missing data using multiple imputation and complete-case analysis instead of the missing-category approach; adjusted the models for combined categories of frailty, CCI, and other age-related diseases; adjusted for alcohol use disorder (ICD-10 F10) and psychotic disorders (ICD-10 F20–F29); stratified follow-up into early (≤5 years) and late (>5 years); and split the analysis by ethnic background (self-reported as White *vs* other). For multiple imputation, we used fully conditional specification (also known as chained equations) with substantive model modification,[25] using ten iterations and 25 imputations.

To examine reproducibility, we repeated the main analyses in the Whitehall II study and conducted several post-hoc supplementary analyses with follow-up until March 1, 2023. To assess robustness using a biomarker-based indicator of frailty, we used the alternative plasma

	UK Biobank (n=449 223)	Whitehall II study (n=6106)
Age	56·5 (8·1)	60·6 (6·0)
Sex		
Female	245 139 (54·6%)	1772 (29·0%)
Male	204 084 (45·4%)	4334 (71·0%)
Ethnicity		
White	424 405 (94·5%)	5616 (92·0%)
Mixed	2606 (0·6%)	..
Asian	9706 (2·2%)	..
South Asian	..	282 (4·6%)
Black	6829 (1·5%)	152 (2·5%)
Other	3904 (0·9%)	..
Other or did not respond	..	56 (0·9%)
Not available	1549 (0·3%)	..
Education		
Low	73 333 (16·3%)	2109 (34·5%)
Intermediate	222 702 (49·6%)	1625 (26·6%)
High	148 746 (33·1%)	2179 (35·7%)
Not available	4442 (1·0%)	193 (3·2%)
Area deprivation		
1st quintile (least deprived)	209 199 (46·6%)	1296 (21·2%)
2nd quintile	99 427 (22·1%)	1273 (20·8%)
3rd quintile	65 150 (14·5%)	1199 (19·6%)
4th quintile	51 824 (11·5%)	1090 (17·9%)
5th quintile (most deprived)	23 068 (5·1%)	949 (15·5%)
Not available	555 (0·1%)	299 (4·9%)
Marital status		
Married or cohabiting	119 054 (26·5%)	1485 (24·3%)
Other	327 625 (72·9%)	4621 (75·7%)
Not available	2544 (0·6%)	0
Smoking status*		
Never	248 170 (55·2%)	2964 (48·5%)
Former	154 093 (34·3%)	2654 (43·5%)
Current	45 381 (10·1%)	488 (8·0%)
Not available	1579 (0·4%)	0
Alcohol consumption†		
Never	18 948 (4·2%)	..
Former	14 858 (3·3%)	..
Special occasions	50 031 (11·1%)	..
1–3 times per month	49 885 (11·1%)	..
<1 drink in the past 7 days	..	1001 (16·4%)
Moderate‡	231 260 (51·5%)	4255 (69·7%)
Intermediate‡	34 926 (7·8%)	391 (6·4%)
Heavy‡	43 428 (9·7%)	395 (6·5%)
Not available	5887 (1·3%)	64 (1·0%)
BMI		
<18·50 kg/m^2	2232 (0·5%)	45 (0·7%)
18·50–24·99 kg/m^2	148 157 (33·0%)	2186 (35·8%)
25·00–29·99 kg/m^2	192 580 (42·9%)	2743 (44·9%)
≥30·00 kg/m^2	106 254 (23·7%)	1132 (18·5%)
Hypertension		
No	198 101 (44·1%)	3693 (60·5%)
Yes	250 701 (55·8%)	2413 (39·5%)
Not available	421 (0·1%)	0

(Table continues on next page)

	UK Biobank (n=449 223)	Whitehall II study (n=6106)
(Continued from previous page)		
Depression§		
No	398 536 (88·7%)	5652 (92·6%)
Yes	24 464 (5·4%)	294 (4·8%)
Not available	26 223 (5·8%)	160 (2·6%)
Diabetes (of any type)		
No	398 536 (88·7%)	4988 (81·7%)
Yes	24 464 (5·4%)	887 (14·5%)
Not available	26 223 (5·8%)	231 (3·8%)
History of coronary heart disease		
No	433 469 (96·5%)	5910 (96·8%)
Yes	15 754 (3·5%)	196 (3·2%)
History of stroke		
No	447 310 (99·6%)	6092 (99·8%)
Yes	1913 (0·4%)	14 (0·2%)

Data are n (%) or mean (SD). *In UK Biobank, self-reported current smoking was defined as smoking tobacco now on most or all days or occasionally. Past smoking was defined as not smoking tobacco now but having smoked on most or all days or occasionally in the past. In the Whitehall II study, self-reported current smoking was defined as smoking cigarettes now ("yes" or "social or occasional smoker"). Former smoking was defined as not smoking cigarettes now but having smoked in the past. †Self-reported alcohol consumption was converted to drinks containing 10 g of pure alcohol. In UK Biobank, participants were inquired about the frequency of drinking in an average week. In the Whitehall II study, participants reported the amount of alcohol consumed in the last 7 days. ‡Moderate (defined as <22 drinks per week for men or <15 drinks per week for women), intermediate (defined as 22–27 drinks per week for men or 15–21 drinks per week for women), and heavy (defined as >28 drinks per week for men or >22 drinks per week for women) drinking within 1–7 days per week. §In UK Biobank, self-reported depression was defined as having felt down, depressed, or hopeless more than half the days over the past 2 weeks. In the Whitehall II study, depression was defined as scoring at least 16 points on the Center for Epidemiologic Studies Depression Scale.

Table: **Baseline characteristics of participants**

Proteomic Frailty Index. To minimise reverse causation, whereby preclinical dementia might increase susceptibility to infections, we additionally adjusted for baseline cognitive function. To reduce ascertainment bias arising from greater medical contact among individuals with severe infections, we replaced dementia as the outcome with dichotomised rate of cognitive decline, using logistic regression to compute adjusted odds ratios (OR).

All CIs are reported at the 95% level. We analysed all data using Stata MP (versions 17–19). Statistical codes are available in the appendix (pp 70–184).

Role of the funding source

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

Results

We included 449 223 participants without severe infection or dementia from the UK Biobank study and 6106 from the Whitehall II prospective cohort study. In UK Biobank, the mean age of participants was 56·5 years (SD 8·1), of whom 245 139 (54·6%) were female and 204 084 (45·4%) were male (figure 1; table). 267 456 (59·5%) participants were classified as non-frail, 167 500 (37·3%) as pre-frail, and 14 267 (3·2%) as frail. 22 607 (5·0%) participants had at least one comorbidity according to the CCI, and 94 947 (21·1%) had at least one of the 78 age-related diseases. Most participants were White (424 405 [94·5%]).

During a mean follow-up of 12·2 years (SD 3·4), comprising 5 472 239 person-years, 94 840 (21·1%) UK Biobank participants had a record of severe infection; the most common being unspecified gastroenteritis (12 867 [13·6%]; ICD-10 A09), pneumonia (11 328 [11·9%]; ICD-10 J18), and urinary tract infection (8379 [8·8%]; ICD-10 N39·0). After multivariable adjustments, pre-frail participants (HR 1·25 [95% CI 1·23–1·27]) and frail participants (1·88 [1·82–1·93]) had increased risk of any severe hospital-treated infection compared with non-frail participants. Associations between frailty status and different types of infections were very similar (figure 2A; appendix p 6). Likewise, the CCI (1 or ≥2 *vs* 0) and age-related diseases (1 or ≥2 *vs* 0) were associated with an increased risk of infections (appendix pp 7–8).

Frailty was also associated with an increased risk of incident dementia in pre-frail participants (adjusted HR 1·36 [95% CI 1·30–1·43]) and frail participants (2·20 [2·00–2·41]) compared with non-frail participants. Additional adjustment for *APOE* genotype did not change the results considerably (figure 2B; appendix p 9). Similarly, the CCI and age-related diseases were associated with increased dementia risk, although the HRs for dementia were slightly lower than those related to frailty (appendix pp 9–10).

Next, we assessed whether the associations between severe infections and dementia are confounded by frailty. Of 435 957 participants with dementia follow-up, 23 860 (5·5%) had a record of severe infection during the 5-year exposure period. After a 2-year washout period, the remaining follow-up for dementia occurred for a mean of 6·5 years (SD 1·2). During 2 851 221 person-years at risk, 6756 participants developed incident dementia, corresponding to an incidence of 2·37 (95% CI 2·31–2·43) per 1000 person-years. Dementia incidence by subgroup is shown in the appendix (p 11). The mean interval from infection to dementia was 8·0 years (SD 2·5).

Adjustment for frailty resulted in no statistically significant attenuation of the infection and dementia association (adjusted HR 1·54 [95% CI 1·43–1·67] for presence *vs* absence of severe infections before adjustment for frailty and 1·49 [1·37–1·61] after adjustment; appendix p 14). Furthermore, the association was also evident within a subgroup of non-frail participants (1·34 [1·18–1·53]). We combined pre-frail and frail participants to obtain sufficient statistical power, with a higher corresponding adjusted HR (1·62 [1·47–1·79]; appendix p 12).

Similar robust associations were observed for most specific infectious diseases (figure 3; appendix p 12). Bacterial infections, viral infections, pneumonia, lower respiratory tract infections, and urinary tract infections were associated with an increased risk of dementia among non-frail and pre-frail or frail participants versus those without such infections. For gastrointestinal infections, skin or subcutaneous tissue infections, and sepsis, the associations with dementia were statistically significant in pre-frail or

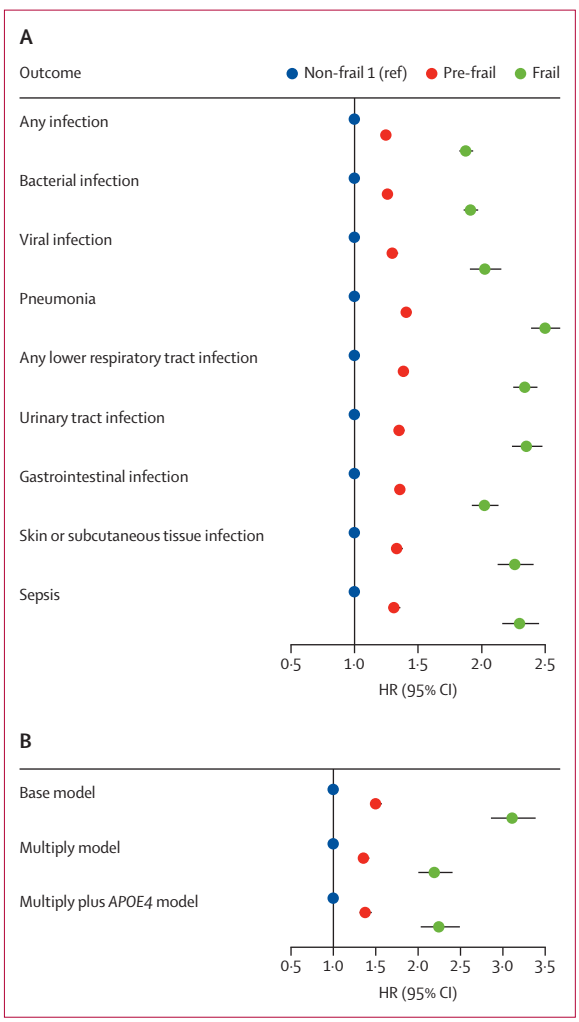

Figure 2: **Associations of frailty with severe infections and dementia in the UK Biobank**

(A) Multiply adjusted associations between frailty and incident severe (hospital-treated) infectious diseases (some 95% CIs are not visible because they are narrower than the point estimate). (B) Association of frailty with the risk of dementia. The base model was adjusted for age, sex, and area of residence. The multiply model was additionally adjusted for socioeconomic status, area deprivation, smoking, alcohol consumption, hypertension, diabetes, BMI, history of coronary heart disease, history of stroke, and marital status. The multiply plus *APOE4* model was additionally adjusted for the presence of *APOE4*. *APOE4*=apolipoprotein E ε4 allele. HR=hazard ratio.

frail participants; among non-frail participants, the point estimates suggested increased risk, but the associations were not statistically significant. Additional adjustment for *APOE* genotype had little effect on the findings (appendix p 13).

The associations between severe infections and an increased risk of dementia were also consistent across sexes and subtypes of dementia, although the relative risk of vascular dementia after severe infection was higher than that of Alzheimer's disease and frontotemporal dementia was not statistically significant (appendix p 14). These associations remained similar after adjustment for frailty.

In sensitivity analyses, findings did not change at 3-year or 7-year exposure periods for severe infections; when split by ethnicity; when accounting for competing risk of death; when dementia diagnoses were ascertained from hospital records (excluding those identified from death records); when missing data were addressed using multiple imputation or complete-case analysis; and after adjustment for combined categories of frailty, CCI, and other comorbidities, or for alcohol use disorder and psychotic disorders (appendix p 14). The adjusted HR for the association between severe infections and dementia was 1·61 (95% CI 1·46–1·77) during the first 5 years of follow-up and 1·43 (1·25–1·64) thereafter and after additional adjustment for frailty, the corresponding HRs were 1·55 (95% CI 1·41–1·70) and 1·38 (1·20–1·59), respectively.

We examined the confounding role of comorbid diseases in the associations between severe infections and dementia. Associations between severe infections and dementia were evident before versus after adjustment for the CCI (adjusted HR 1·59 [95% CI 1·47–1·72] *vs* 1·54 [1·43–1·67]) and age-related diseases (1·60 [1·48–1·73] *vs* 1·52 [1·41–1·65]). These associations were also evident within subgroups of individuals without and with pre-existing comorbid conditions (figure 3; appendix p 12) and after additional adjustment for *APOE* genotype (appendix pp 15–16). Similar patterns were observed for most infectious diseases and disease categories.

Severe infections were also associated with dementia among non-frail participants without pre-existing comorbid conditions assessed by the CCI or age-related diseases (adjusted HR 1·37 [95% CI 1·16–1·63]); the corresponding HR was 1·59 (1·46–1·74) for participants who were pre-frail or frail or had at least one comorbidity (figure 3; appendix p 12).

The main analyses were repeated in the Whitehall II cohort study. At baseline, the mean age of participants was 60·6 years (SD 6·0), of whom 1772 (29·0%) of 6106 were female and 4334 (71·0%) were male (table 1; appendix p 18). Most participants were White (5616 [92·0%]). Of 5824 participants available for dementia follow-up, 237 (4·1%) had a record of infection during the 5-year exposure period. After a 2-year washout period, the remaining mean follow-up for dementia was 11·3 years (SD 2·9). During 65 555 person-years at risk, 545 incident cases of dementia were recorded (incidence 8·3 per 1000 person-years). The mean interval from infection to dementia was 12·6 years (SD 3·5).

Participants with any severe infection had an increased risk of dementia compared with those who did not have severe infection (adjusted HR 1·43 [95% CI 1·02–2·01]; appendix p 14). The adjusted HR remained similar after additional adjustment for frailty (1·41 [1·00–1·98]), CCI (1·42 [1·01–2·00]), and age-related diseases (1·42 [1·01–1·99]).

In sensitivity analyses using a plasma Proteomic Frailty Index as an alternative indicator of baseline frailty, and in models additionally adjusted for baseline cognitive function, point estimates remained unchanged (adjusted HR 1·43 before and 1·42–1·43 after the adjustments;

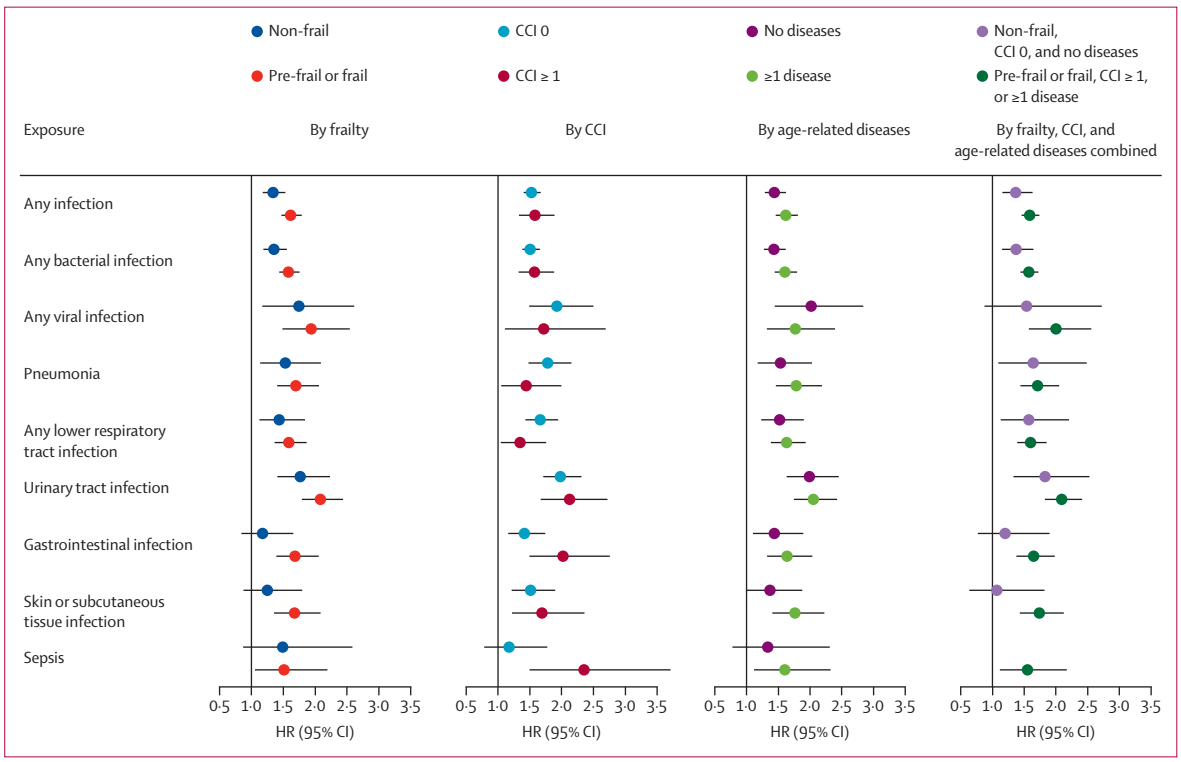

Figure 3: **Associations of severe infections with the risk of incident dementia in the UK Biobank**
Models related to frailty were adjusted for age, sex, area of residence, socioeconomic status, area deprivation, smoking, alcohol consumption, hypertension, diabetes, BMI, history of coronary heart disease, history of stroke, and marital status. Models related to CCI were not adjusted for diabetes, coronary heart disease, and stroke because these are already included in the index. Models related to age-related diseases or frailty, CCI, and age-related diseases combined were not adjusted for hypertension, diabetes, coronary heart disease, and stroke because these are already included in age-related diseases. CCI=Charlson Comorbidity Index. HR=hazard ratio.

appendix p 14). In further sensitivity analyses replacing dementia with cognitive decline as the outcome, severe infections showed a similar non-statistically significant association with cognitive decline before adjustment for baseline frailty (adjusted OR 1·32–1·38 depending on the SD threshold) and after (1·32–1·37; appendix p 17).

Discussion

In this study, severe infections were associated with a higher risk of dementia later in life, irrespective of phenotypic frailty status, comorbidities, or other age-related diseases. This association was observed for non-specific severe infections, bacterial and viral infections, and several clinically important infectious diseases (including pneumonia, lower respiratory tract infections, and urinary tract infections). An elevated risk of dementia was also evident among individuals without frailty or comorbidities before severe infection onset. These findings were consistent across two independent cohort studies, alternative measures of frailty (phenotypic frailty and a biomarker-based frailty index), two outcomes (clinically diagnosed dementia and preclinical cognitive decline), and across multiple analytical approaches. This evidence argues against confounding by pre-existing frailty or comorbidities and suggests that the association between severe infections and dementia is unlikely to be explained by underlying age-related physical conditions.

One previous study has assessed the contribution of frailty and comorbidities to the association between severe infections and dementia. Consistent with our findings, the study found that pneumonia was associated with dementia among non-frail and pre-frail or frail participants, although the estimates were less precise.[15] Our analyses included a wide range of infectious diseases and findings were broadly similar across most subtypes. An exception was gastrointestinal infections, skin and subcutaneous tissue infections, and sepsis, which were significantly associated with dementia only among pre-frail and frail participants. However, these infections were uncommon in non-frail participants, limiting statistical power and precluding firm conclusions in this group.

In line with earlier studies,[1,2,26] we found that severe infections were more strongly associated with vascular dementia than Alzheimer's disease. Several mechanisms might contribute to these findings. The inflammatory response related to severe infections might lead to blood–brain barrier damage, increasing the entry of neurotoxic plasma components, blood cells, and pathogens into the brain; thromboinflammation (ie, an inflammation-induced systemic prothrombotic state); endothelial

dysfunction; microbleeds; and microinfarcts.[27–29] Severe infections are also associated with an increased risk of stroke, which is a well established risk factor for dementia.[12,13,23]

Our study has several limitations. First, the observational design precludes causal inference. Reverse causation is possible if preclinical dementia increases susceptibility to infections. To address this issue, we adjusted associations for baseline cognitive performance and the results remained unchanged. Second, dementia ascertainment relied on national hospital and death records, which might miss milder or undiagnosed cases and delay identification of disease onset.[30] Ascertainment bias is also possible because individuals with severe infections are more likely to receive medical care and for any underlying dementia to be detected. To mitigate these biases, we repeated analyses using cognitive decline (based on repeated cognitive assessments) as an alternative outcome. Because these measures capture preclinical cognitive impairments equally across participants and are not dependent on clinical contact, they help to reduce biases arising from under-ascertainment, delayed diagnosis, or unbalanced clinical surveillance. Third, frailty assessment using the Fried Frailty Scale might be imprecise in middle-aged populations (mean age 56·5 in the UK Biobank study and 60·6 years in the Whitehall II study), because physical frailty components (including shrinking, weakness, exhaustion, slowness, and low activity) are uncommon at these ages. To address this limitation, we used an alternative continuous frailty indicator based on 25 plasma proteins.[18] Repeating the analyses with this validated biomarker-based measure did not change the findings considerably. Fourth, the generalisability of our findings should be interpreted with caution. All data were from the UK and age-specific dementia incidence rates in both cohorts were lower than those reported in the general population. In addition, participants were predominantly White and the proportion with severe infections was smaller in the Whitehall II study than in UK Biobank, resulting in less precise risk estimates. Further research is needed to establish whether our findings can be replicated in other study populations, including minority ethnic populations and across different countries and settings.

In conclusion, findings from two UK-based cohort studies show that although frailty, comorbidities, and other age-related diseases were associated with a higher risk of dementia, they did not account for the elevated dementia risk observed after severe infections. These results are consistent with the possibility that severe infections might accelerate neurodegenerative processes; however, mechanistic studies and interventional research targeting infection-related pathways are needed to test whether targeting infections lowers dementia incidence and inform dementia prevention strategies.

Contributors

PNS and MK designed the study. PNS analysed the data, conducted the literature review, and wrote the first draft of the manuscript. MRD and KAW provided domain expertise and critical revision of the manuscript. PNS, JVL, and MK obtained funding for the study. PNS and JP accessed and verified the UK Biobank data. PNS and PF accessed and verified the Whitehall II data. All authors contributed to the study design, analysis, or interpretation of the data; and critical revision of the manuscript for intellectual content. All authors could access the study data. PNS and MK had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

KAW is on the Board of Directors for the National Academy of Neuropsychology. TES reports consulting on vaccines for GSK, MSD, and the Finnish Institute for Health and Welfare; participation on a Data Safety Monitoring Board or Advisory Board for the FINGER and MET-FINGER trials; and is a chairperson for the Finnish national guideline group for cognitive disorders. All other authors declare no competing interests.

Data sharing

Data, protocols, and other metadata from the UK Biobank are available to the scientific community by referring to the UK Biobank data sharing policy (https://www.ukbiobank.ac.uk/enable-your-research/register). Pseudonymised data of the Whitehall II study are available to researchers by applying on the Dementias Platform UK (https://www.dementiasplatform.uk). Statistical codes are available in the appendix (pp 70–184).

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