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FEATURED ARTICLE

Incidence, morbidity, mortality and disparities in dementia: A population linked electronic health records study of 4.3 million individuals

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Abstract

Introduction: We report dementia incidence, comorbidities, reasons for health-care visits, mortality, causes of death, and examined dementia patterns by relative deprivation in the UK.

Method: A longitudinal cohort analysis of linked electronic health records from 4.3 million people in the UK was conducted to investigate dementia incidence and mortality. Reasons for hospitalization and causes of death were compared in individuals with and without dementia.

Results: From 1998 to 2016 we observed 145,319 (3.1%) individuals with incident dementia. Repeated hospitalizations among senior adults for infection, unknown morbidity, and multiple primary care visits for chronic pain were observed prior to dementia diagnosis. Multiple long-term conditions are present in half of the individuals at the time of diagnosis. Individuals living in high deprivation areas had higher dementia incidence and high fatality.

Discussion: There is a considerable disparity of dementia that informs priorities of prevention and provision of patient care.

KEYWORDS
Alzheimer's disease, cause of death, comorbidity, dementia, electronic health records, epidemiology, health inequality, health-care use, hospitalizations, incidence, mortality, United Kingdom, vascular dementia

1 | INTRODUCTION

Dementia is a leading cause of mortality and morbidity in the senior adults' population worldwide.[1–3] In the UK, dementia is the most common cause of death in women since 2011 and the second most frequent cause in men since 2015.[4] Individuals with dementia are likely to have comorbid conditions, which over and above their dementia-associated disease will require increased health-care attention.[2,5] As such, both dementia and multiple long-term conditions are likely to place a significant burden on patients' health, health-care use, and social care services.[2,5]

Dementia is defined by a decline in cognitive function sufficient to affect activities of daily living or social functioning.[5] Alzheimer's disease (AD) and vascular dementia are the commoner types of

dementia,[5] when information on dementia subtype is available.[6] Understanding population-level dementia incidence, mortality, associated diseases, and how patients present to and progress through the health-care system are necessary to plan and develop interventions that may be of value at specific points in the development of the disease to support the individual and reduce the societal burden of dementia. A detailed understanding of how, when, and why dementia patients present to the health-care system is currently lacking. While previous studies on dementia provide insights into disease burden,[7–12] they are limited in scope as reports on regional cohorts[10] or surveys[8,9,11,12] are unable to provide precise estimates on dementia comorbidity and health-care resource use.

Here we overcome this limitation by using routinely collected primary electronic health record (EHR) data, linked to secondary care and mortality data in the UK for 4.3 million individuals. We investigated the incidence, comorbidities, reasons for clinical visits, mortality, and causes of death. Disease patterns in subgroups, including sex and deprivation, were studied. These begin to provide insights into the dementia progression as recorded in the health-care system, to guide targeted interventions along the disease pathway.

2 | METHODS

2.1 | Data sources

The Clinical Practice Research Datalink (CPRD) was established in 1987.[13,14] Clinical records were available from 1993,[13,14] and in 2019 include 8,041,308 patients in the UK for data linkage. The data are generally representative of the age, sex, and geographic distribution of the UK population.[14,15] EHR from consented general practices (GP) were linked to hospital data from Hospital Episodes Statistics and death registry data (Office for National Statistics [ONS]) for research.[16] This study was performed as part of the CALIBER resource (https://www.ucl.ac.uk/health-informatics/caliber).[17,18] CALIBER is an open-access research resource consisting of information, tools, and phenotyping algorithms available through the online portal (https://caliberresearch.org/portal). The study was approved by the Medicines and Healthcare Product Regulatory Agency (UK) Independent Scientific Advisory Committee [18_228], under Section 251 (National Health Service [NHS] Social Care Act 2006) and followed the Reporting of Studies Conducted Using Observational Routinely Collected Health Data (RECORD) recommendations.

2.2 | Study population and study design

2.2.1 | Longitudinal cohort for incidence, case fatality, risk factors, and comorbidities

To study the dementia incidence, case fatality, and risk factors[2,5] for a dementia diagnosis, and include young-onset dementia, we identified all individuals aged 30 years or older, registered in a primary care prac-

RESEARCH IN CONTEXT

1. **Systematic Review**: We searched PubMed for clinical studies included "dementia" or "Alzheimer" in the title and "electronic health records" or "EHR" in the text. We also reviewed references for relevant studies. While previous studies provide insights into dementia disease burden, a systematic and comprehensive study on the population-level dementia incidence, mortality, associated diseases, and patient journey was absent.

2. **Interpretation**: Our study offers new knowledge on the incidence and fatality of dementia, comorbid conditions, and how patients present to and progress through the health-care system. There is a substantial discrepancy in dementia disease burden across the population, and individuals from areas with higher deprivation in socioeconomic status had both higher dementia incidence and fatality.

3. **Future Directions**: Further studies of mortality discrepancy by comorbidities and socioeconomic status are required. Studies to investigate young-onset dementia and potential new risk factors of dementia identified in our study, such as chronic pain, are warranted.

tice for at least 1 year. The study period was between January 1, 1998 and May 31, 2016, and patients were excluded if they had a prior history of dementia before study entry. Follow-up ceased at the following: death, the end of registration with the practice, cessation of the contribution of data to the CPRD by the GP, or the end of the study period. The definition of dementia in CALIBER was published elsewhere,[6] using 111 terms from the Read (Read V2) and International Classification of Diseases, 10th revision (ICD-10) controlled clinical terminologies to identify a dementia diagnosis from hospital admissions, primary care records, and cause of death. Incident dementia patients were further categorized into subtypes[6] of AD, vascular dementia, other dementia, more than one dementia subtype, and unspecified dementia (Table S1 in supporting information). The overall validity of diagnoses in the CPRD is high[19] and a previous review reported a high validity of dementia diagnosis in the study sources (positive predict value: 0.80 to 0.85 for hospital episodes statistics (HES), 0.73 to 1.0 for CPRD).[20]

2.2.2 | Matched case-control for reasons for clinical visits, mortality risk, and cause of death

To investigate comorbidities and causes of death in individuals with dementia, we conducted a matched case-control study within the longitudinal cohort (also known as a nested case-control study). All individuals with incident dementia were included as cases, and the index date was defined as the date of the first recorded dementia diagnosis. For each case, we randomly selected one dementia-free individual as

control from the study cohort. Controls were matched to the sex and age at diagnosis of individuals with incident dementia.

2.3 | Risk factors and comorbidities

We calculated an average value for all weight and height measurements within 1 year before and 1 year after the diagnosis of dementia. Body mass index (BMI) was calculated at baseline and recoded for obesity (BMI $\geq$ 30 kg/m^2). To describe socioeconomic status, we used the Index of Multiple Deprivation (IMD), a measure of relative deprivation at a small area level (clusters of adjacent postcodes). The measure is composed of indicators for various domains of material deprivation, including income, employment, education and skills, health, housing, crime, access to services, and living environment. Each domain score may be derived from subdomain indicators.[21] The IMD measure ranked in ascending order of deprivation score and grouped in equal twentieths with the lowest category representing the least deprived area and highest representing the most deprived.[22] We recoded the IMD values into a binary variable (less and greater than median IMD values): low deprivation (first to ninth twentiles) and high deprivation (10th to 20th twentiles) and a five-category variable: least deprived (first to third twentiles), second lowest (fourth to seventh twentiles), middle (eighth to eleventh twentiles), second highest (12th to 15th twentiles), highest deprived (16th to 20th twentiles).

For individuals with incident dementia, we examined the presence of risk factors and comorbidities previously reported to be associated with risk of dementia,[2,6,23] or with high prevalence observed in the study cohort: These include smoking, hypertension, diabetes, obesity, sleep apnea, hypercholesterolemia, hearing loss, thyroid dysfunction (hypothyroidism or hyperthyroidism), depression, stable angina, other atherosclerotic heart diseases (composite of unstable angina and acute myocardial infarction), peripheral artery disease, atrial fibrillation (AF), heart failure, congenital heart disease, transient ischemic attack, stroke, cancer, chronic kidney disease, liver disease, chronic obstructive pulmonary disease. The phenotyping methods of the risk factors and comorbidities are summarized in Table S2 in supporting information and available at www.caliberresearch.org/portal.[17] Previous research reported good validity of the definitions of clinical conditions.[24] For each condition, we reported the percentage of patients with a diagnosis recorded in their primary care or the primary cause of hospitalization before their initial diagnosis of dementia. Patients without a recorded diagnosis in primary care or hospitalization records were assumed to be free from that condition.

2.4 | Outcomes

2.4.1 | Dementia incidence

Age- and sex-specific cumulative incidence was calculated by dividing the number of newly diagnosed dementia patients by disease-free eligible individuals in the cohort. To calculate standardized rates, we applied direct age- and sex standardization to the 2013 European Standard Population[25] using 5-year age bands. Incidence rates were obtained from the Kaplan–Meier estimator where the population at risk was restricted to dementia-free individuals at any follow-up time.

2.4.2 | Reason for receiving primary and hospital care

We identified the primary diagnoses relating to inpatient episodes among individuals with dementia and their matched controls within 5 years before and after the index date (recorded diagnosis of dementia and cohort entry date for controls). Based on all hospitalization records of each individual, we calculated the frequency of different primary diagnoses, and the most frequent primary diagnosis of each person was used to identify the leading reasons for hospitalization among dementia patients and controls in the 4- to 5-year, 2- to 3-year, and 1-year intervals pre- and post-index date. The process was repeated for GP consultations. We numerically ranked the leading diagnoses associated with hospitalization or GP visits among dementia patients and compared to the corresponding proportions in controls.

2.4.3 | Mortality

Death data including date and the underlying cause of death were identified using mortality data from the ONS records. The cumulative case-fatality proportion was defined as the percentage of deaths among all incidence dementia patients. Rates of death included dementia fatality rate and mortality of controls at 30-day, 1-year, and 5-year.

2.5 | Statistical analysis

Baseline characteristics were presented as frequencies (%) for categorical data or means and standard deviation (SD) for normally distributed continuous data. Information was stratified by dementia types, sex, and socioeconomic categories.

In the longitudinal cohort, we reported observed incidence and cumulative case-fatality in men and women, which were then standardized to the 2013 European Standard Population[25] by 5-year age bands and sex. We compared the dementia incidence by multiple deprivation categories by Kaplan–Meier curves, controlling for age and sex.

In the matched case-control study, we reported differences in comorbidity and mortality between incident dementia cases and their age and sex-matched controls. We reported major diagnoses for hospitalization and GP consultation within 4- to 5-year, 2- to 3-year, and 1-year pre- and post-index date, comparing cases to controls. We assessed the rate of death using Kaplan–Meier curves; estimated mortality at 1- and 5-year follow-up in dementia cases and controls; and stratified by dementia types, sex, geographic region, ethnicity, and multiple deprivation categories. Additional sensitivity analyses were also performed exploring individuals with prodromal stages of dementia (ICD-10 code G31.8 and corresponding Read terms). The distribution

of the primary causes of deaths was compared between cases and their controls.

We performed the analyses in a secured data safe haven environment, meeting the data safety and information government requirements by the University College London, NHS Digital, and the ONS. The statistical software used for data curation are Python, MySQL, and R. Analyses were performed in SAS (version 9.4), and R (version 3.6.1).

3 | RESULTS

3.1 | Longitudinal cohort

We analyzed data for 4,309,481 eligible individuals in the UK (Figure S1 in supporting information) between January 1, 1998, and May 31, 2016. We found 145,319 (3.4%) incident dementia patients over a median of 9.5 years (interquartile range: 4.3 and 14.7 years) of follow-up. The diagnosis of unspecified dementia decreased with time, and among people with specified dementia types, 54% had AD, 46% vascular dementia, and 8% other dementia subtypes. The overall mean age at dementia diagnosis was 82.1 years (SD: 9.3 years) and 64.8% were women. The mean age at diagnosis was 83.3 years (SD: 8.8) for women and 80.0 (SD: 9.7) for men (Table 1). Dementia patients in the study were primarily White in ethnicity (92%, 128,785/145,319). Among all dementia patients, two in three (66.3%) patients had multicomorbidity (two or more morbidities) at the time of diagnosis, which was 79.4% among vascular dementia, compared to 53.8% in AD and 56.9% in patients with other dementia. Individuals with dementia recorded as living in the most deprived areas had a higher prevalence of obesity and comorbidities and were younger in age at the time of dementia diagnosis compared to those living in the most affluent areas. In sensitivity analyses, we found 3687 (0.09% of the total population) individuals with incident other nervous degenerative diseases, who were younger and with fewer comorbidities compared to patients with incident dementia (Table S3 in supporting information). The majority (2918, 79%) of these individuals developed incident dementia during the study period and were included in the main analyses.

The standardized cumulative incidence of dementia increased with age and was greater in women than in men. The observed cumulative incidence per 1000 people ranged from <5 (30–34, 35–39, 40–44, 45–49 years) in both sexes to 184.9 (80–84 years) in men and 256.2 (80–84 years) in women. Similarly, the cumulative case fatality increased with age, from 0.04% (30–34 years) to 76.8% (≥90 years) in men and from 0.02% (30–34 years) to 78.3% (≥90 years) in women (Figure 1). Compared to individuals aged 70 to 89 at study entry, dementia incidence was lower among participants who were 90 years or older at baseline. The age- and sex-standardized cumulative dementia incidence was 5.6% (4.9% in males and 6.4% in females), with reference to the 2013 European Standard Population. The incidence rates at the first year, fifth year, and tenth year of follow-up were 0.0018 (95% confidence interval [CI]: 0.0017 to 0.0018), 0.011 (0.0109 to 0.011), and 0.029 (0.028 to 0.029). Individuals living in affluent areas (the least deprived) had lower dementia incidence than the population

in the second-least, second-most, and most-deprived neighborhoods (Figure 2, left panel).

3.2 | Matched case-control study: causes of hospitalization and GP consultation

We identified a total of 145,319 controls matched to the age and sex of the 145,319 incident dementia patients. The mean age was 82.1 years in patients and 82.0 years in controls. Compared to controls, the leading causes of hospitalization prior to the first recorded diagnosis of dementia were urinary tract infection, senility, and cerebral infarction. Hospitalization for disorientation was frequent in the year prior to diagnosis (Table 2). After a dementia diagnosis, patients were frequently admitted to the hospital for urinary tract infection, dementia/AD, pneumonia or lower respiratory tract infection, syncope, and collapse. Frequent hospitalization for pneumonitis because of food and vomit was observed among dementia patients 4 to 5 years after diagnosis.

Compared to controls, type 2 diabetes, pain, and urinary tract infection were the leading conditions for GP consultation among dementia patients prior to diagnosis. However, more than half (85,532, 59%) of the individuals with dementia did not have inpatient records and ≈40% had no recorded primary care visit in the year prior to their initial diagnosis of dementia (Table S4 in supporting information). The lower-level primary care use was associated with a higher level of socioeconomic deprivation (Table S5 in supporting information) and varied by geographic region. Almost all dementia patients received primary or secondary medical care within the first year after initial diagnosis. After diagnosis, unitary tract infection, cellulitis, and type 2 diabetes were the frequently recorded reasons for GP consultation among dementia patients.

3.3 | Mortality rate

The mean duration of follow-up for survival analysis in the matched case-control population was 4.3 years. The observed rate of death was higher among individuals with dementia compared to matched controls (Figure 3). The mortality curves diverged steeply at the beginning of follow-up, as dementia patients experienced much higher death rates, and the discrepancy between dementia patients and controls then levelled off with time. Similar trends were observed in subgroups defined by sex (Figure 3).

About a quarter of incident dementia patients died within the first year of follow-up (23.0%, 95% CI: 22.8% to 23.3%) and the death rate increased to 61.9% (61.6% to 62.2%) within 5 years. One-year mortality among AD patients (11.0% [10.7% to 11.3%]) was lower than in patients with a vascular (21.4% [20.9% to 21.8%]) or other dementia diagnosis (19.8% [18.7% to 21.0%], Table S4). Dementia was the leading cause of death among diagnosed individuals, whereas cardiovascular causes were the top cause of death among non-dementia controls (Figure 4).

TABLE 1 Characteristics of patients with incident dementia

	All patients	Dementia subtype					Sex		Multiple deprivation categories	
		AD	Vascular	Other	Multiple type	Unspecified	Male	Female	Least deprived	Most deprived
	(n = 145 319)	(n = 42 902)	(n = 33 106)	(n = 5 122)	(n = 9 587)	(n = 54 602)	(n = 51 102)	(n = 94 217)	(n = 24 055)	(n = 28 840)
Age (years)	82.1 (9.3)	79.7 (10.4)	82.5 (7.6)	76.0 (10.9)	80.0 (7.6)	84.7 (8.3)	80.0 (9.7)	83.3 (8.8)	82.5 (9.1)	81.2 (9.6)
Women	94217 (64.8%)	28831 (67.2%)	19732 (59.6%)	2235 (43.6%)	5410 (56.4%)	38009 (69.6%)	–	–	15622 (64.9%)	14058 (64.1%)
BMI >= 30	4772 (3.3%)	1513 (3.5%)	1288 (3.9%)	144 (2.8%)	319 (3.3%)	1508 (2.8%)	1887 (3.7%)	2885 (3.1%)	456 (1.9%)	634 (2.9%)
Smoking	46871 (32.3%)	13205 (30.8%)	12275 (37.1%)	1705 (33.3%)	3022 (31.5%)	16664 (30.5%)	22701 (44.4%)	24170 (25.7%)	6966 (29%)	8307 (37.9%)
Hypercholesterolemia	14331 (9.9%)	3004 (7%)	4867 (14.7%)	474 (9.3%)	1098 (11.5%)	4888 (9%)	5961 (11.7%)	8370 (8.9%)	2297 (9.5%)	2487 (11.3%)
Socioeconomic status categories										
Least deprived	24055 (16.6%)	7485 (17.5%)	5487 (16.6%)	792 (15.5%)	1539 (16.1%)	8752 (16.1%)	8433 (16.5%)	15622 (16.6%)	–	–
Most deprived	28840 (19.9%)	8003 (18.7%)	6684 (20.2%)	1001 (19.6%)	2008 (21%)	11144 (20.4%)	10370 (20.3%)	18470 (19.6%)	–	–
Comorbidities										
Hypertension	77769 (53.5%)	19230 (44.8%)	21809 (65.9%)	2234 (43.6%)	5381 (56.1%)	29115 (53.3%)	26135 (51.1%)	51634 (54.8%)	12760 (53%)	12192 (55.6%)
Diabetes	22150 (15.2%)	4882 (11.4%)	6716 (20.3%)	614 (12%)	1531 (16%)	8407 (15.4%)	9281 (18.2%)	12869 (13.7%)	3163 (13.1%)	3974 (18.1%)
Hearing loss	27747 (19.1%)	7533 (17.6%)	6708 (20.3%)	818 (16%)	1702 (17.8%)	10986 (20.1%)	10685 (20.9%)	17062 (18.1%)	4726 (19.6%)	4174 (19%)
Depression	29707 (20.4%)	7775 (18.1%)	7363 (22.2%)	1309 (25.6%)	1857 (19.4%)	11403 (20.9%)	8462 (16.6%)	21245 (22.5%)	4815 (20%)	4723 (21.5%)
Sleep apnea	621 (0.4%)	144 (0.3%)	227 (0.7%)	40 (0.8%)	45 (0.5%)	165 (0.3%)	467 (0.9%)	154 (0.2%)	116 (0.5%)	83 (0.4%)
Hypothyroidism or Hyperthyroidism	17556 (12.1%)	4811 (11.2%)	4285 (12.9%)	501 (9.8%)	1054 (11%)	6905 (12.6%)	2946 (5.8%)	14610 (15.5%)	2819 (11.7%)	2738 (12.5%)
Angina	21535 (14.8%)	4781 (11.1%)	6417 (19.4%)	709 (13.8%)	1556 (16.2%)	8072 (14.8%)	8993 (17.6%)	12542 (13.3%)	3182 (13.2%)	3740 (17.1%)
Atherosclerotic heart disease	15766 (10.8%)	3154 (7.4%)	4872 (14.7%)	463 (9%)	1152 (12%)	6125 (11.2%)	7397 (14.5%)	8369 (8.9%)	2501 (10.4%)	2668 (12.2%)
Heart failure	13845 (9.5%)	1884 (4.4%)	4033 (12.2%)	307 (6%)	625 (6.5%)	6996 (12.8%)	5230 (10.2%)	8615 (9.1%)	2058 (8.6%)	2376 (10.8%)
Atrial fibrillation	27816 (19.1%)	4681 (10.9%)	8633 (26.1%)	676 (13.2%)	1556 (16.2%)	12270 (22.5%)	10874 (21.3%)	16942 (18%)	4695 (19.5%)	4184 (19.1%)
Transient ischemic attack	13610 (9.4%)	2023 (4.7%)	5141 (15.5%)	341 (6.7%)	958 (10%)	5147 (9.4%)	5465 (10.7%)	8145 (8.6%)	2261 (9.4%)	2086 (9.5%)
Stroke	20083 (13.8%)	2115 (4.9%)	8389 (25.3%)	440 (8.6%)	1137 (11.9%)	8002 (14.7%)	8504 (16.6%)	11579 (12.3%)	3108 (12.9%)	3331 (15.2%)
Congenital heart disease	18873 (13%)	2910 (6.8%)	5315 (16.1%)	417 (8.1%)	873 (9.1%)	9358 (17.1%)	6974 (13.6%)	11899 (12.6%)	2876 (12%)	3160 (14.4%)
Peripheral artery disease	10587 (7.3%)	2051 (4.8%)	3489 (10.5%)	296 (5.8%)	672 (7%)	4079 (7.5%)	4767 (9.3%)	5820 (6.2%)	1469 (6.1%)	1890 (8.6%)
Cancer	30013 (20.7%)	8086 (18.8%)	7222 (21.8%)	919 (17.9%)	1830 (19.1%)	11956 (21.9%)	12666 (24.8%)	17347 (18.4%)	5275 (21.9%)	4040 (18.4%)
Chronic kidney disease	30950 (21.3%)	6844 (16%)	8856 (26.8%)	860 (16.8%)	1785 (18.6%)	12605 (23.1%)	11184 (21.9%)	19766 (21%)	4750 (19.7%)	5144 (23.5%)

(Continues)

TABLE 1 (Continued)

	All patients (n = 145 319)	Dementia subtype					Sex		Multiple deprivation categories	
		AD (n = 42 902)	Vascular (n = 33 106)	Other (n = 5 122)	Multiple type (n = 9 587)	Unspecified (n = 54 602)	Male (n = 51 102)	Female (n = 94 217)	Least deprived (n = 24 055)	Most deprived (n = 28 840)
Chronic obstructive pulmonary disease	14016 (9.6%)	3091 (7.2%)	3916 (11.8%)	371 (7.2%)	816 (8.5%)	5822 (10.7%)	6342 (12.4%)	7674 (8.1%)	1776 (7.4%)	2894 (13.2%)
Liver disease	838 (0.6%)	154 (0.4%)	196 (0.6%)	74 (1.4%)	38 (0.4%)	376 (0.7%)	393 (0.8%)	445 (0.5%)	117 (0.5%)	183 (0.8%)
>=2 comorbidities at baseline	96329 (66.3%)	23098 (53.8%)	26301 (79.4%)	2915 (56.9%)	6310 (65.8%)	37705 (69.1%)	34758 (68%)	61571 (65.4%)	15549 (64.6%)	15125 (69%)
>=3 comorbidities at baseline	69088 (47.5%)	14432 (33.6%)	20621 (62.3%)	1931 (37.7%)	4367 (45.6%)	27737 (50.8%)	25783 (50.5%)	43305 (46%)	10996 (45.7%)	11239 (51.3%)
>=4 comorbidities at baseline	47015 (32.4%)	8564 (20%)	15068 (45.5%)	1251 (24.4%)	2835 (29.6%)	19297 (35.3%)	18259 (35.7%)	28756 (30.5%)	7281 (30.3%)	7908 (36.1%)

Note: Data are mean (SD) or n (%). Socioeconomic status refers to Index of Multiple Deprivation 2015 categories, with the least deprived referring to the most affluent and most deprived the poorest areas. Number of comorbidities refers to any of the 20 conditions listed (obesity, hypertension, diabetes, hearing loss, depression, sleep apnea, thyroid dysfunction, angina, atherosclerotic heart disease, heart failure, atrial fibrillation, transient ischemic attack, stroke, congenital heart disease, peripheral artery disease, cancer, chronic kidney disease, chronic obstructive pulmonary disease, liver disease).

*P-values for differences between group defined by dementia subtypes, sex, and multiple deprivation status are all <0.001.

Abbreviations: AD, Alzheimer's disease; BMI, body mass index; SD, standard deviation.

Dementia incidence and fatality were both inversely associated with socioeconomic inequalities (Figure 2), with most deprived dementia patients having the highest death rate (fifth-year dementia-fatality: 64.1% [63.4% to 64.9%]) compared to the least deprived patients (59.5% [58.6% to 60.3%]) (Table S6 in supporting information). Similar results were observed in dementia disease burden by binary socioeconomic deprivation categories (Figure S2 in supporting information).

4 | DISCUSSION

In the study, we report the clinical progression of dementia in a real-world nationally representative cohort. To our knowledge, this is the largest study that specifically focuses on documenting the clinical progression of dementia, including incidence, the occurrence of comorbidities, mortality, and cause of death. The most frequent comorbidities were hypertension, cataracts, chronic kidney disease, cancer, depression, hearing loss, and AF. One in two dementia patients had three or more comorbidities at the time of diagnosis. Urinary tract infections and type 2 diabetes were the main causes of clinical visits before and after a dementia diagnosis. Post diagnosis, patients were over time increasingly hospitalized for an infection in the respiratory system. About a quarter of incident dementia patients died within the first year, and nearly half died within 5 years of diagnosis. Dementia was the main cause of excess deaths in dementia patients when compared to age- and sex-matched controls; diseases of the circulatory system contributed to a higher percentage of deaths in both groups.

Among the very old (those aged 90 years and older) our study reported a temporal trend of reduced dementia incidence, decreased cumulative incidence, and mortality of dementia. A lower prevalence of dementia in the very old has also been observed previously.[26] In the UK, dementia indicators were introduced into the Quality and Outcomes Framework (QOF) since 2006–2007, and there has been a gradual increase in dementia case reporting.[27] Previous research in China reported individuals aged between 95 and 99 years with the highest dementia prevalence.[7] The difference in the between-country burden of dementia may be partially due to risk profiles such as the prevalence of metabolic or cardiovascular risk factors[5,23] and potentially the awareness and reporting of dementia.

Our study showed that 80% of patients were diagnosed at the age of 76 years or older when multi-comorbidity is common. Hypertension, hearing loss, AF, chronic kidney disease, depression, and cancer were prevalent co-occurrence conditions at the time of diagnosis and higher in vascular dementia than in AD or other dementia. In this cohort of incident dementia patients prevalence of AF at the time of diagnosis is 19.1%. This confirms the previously described association between AF and dementia.[28] However, in our study, this finding was primarily found in vascular dementia. For AD dementia, the AF prevalence is much lower.

Our results showed more patients seeking dementia treatment at primary care after diagnosis, reflecting that individuals with dementia were primarily managed within the community. Infections were common among patients with advanced dementia, and our findings
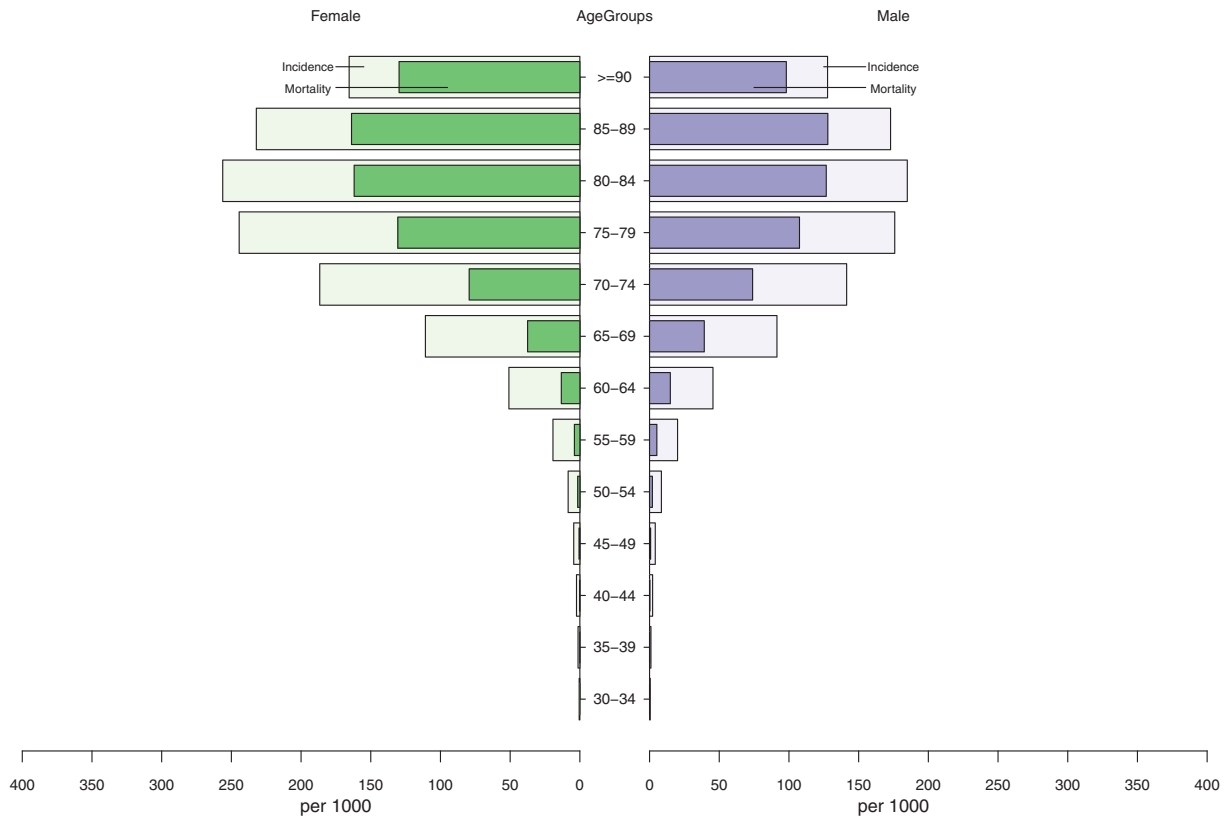
FIGURE 1 Observed cumulative dementia incidence and estimated mortality among incident cases by age groups in men and women
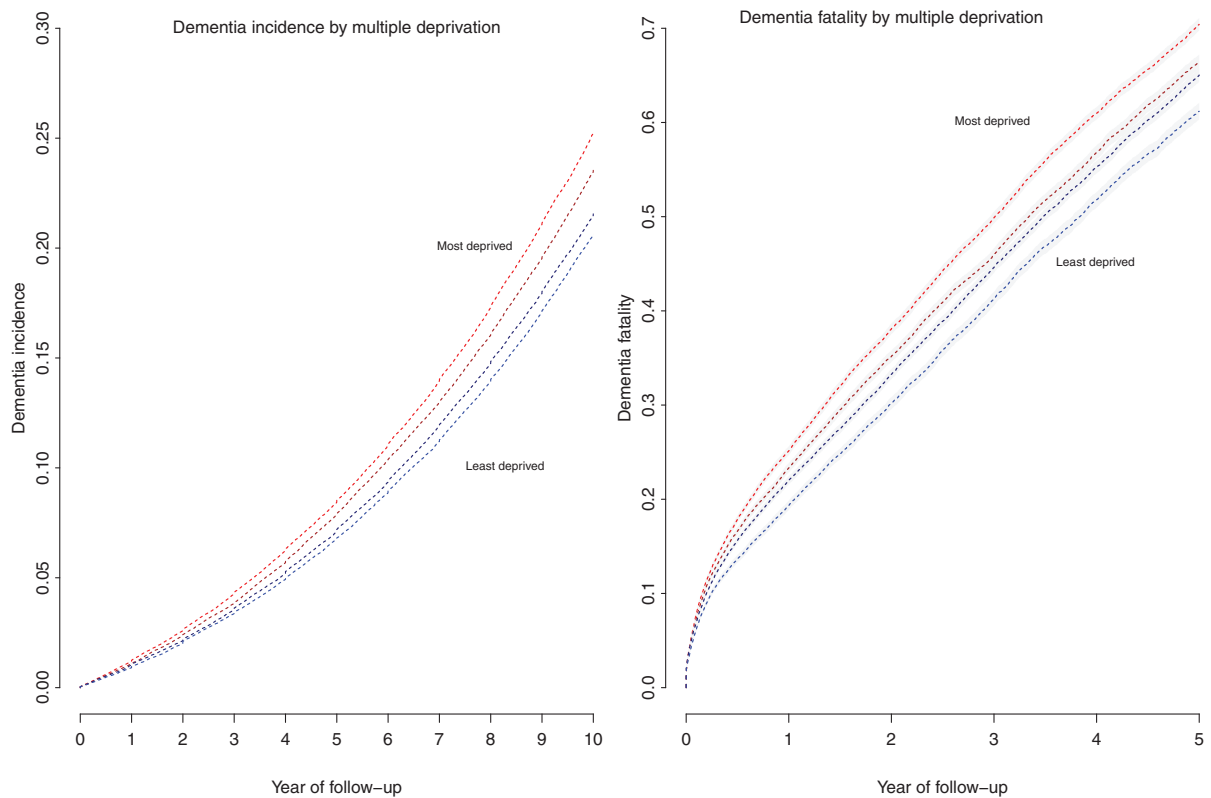
FIGURE 2 Dementia incidence rate and fatality by socioeconomic deprivation categories

TABLE 2 Top 10 reasons for hospitalization and general practice consultation in dementia patients prior to incident dementia diagnosis

(A) Hospitalisation

Ranks	4–5 years before	Cases%	Ctrls%	Ratio	2–3 years before	Cases%	Ctrls%	Ratio	1 year before	Cases%	Ctrls%	Ratio
	Term				Term				Term			
1	Cataract, unspecified (H26.9)	7.177	9.063	0.79	Cataract, unspecified (H26.9)	5.64	8.177	0.69	▲Urinary tract infection, site not specified (N39.0)	6.714	1.432	**4.69**
2	Urinary tract infection, site not specified (N39.0)	1.989	0.854	**2.33**	Urinary tract infection, site not specified (N39.0)	3.573	1.124	**3.18**	★Disorientation, unspecified (R41.0)	3.014	0.285	**10.58**
3	Senile nuclear cataract (H25.1)	1.885	1.51	1.25	▲Syncope and collapse (R55)	2.002	0.973	2.06	▲Unknown & unspecified causes of morbidity (R69)	2.909	1.709	1.7
4	Atrial fibrillation and flutter (I48)	1.689	1.594	1.06	▲Fracture of neck of femur (S72.0)	1.814	1.5	1.21	▼Cataract, unspecified (H26.9)	2.730	6.431	0.42
5	Fracture of neck of femur (S72.0)	1.668	1.51	1.1	▼Senile nuclear cataract (H25.1)	1.787	1.442	1.24	▲Senility (R54)	2.348	0.847	**2.77**
6	Syncope and collapse (R55)	1.589	0.844	**1.88**	Atrial fibrillation and flutter (I48)	1.74	1.691	1.03	Fracture of neck of femur (S72.0)	2.266	1.63	1.39
7	Senile cataract, unspecified (H25.9)	1.508	2.146	0.7	▲Unspecified acute lower respiratory infection (J22)	1.534	1.349	1.14	Syncope and Collapse (R55)	2.208	1.027	2.15
8	Unknown and unspecified causes of morbidity (R69)	1.308	0.938	1.39	★Senility (R54)	1.477	0.518	**2.85**	Unspecified acute lower respiratory infection (J22)	2.057	1.57	1.31
9	Chest pain, unspecified (R07.4)	1.286	0.896	**1.44**	★Cerebral infarction, unspecified (I63.9)	1.427	0.562	**2.54**	Cerebral infarction, unspecified (I63.9)	1.796	0.753	2.38
10	Unspecified acute lower respiratory infection(J22)	1.148	0.969	1.18	Unknown and unspecified causes of morbidity (R69)	1.411	1.237	1.14	★Lobar pneumonia, unspecified (J18.1)	1.671	0.652	2.56

Incident dementia

Ranks	1 years before	Cases%	Ctrls%	Ratio	2-3 years before	Cases%	Ctrls%	Ratio	4-5 year before	Cases%	Ctrls%	Ratio
	Term				Term				Term			
1	Urinary tract infection, site not specified (N39.0)	7.442	1.726	**4.31**	Urinary tract infection, site not specified (N39.0)	7.634	1.822	**4.19**	Urinary tract infection, site not specified (N39.0)	7.832	2.271	**3.45**
2	★Unspecified dementia (F03)	4.073			▲Fracture of neck of femur (S72.0)	3.187	2.109	1.51	Fracture of neck of femur (S72.0)	3.722	2.165	1.72
3	▲Fracture of neck of femur (S72.0)	2.885	1.903	1.52	▲Unspecified acute lower respiratory infection (J22)	3.039	1.872	1.62	Lobar pneumonia, unspecified (J18.1)	3.33	0.948	3.51

TABLE 2 (Continued)

Incident dementia											
	1 years before				**2-3 years before**				**4-5 year before**		
Ranks	Term	Cases%	Ctrls%	Ratio	Term	Cases%	Ctrls%	Ratio	Term	Cases%	Ctrls%	Ratio
4	▲Lobar pneumonia, unspecified (J18.1)	2.776	0.841	**3.3**	Lobar pneumonia, unspecified (J18.1)	3.005	0.864	**3.48**	Unspecified acute lower respiratory infection (J22)	3.148	1.821	1.73
5	▲Unspecified acute lower respiratory infection (J22)	2.63	2.077	1.27	▼Unspecified dementia (F03)	2.673			▲Pneumonia, unspecified (J18.9)	2.724	1.066	**2.56**
6	★Pneumonia, unspecified (J18.9)	2.236	0.714	**3.13**	Pneumonia, unspecified (J18.9)	2.302	0.964	**2.39**	▼Unspecified dementia (F03)	2.272		
7	★Vascular dementia, unspecified (F01.9)	2.1			▲Syncope and collapse (R55)	1.998	0.989	2.02	Syncope and collapse (R55)	2.262	1.106	2.05
8	▼Senility (R54)	1.896	1.012	1.87	Unknown and unspecified causes of morbidity (R69)	1.741	2.205	0.79	▲Alzheimer's disease, unspecified (G30.9)	1.922		
9	Unknown & unspecified causes of morbidity (R69)	1.754	1.83	0.96	★Alzheimer's disease, unspecified (G30.9)	1.703			★Pneumonitis due to food and vomit (J69.0)	1.437	0.182	**7.91**
10	▼Syncope and collapse (R55)	1.746	0.92	1.9	★Cataract, unspecified (H26.9)	1.618	6.196	0.26	★Vascular dementia, unspecified (F01.9)	1.423		

(B) General Practice Consultation											
	4-5 years before				**2–3 years before**				**1 year before**		
Ranks	Term	Cases%	Ctrls%	Ratio	Term	Cases%	Ctrls%	Ratio	Term	Cases%	Ctrls%	Ratio
1	Hypertension	5.240	5.844	0.9	Hypertension	4.003	5.679	0.7	▲Urinary tract infection	5.886	3.871	**1.52**
2	Chest_infection	3.405	4.5	0.76	Chest_infection	3.836	4.971	0.77	Chest infection	4.486	5.295	0.85
3	Urinary tract infection	2.975	2.735	1.09	Urinary tract infection	3.835	3.273	1.17	▼Hypertension	2.450	4.402	0.56
4	Cataract	1.824	2.102	0.87	Cataract	1.623	2.19	0.74	Low back pain	1.366	1.137	1.2
5	Low back pain	1.629	0.708	**2.3**	Low back pain	1.607	0.757	**2.12**	Shoulder pain	1.232	1.064	1.16
6	Shoulder pain	1.575	1.069	1.47	Shoulder pain	1.541	1.057	**1.46**	★Cellulitis NOS	1.215	0.262	**4.64**
7	Cervicalgia - pain in neck	1.551	0.88	**1.76**	Cervicalgia - pain in neck	1.454	1.009	**1.44**	Hip pain	1.189	0.681	1.75
8	Osteoarthritis	1.479	1.225	1.21	★Hip pain	1.336	0.577	**2.32**	★Type 2 diabetes mellitus	1.109	0.346	**3.2**
9	Type 2 diabetes mellitus	1.32	0.342	**3.86**	▲Wax in ear	1.317	1.82	0.72	▼Cataract	1.064	1.823	0.58
10	Wax in ear	1.281	2.007	0.64	▼Osteoarthritis	1.295	1.148	1.13	▼Cervicalgia/pain in neck	1.008	0.893	1.13

(Continues)

TABLE 2 (Continued)

Incident dementia											
	1 years before				**2–3 years before**				**4–5 year before**		
Ranks	Term	Cases%	Ctrls%	Ratio	Term	Cases%	Ctrls%	Ratio	Term	Cases%	Ctrls%	Ratio
1	Urinary tract infection	6.798	4.094	**1.66**	Urinary tract infection	8.382	4.242	1.98	Urinary tract infection	9.525	4.124	**2.31**
2	Chest infection	5.322	5.385	0.99	Chest_infection	7.764	5.653	1.37	Chest_infection	9.456	5.404	**1.75**
3	★Senile dementia	3.446			Senile_dementia	1.816	0	0	Senile_dementia	1.679	0	0
4	★Alzheimer's disease	3.291			Alzheimer's_ disease	1.807	0	0	Alzheimer's_ disease	1.675	0	0
5	▼ Hypertension	1.943	4.245	0.46	Hypertension	1.693	5.29	0.32	▲Acute conjunctivitis	1.504	0.625	**2.4**
6	★Vascular dementia	1.616			▲Cellulitis NOS	1.421	0.646	**2.2**	Cellulitis NOS	1.45	0.86	1.69
7	★Unspecified dementia	1.269			★Acute conjunctivitis	1.172	0.576	**2.03**	▼Hypertension	1.294	5.2	0.25
8	▼Cellulitis NOS	1.163	0.47	**2.47**	★Hip pain	1.168	0.921	1.27	★Upper respiratory infection NOS	1.172	0.942	1.24
9	★Fracture of the neck of the femur	1.138	0.412	**2.76**	★Type 2 diabetes mellitus	1.157	0.547	**2.11**	Type 2 diabetes mellitus	1.116	0.665	1.68
10	▼Low back pain	0.956	1.331	0.72	★Shoulder pain	1.139	1.118	1.02	▼Hip pain	1.05	1.169	0.9

Note: The highest three ratios comparing dementia patients to controls are in bold. ★condition was absent in the top 10 rank in the previous range and appeared in the current range. The ranking and proportion of the condition in dementia patients was higher (▲) or lower (▼) in the current range compared to the previous range.

suggest that hospitalizations for urinary tract infection may occur about two to three times more often in dementia patients than in controls within 5 years to 1 year before and after a dementia diagnosis. Cerebrovascular disease is a risk factor of dementia,[5] and we observed multiple hospitalizations for cerebral infarction within 3 years preceding diagnosis. After diagnosis, the present study reports an increased hospital admission among dementia patients for pneumonia and lower respiratory tract infection, and at a later stage, pneumonitis due to food and vomit. In primary care, compared to controls, individuals with dementia repeatedly consulted their GPs for pain (in the neck, shoulder, lower back, or hip) 5 years before diagnosis. Diabetes has been reported as one of the modifiable risk factors of dementia,[2,5] and our findings showed that a greater tendency of dementia patients to have primary care consultation for diabetes within 5 years before and after the dementia diagnosis.

Dementia shortens life, even after controlling for age, and we found one out of four individuals with dementia died within the first year after diagnosis, and nearly two in every three dementia patients within 5 years. AD appeared to have lower mortality compared to vascular or other dementia, which may be attributed to fewer comorbidities in patients with AD. Dementia was the leading cause of death among diagnosed individuals, followed by disease of the circulatory system. Although infection was common among dementia patients, the proportion with infection recorded as the primary cause of death was similar among individuals with dementia and their age and sex-matched controls.

4.1 | Practice implications and future research

The notable proportion of dementia patients not receiving any primary care input or hospitalization prior to their initial diagnosis indicates a potential delayed diagnosis of dementia.[29,30] Efforts to increase the awareness of dementia for the public, and reduce the stigma of dementia diagnosis, are of utmost importance.[29,30] The incidence of other nervous degenerative diseases in the study was lower than that reported in the recent meta-analyses,[31] although estimates might not be directly comparable due to the heterogeneity of study populations and design. It is possible that more complete documentation of the prodromal stage of dementia in routine care may aid in the early diagnosis and care for dementia. The clinical signal of a presence of multiple dementia risk factors, AF or cardiovascular comorbidity, repeated inpatient or primary care visits for infections, or unknown causes of morbidity in senior adults should alert clinicians to associated cognitive impairment. Urinary tract infections may be associated with dementia or related conditions and require both dementia and comorbidity management. Frequent hospitalization for disorientation suggests significant cognitive impairment even though these were observed 3 years
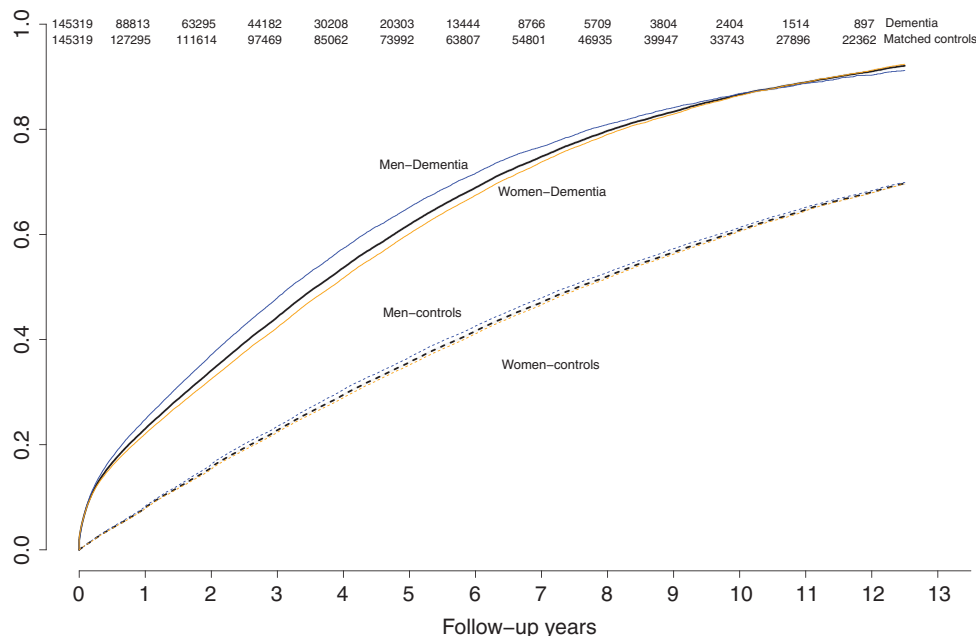
FIGURE 3 The mortality rate in incident dementia cases and their age and sex-matched controls
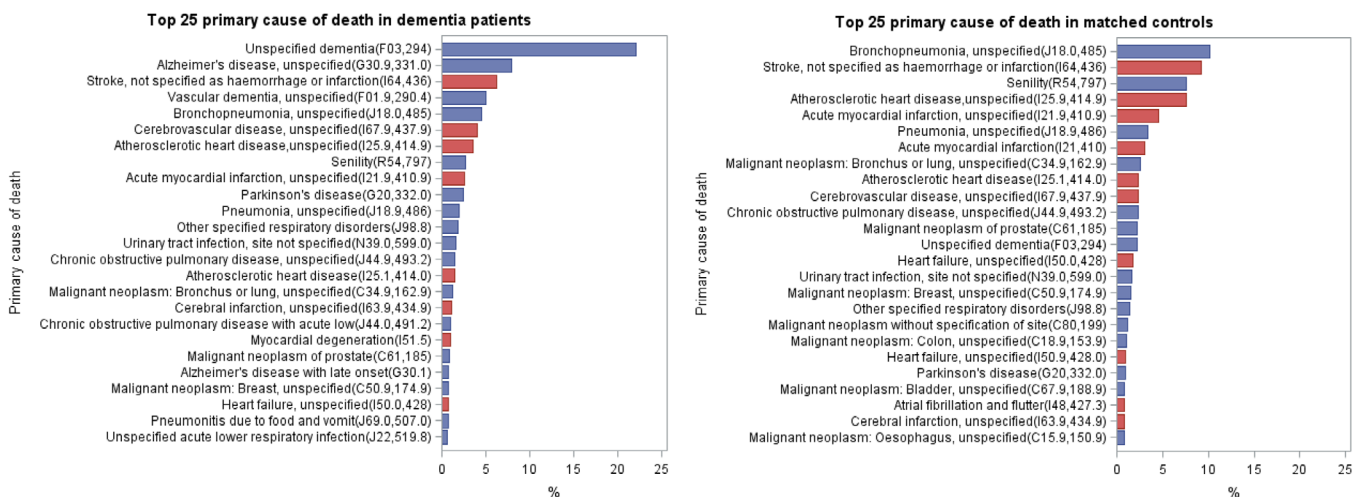
FIGURE 4 Leading primary cause of death in dementia patients and in age and sex-matched controls

before a dementia diagnosis was made. With the high possibility of infections, antimicrobial treatments may need to be carefully given to dementia patients to minimize the risk of multidrug-resistant organisms. Our study showed a higher dementia incidence and mortality among people living in higher deprived areas than in affluent neighborhoods. A previous survey also reported higher dementia incidence rates in the more deprived areas.[9] Dementia patients living in higher deprived areas were diagnosed at a younger age, suggesting underdiagnosis may be less likely, and the greater dementia burden may be due to the higher prevalence of risk factors and comorbidities in these areas. Efforts to reduce comorbidities and risk factors in individuals living in areas with high deprivation may facilitate the reduction of dementia incidence and deaths.

Future studies of mortality discrepancy by comorbidities and differences in comorbidities by socioeconomic status are required. Our study reported repeated primary care consultation for pain was more frequent in dementia patients than controls; a recent review summarized the structural and functional change of the brain associated with chronic pain.[32] Future studies are required to investigate if chronic pain is a risk factor of dementia and its underlying mechanism. Although with a small occurrence, our study reported dementia diagnosed at middle age. Non-White ethnicity (the minority in this population) was reported to be associated with deprivation and access to dementia care.[33] Though a detailed ethnicity analysis was beyond the scope and capability of the data, future research of ethnicity differentials and interaction with deprivation on dementia care and patient

outcomes could inform health policy and practice recommendations. Further research to study young-onset dementia, its risk factors, and care are required to ease the extended disease burden.

This study has several strengths. First, the nationally representative population provided precise estimates with large sample size. Second, by including all patients the outcome can be representative of the national population of patients. Third, the use of a wide range of predictor variables, including sociodemographic, and the unique data on clinical factors enables a detailed investigation of risk factors and comorbidities. Fourth, the study provides a new depth and richness to understanding the way in which dementia patients present to the health-care system both prior to and after diagnosis, and fifth, the prospective longitudinal design enabled the investigation of prognosis during extended follow-up years.

There are also limitations. As data linkage was available for consented general practices, the data did not include all practices in the nation, whereas it was representative of the UK population. As routinely collected clinical information, our data did not have information on certain risk factors for dementia, such as education, social isolation, or management of comorbidities prior to diagnosis,[2] which may be available in longitudinal cohorts specifically designed for dementia research.[8,9] Genetic disposition (apolipoprotein E ε4 allele)[5,34] and air pollution[2] are also risk factors for dementia, but this information is not available in our data. BMI at diagnosis was available for 40% of dementia patients. In the UK, documentation of obesity in primary health care records is one of the national quality of care indicators.[35] We thus assumed those with missing BMI (thus missing obesity) were not obese. Although the risk factors and comorbid conditions were diagnosed prior to the initial diagnosis of dementia, conditions such as depression may be caused by the preclinical progression of dementia-associated disease. Information on neuropsychological assessments was unavailable and there may be uncertainty in the recording of diagnosis at early stages, but the use of diagnostic codes (ICD-10 and Read terms) were consistent during the study period. Clinical diagnosis of the underlying disease causing dementia is difficult in the absence of reliable biomarkers and no neuropathological confirmation was available.

Our findings highlight the need for future research to target different prevention strategies, such as risk factor control and comorbidity treatment, on dementia incidence, as well as for the evaluation of the effectiveness of dementia management strategies/models of care on prognosis and mortality. Results of the study aid understanding of dementia epidemiology, how dementia patients present to the healthcare system, and their subsequent clinical course, and therefore can help inform strategies for the early detection and care for individuals with dementia.

4.2 | Contributors

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. SCC accesses and analyzes the data in the study and had final responsibility for the decision to submit for publication.

4.3 | Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting of our research. We plan to involve patient groups in the dissemination of the study results.

CONFLICTS OF INTEREST

JCW is an employee of GSK and owns shares in GSK. All other authors declare no conflict of interest.

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