Risk of suicide after dementia diagnosis: a longitudinal population-based study

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Key points (100 words)

Question: Is there an association between a dementia diagnosis and a higher risk of suicide?

Findings: In this nationally representative case-control study including 594674 persons in England from 2001 through 2019, we delineated subgroups of patients with dementia who were at increased suicide risk: those diagnosed before age 65 (particularly in the three months post-diagnostic period), those in the first three months following diagnosis, and those with known psychiatric comorbidities.

Meaning: Given the current efforts to improve rates of dementia diagnosis, the available evidence emphasizes the importance of concurrent implementation of suicide risk assessment for the identified high-risk groups.

Twitter (146 characters)

In this longitudinal population study, Alothman et al. report increased suicide risk in patients with young-onset dementia and those within 3 months of dementia diagnosis

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Abstract (338 words)

Importance: Patients with dementia may be at an increased suicide risk. Identifying groups at greatest risk of suicide would support targeted risk reduction efforts by clinical dementia services.

Objectives: To examine the association between a dementia diagnosis and suicide risk in the general population, and to identify high-risk subgroups.

Study design

A population-based case-control study in England from 2001 through 2019 (N=594 674).

Setting

Multiple linked electronic records from primary care, secondary care and the Office for National Statistics (ONS).

Participants

All patients aged ≥15 registered in the ONS in England with a death coded as suicide/open verdict from 2001 to 2019 (n=14515). Up to 40 live controls per suicide case were randomly matched on primary care practice and suicide date.

Exposure:

Patients with codes referring to a dementia diagnosis were identified in primary care and secondary care databases (n=4940).

Main outcome and measures

Odds ratios (ORs) were estimated using conditional logistic regression, adjusted for gender and age at suicide/index date.

Results

From the total sample of 594674 patients, 14515 (2.44%) died by suicide (74.75% males; median age at death, 47.43; interquartile range (IQR) 36.03-59.72). Among those who have died of suicide, 95 patients (1.92%) had a recorded dementia diagnosis (61.05% males; median age at death, 79.52; IQR, 67.12-85.48; median duration of follow-up, 2.27 years; IQR 0.99-4.42). There was no overall significant association between a dementia diagnosis and suicide risk (adjusted OR 1.05; 95% CI: 0.85-1.29). However, suicide risk was significantly increased in patients diagnosed with dementia before age 65 (adjusted OR 2.82; 95% C: 1.84-4.33), in the first three months after diagnosis (adjusted OR 2.47; 95% CI: 1.49-4.09) and in patients with dementia and psychiatric comorbidity (adjusted OR 1.5; 95% CI: 1.21-1.93). In patients below age 65 and within three months of diagnosis, suicide risk was 6.69 times (95% CI: 1.49-30.12) higher than in patients without dementia.

Conclusion and relevance

Our findings suggests that diagnostic and management services for dementia, in both primary and secondary care settings, should target suicide risk assessment to the identified high-risk groups.

Background (371 words)

Risk of death from suicide may be increased following a dementia diagnosis, due to both the psychological reaction to the diagnosis, and the neuropsychiatric phenomenology of dementia syndromes[1,2]. However, the relationship between dementia diagnosis and suicide risk has not been clearly demonstrated. For example, one cohort study in Denmark between 1990 and 2000 reported increased suicide risk in patients with dementia compared to those without dementia[3] while a second more recent cohort study conducted between 1980 and 2016 demonstrated decreased suicide risk[4]. The hospital-based nature of those studies potentially limits the generalisability of those results to the wider population. Further inconsistency in results was observed from a Korean study incorporating both patients with dementia and mild cognitive impairment which pointed to the absence of a significant association between dementia and suicide risk[5]; the inclusion of mild cognitive impairment may have modified the results.

Specific factors in relation to dementia have been suggested to be potential markers of suicide risk. According to a study in Georgia, the United States, young age at dementia diagnosis and a recent diagnosis were independent predictors for suicide risk, but the study excluded most patients below 65 years[6]. Young-onset dementia was also overlooked in other studies involving patients above 60[7] and 65[8] years, which showed that a recent diagnosis was associated with a high risk of suicide death. Improved understanding of high-risk groups is required to support targeted suicide risk assessment in dementia services, especially in view of policy initiatives designed to deliver higher rates of timely dementia diagnosis.

In order to clarify the association between dementia and suicide risk, we employed a large population dataset that was able to capture dementia diagnoses from both

community and hospital settings, as well as accurate data on causes of death. We hypothesised that relative to the general population, risk of suicide following a dementia diagnosis would be increased among those with young-onset dementia, those in the immediate post-diagnostic period, and those with known psychiatric comorbidities. We also sought to explore for the first time whether acetylcholinesterase inhibitors and memantine might influence suicide risk among patients with dementia, and whether suicide risk was greater among those with "unspecified dementia" diagnoses (which is a proxy for the quality of diagnostic services[9]).

Methods (964 words)

Study design, data source and participants

The study design was a case-control study in England between 2001 and 2019 using integrated electronic health records from three sources that allowed us to link information from primary care records, secondary care records and death certificate data: the Clinical Practice Research Datalink (CPRD); the Hospital Episode Statistics (HES) and the Office for National Statistics (ONS). Covering 6.9% of the UK population and being nationally representative with regards to age, gender and ethnicity[10], CPRD (both GOLD and Aurum) was employed as the source for primary care records. HES was used to complement data from secondary care inpatient records in England and the ONS was used to obtain death records related to suicide in England. The ONS is regarded as the gold standard for records of cause of death, including for suicide[11]. Patients were eligible for inclusion in this study if they had linkable data across all three databases and fulfilled the CPRD threshold for data

quality: “acceptable” patient records and “up-to-standard” general practice records (for CPRD GOLD).

Cases:

We included all patients in England from 2001 through 2019 with a cause of death coded as suicide or open verdict (suspicious death of which the cause was not specified by the coroner verdict) in the ONS records who fulfilled the study’s criteria. The inclusion of open verdict is recommended practice in studies of suicide death, as a large majority of open verdicts are due to suicide[12]. For patients to be included in the study, they had to be at least 15 years old at time of death, have at least one year of complete records in CPRD prior to death and meet the rest of the study’s eligibility criteria.

Controls

Controls were selected from the same primary care practice as the corresponding case and the selection process was conducted longitudinally over time through matching controls to cases on date of suicide death (risk-set sampling). The corresponding matched date of controls is hereafter known as the index date. For every suicide case, to maximise statistical efficiency, up to 40 live controls were selected from the cohort of subjects who met the study eligibility criteria. We chose a risk-set sampling approach so that important time-dependant factors (like competing risks and loss to follow-up) were indirectly addressed[13,14].

We only included controls who were at least 15 years old at index date and had at least one year of complete records in CPRD prior to index date. Of the 14515 suicide cases analysed in our study, 14240 cases (98.1% of cases) had 40 matched controls

and 275 cases (1.9% of cases) had between 9 and 39 matched controls. Figure 1 depicts our sampling process.

Exposure:

Dementia

Our exposure of interest was diagnosis of dementia in patients aged 45 years or above (below this age diagnoses of dementia are likely to represent rare neurometabolic disorders[15]). We used records from CPRD and HES for codes that refer to a dementia diagnosis at any point in a patient's clinical history up to suicide/index date. A full list of dementia terms and codes is available in Supplementary Information 1 together with data on the accuracy of dementia diagnosis records in CPRD[16]. Patients who were prescribed medications for dementia (donepezil, rivastigmine, galantamine and memantine) but had no documented dementia diagnosis in either CPRD or HES were included as patients with dementia given that those medications are exclusively indicated for use in dementia.

We also examined suicide risk in patients with dementia by age at diagnosis and recency of diagnosis. For those factors, we obtained records of the earliest ever documented date of dementia diagnosis in either dataset (CPRD or HES). We also performed a focused analysis of suicide risk stratified by age at diagnosis (<65 or ≥65). As a proxy for quality of health care, we assessed suicide risk according to whether patients had a specific dementia subtype diagnosed, or whether they had "unspecified dementia"[9]. While "unspecified dementia" may be applied as an interim diagnosis prior to dementia subtyping, in those who never receive a clear subtype

diagnosis it reflects a lack of access to appropriate specialist care[17]. We therefore defined those who received any subsequent subtype diagnosis as “specified dementia”, and only those who never received a clear dementia subtype diagnosis as “unspecified dementia”.

We collated records from CPRD for the four licensed pharmacological treatments for Alzheimer’s disease (donepezil, rivastigmine, galantamine and memantine) prescribed at any point up to suicide/index date.

Covariates:

Gender and age at suicide/index date were included as covariates in all analyses. Given its strongly nonlinear association with dementia, age (at suicide/index date for cases/controls) was treated as a categorical variable divided into ten quantiles. Further analysis included the presence or absence of psychiatric illnesses in patients with dementia. For psychiatric illnesses, we identified records in CPRD and HES of the following psychiatric illnesses: affective disorders, schizophrenia spectrum (and other psychosis), anxiety including obsessive compulsive disorders, personality disorders, eating disorders, sleep disorders, and substance misuse. See Supplementary Table 2 for a full list of terms and codes used for psychiatric illnesses.

Analysis

Conditional logistic regression was used to estimate odds ratios (ORs). ORs in our study can be interpreted as rate ratios given the risk-set sampling nature of the

study[14]. Age (at suicide/index date for cases/controls) was fitted categorically into 10 quantiles in the multivariable model. Interaction with gender and age (at suicide/index date) were assessed using the likelihood ratio test (LRT) by fitting an interaction term. To obtain single P-values across categories, the LRT was also employed.

The study was approved by the MHRA Independent Scientific Advisory Committee (reference number 20_186RA). The requirement for informed consent was waived as generic ethics approval is granted for CPRD for the examination of de-identified patients in observational research. We followed RECORD guidelines for reporting our study[18].

Results (519 words)

As presented in Table 1, there were 594674 patients in our study: 14515 (2.44%) were suicide cases and 580159 (97.56%) were controls. In total, there were 4940 patients identified with a dementia diagnosis (median duration of follow-up, 2.27 years; Interquartile range IQR 0.99 to 4.42) of whom 95 patients (1.92% of patients with dementia) had died from suicide. Patients with dementia who died by suicide had a median age at death of 79.52 years (IQR: 67.12 to 85.48) which was significantly younger than the median age of death of patients with dementia who died from causes other than suicide (87.88 years; IQR: 82.55 to 92.32). Patients with dementia who died by suicide also had a significantly younger age at diagnosis (76.05 years; IQR: 65.35 to 82.62) compared to the age at diagnosis of patients with dementia who died from other causes (80.50 years; IQR: 74.80 to 85.93).

Risk of suicide according to different dementia characteristics is shown in Table 2 and Figure 2. There was overall no significant association between a dementia diagnosis and suicide risk (adjusted OR 1.05, 95% CI: 0.85 to 1.29). However, compared to patients without a dementia diagnosis, patients who were diagnosed with dementia before the age of 65 and patients who were within 3 months of receiving a dementia diagnosis were at 2.82 times (95% CI: 95% CI 1.84 to 4.33) and 2.47 times (95% CI: 1.49 to 4.09) increased risk of suicide after adjusting for age and gender, respectively. In patients diagnosed with dementia before the age of 65, suicide risk was greatest in the first three months following a diagnosis (adjusted OR 6.69; 95% CI: 1.49 to 30.12) and remained significantly increased even after one year of diagnosis (adjusted OR 2.45; 95% CI: 1.50 to 4.02) compared to patients without a dementia diagnosis. In patients diagnosed with dementia at or after the age of 65, suicide risk was also significantly increased in the first three months following a diagnosis (adjusted OR 2.25; 95% CI: 1.31 to 3.86); however, the risk diminished after one year of diagnosis (adjusted OR 0.66; 95% CI: 0.48 to 0.90). Figure 2 is a visual representation of the relative risk of suicide among those diagnosed with dementia before and after the age of 65 relative to those without dementia in the three epochs following diagnosis.

Relative to patients without dementia, patients with dementia without a psychiatric diagnosis were at a statistically significantly lower risk of suicide (adjusted OR 0.48; 95% CI: 0.31 to 0.74) while patients with both a diagnosis of dementia and a psychiatric comorbidity were at a statistically significant increased risk of suicide (adjusted OR 1.52; 95% CI: 1.21 to 1.93). There was no statistically significant association in terms of dementia type specification and suicide risk. There was a

weak evidence of a reduced risk of suicide among patients who were prescribed medications for Alzheimer's disease (adjusted OR 0.37; 95% CI: 0.12 to 1.14; p=0.02 across categories), however this was imprecisely estimated. There was no evidence of significant interaction with either gender or age (at suicide/index date) in the association between dementia and suicide risk (P>0.05).

Discussion (969words)

In this longitudinal population-based study in England, we demonstrated that risk of death from suicide is increased in patients with dementia diagnosed before the age of 65, in patients with a recent dementia diagnosis (within three months), and in patients with existing diagnoses of psychiatric comorbidities. Suicide risk was particularly increased in patients who were diagnosed below 65 years in the three months post-diagnostic period.

The present study corroborates findings from earlier cohort studies which suggested younger age at dementia diagnosis[19] and a recent dementia diagnosis[7,8] as predictors for increased suicide risk. There could be several possible explanations as to why younger patients with dementia were affected by their diagnosis more than older age-groups. The relative rarity and unexpectedness of the diagnosis in younger patients can possibly make the acceptance of and adjustment to the condition by younger age-groups more difficult. Additionally, younger patients, more than older patients with dementia may forecast worse outcomes of their disorder in relation to their life expectancy; they may perceive that they will live long enough to progressively experience the most severe form of the disorder. As explained by the interpersonal theory of suicide, perceived burdensomeness is a critical pillar for suicidal behaviour[20]; that perception of burdensomeness may be higher in younger

patients with dementia who are more likely to be in their work productive years as well as have family caring responsibilities. Time since diagnosis is an important marker for suicide risk and the immediate period after being diagnosed appears to be particularly devastating for patients with early-onset dementia. This period is therefore critical for suicide risk assessment and prevention.

Another key factor contributing to suicidal behavior discussed by the interpersonal theory of suicide is the ability to engage in that behavior[20]. This factor could in part explain the high suicide risk observed in patients with a recent dementia diagnosis. A recent diagnosis could reflect the stage of the disorder in which patients are conscious of the deficit as well as having the functional and cognitive capabilities to plan and execute suicide. There is, however, no consensus in the literature over the definition of a recent diagnosis of dementia nor the period during which the patient remains at high risk of suicide. Based on case reports, the period between dementia diagnosis and suicide death ranged from “several weeks”[21] to two to three years after diagnosis[22–24]. In a Danish cohort study, suicide risk was documented to be highest in the first six months following a hospital-diagnosed dementia[3], and in another national study in the United States suicide risk in older populations (≥65 years) was highest in the first three months post-diagnosis period[8]. Nonetheless, given the high risk of both suicide attempt[25] and suicide death associated with a recent dementia diagnosis, we suggest that the current efforts for prompt dementia diagnosis should be accompanied by suicide risk assessment measures focused on the period immediately after diagnosis and in those with young-onset dementia.

The presence of psychiatric illnesses is an important determinant of suicide risk in patients with dementia. With our current analysis, we do not know whether psychiatric illnesses played a role predominantly as a risk factor for both

dementia[26,27] and suicide[28,29] or were a mediator in the association between dementia and suicide risk, or perhaps both. As potentially modifiable risk factors, screening and management of psychiatric illnesses in patients with dementia may help mitigate the increased suicide risk.

Although we were unable to confirm an association between prescribing of pharmacological treatments for dementia and suicide risk, the statistical significance across strata may be related to a potential protective effect by these medications and/or by the social support and quality of care linked with the prescription of these medications.

There are several strengths in this study. To our knowledge, this is the first large population-based study in England that assessed the relative risk of suicide in patients with dementia. The analysis of a large nationally representative sample allows the generalizability of results to England's population. Furthermore, using multiple integrated electronic databases created an optimal dataset to test the hypotheses of interest. In England, primary care records are the main data repository for each patient, and a diagnosis of dementia would usually be recorded here following diagnosis by a specialist. The confidence in the specificity of a diagnosis of dementia in primary care was confirmed in previous research[16]; accuracy of these records were optimised further by additional ascertainment of records from secondary care data[30,31]. The ability to link these with accurate causes of death from ONS data means that the combined dataset here is likely to have ascertained both exposure and outcome more accurately and completely than in any previous study addressing suicide risk in dementia.

Nevertheless, we acknowledge that there are important limitations in this study. Despite the large sample size, the number of patients with a dementia diagnosis who had died from suicide was small, meaning that some of the subgroup analyses were imprecisely estimated. As a result, we were unable to meaningfully analyse whether specific dementia syndromes are more associated with suicide risk, as highlighted in other studies[32,33]. We also lacked data to assess suicide risk in relation to other relevant information such as the stage of dementia and the type and source of social care provided to patients with dementia.

Our findings have important implications for dementia screening and management and for suicide prevention, both within specialist dementia services and primary care settings. Based on our results, we suggest that the current efforts for timely dementia diagnosis take place hand in hand with robust risk assessment and support, in particular targeting patients with dementia that are most vulnerable to suicide. These include patients diagnosed before the age of 65 years (especially in the immediate post-diagnostic period), patients who have been recently diagnosed, and patients with a diagnosis of psychiatric illness.

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Tables and Figures

Table 1: Descriptive statistics for whole sample

	Dementia,		Whole sample	
	n=4940 (0.83% of dataset)		N=594674	
	Suicide cases	Control	Suicide cases	Control
All				
n (%)	95 (1.92%)	4845 (98.08%)	14515 (2.44%)	580159 (97.56%)
Gender				
males (%)	58 (61.05)	1758 (36.28)	10850 (74.75)	289769 (50.0)
females (%)	37 (38.95)	3087 (63.72)	3665 (25.25)	290390 (50.10)
Median age at death[a] (IQR)	79.52 (67.12 to 85.48)	87.88[b] (82.55 to 92.32)	47.43 (36.03 to 59.72)	81.55[c] (71.95 to 88.37)
Median age at diagnosis (IQR)	76.05 (65.35 to 82.62)	80.50 (74.80 to 85.93)	-	-

Abbreviations: IQR: interquartile range

[a] Mortality data for those who did not die from suicide (controls) but died from other causes was based on death records from CPRD.

[b] 2281 of 4940 (46.17%) patients with dementia have death records from causes other than suicide.

[c] 49920 of 580159 (8.6%) controls have death history from causes other than suicide.

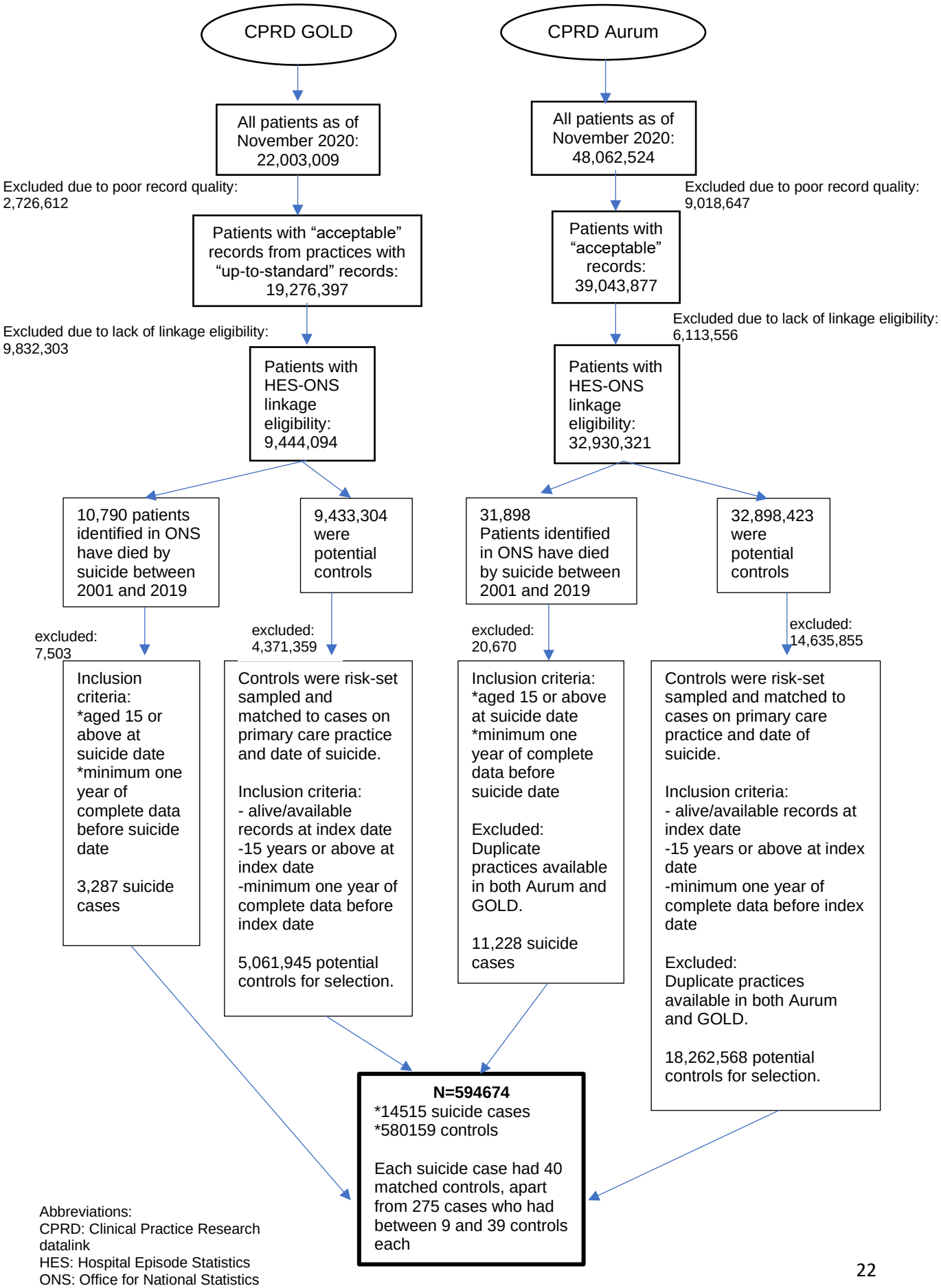
In patients with dementia, and in the whole study sample, P values were all <0.001 for differences in median age at death between those who died from suicide and those who died from other causes according to the Mann-Whitney U test.

Table 2: Relative risk of suicide in patients with a diagnosis of dementia.

Dementia	Adjusted odds ratios (95% CI) [a]
All	
no dementia diagnosis	1
dementia diagnosis	1.05 (0.85 to1.29)
Age at dementia diagnosis	
no dementia diagnosis	1
45 to <65	2.82 (1.84 to 4.33)
65 to <85	0.99 (0.76 to 1.30)
+85	0.56 (0.33 to 0.95)
	P=0.0001 across categories
Recency of dementia diagnosis (non-overlapping periods)	
no dementia diagnosis	1
0 up to <3 months	2.47 (1.49 to 4.09)
3 months to <1 year	1.34 (0.87 to 2.08)
+1 year	0.84 (0.64 to 1.10)
	P= 0.002 across categories
Age < 65 and recency of diagnosis	
no dementia diagnosis	1
0 up to <3 months	6.69 (1.49 to 30.12)
3 months to <1 year	4.50 (1.58 to 12.80)
+1 year	2.45 (1.50 to 4.02)
	P< 0.0001 across categories
Age ≥65 and recency of diagnosis	
no dementia diagnosis	1
0 up to <3 months	2.25 (1.31 to 3.86)
3 months to <1 year	1.14 (0.70 to 1.85)
+1 year	0.66 (0.48 to 0.90)
	P= 0.041 across categories
Status of psychiatric diagnosis	
no dementia diagnosis	1
dementia without psychiatric diagnosis	0.48 (0.31 to 0.74)
dementia with psychiatric diagnosis	1.52 (1.21 to 1.93)
	P= 0.0001 across categories
Dementia specification	
no dementia diagnosis	1
specific dementia diagnosis	1.00 (0.76 to 1.31)
unspecified dementia diagnosis	1.11 (0.82 to 1.52)
	P=0.71 across categories
Status of drugs for dementia	
no dementia diagnosis	1
dementia without dementia medications (n=4523)	1.11 (0.90 to 1.37)
dementia prescribed dementia medications (n=417)	0.37 (0.12 to 1.14) P=0.02 across categories

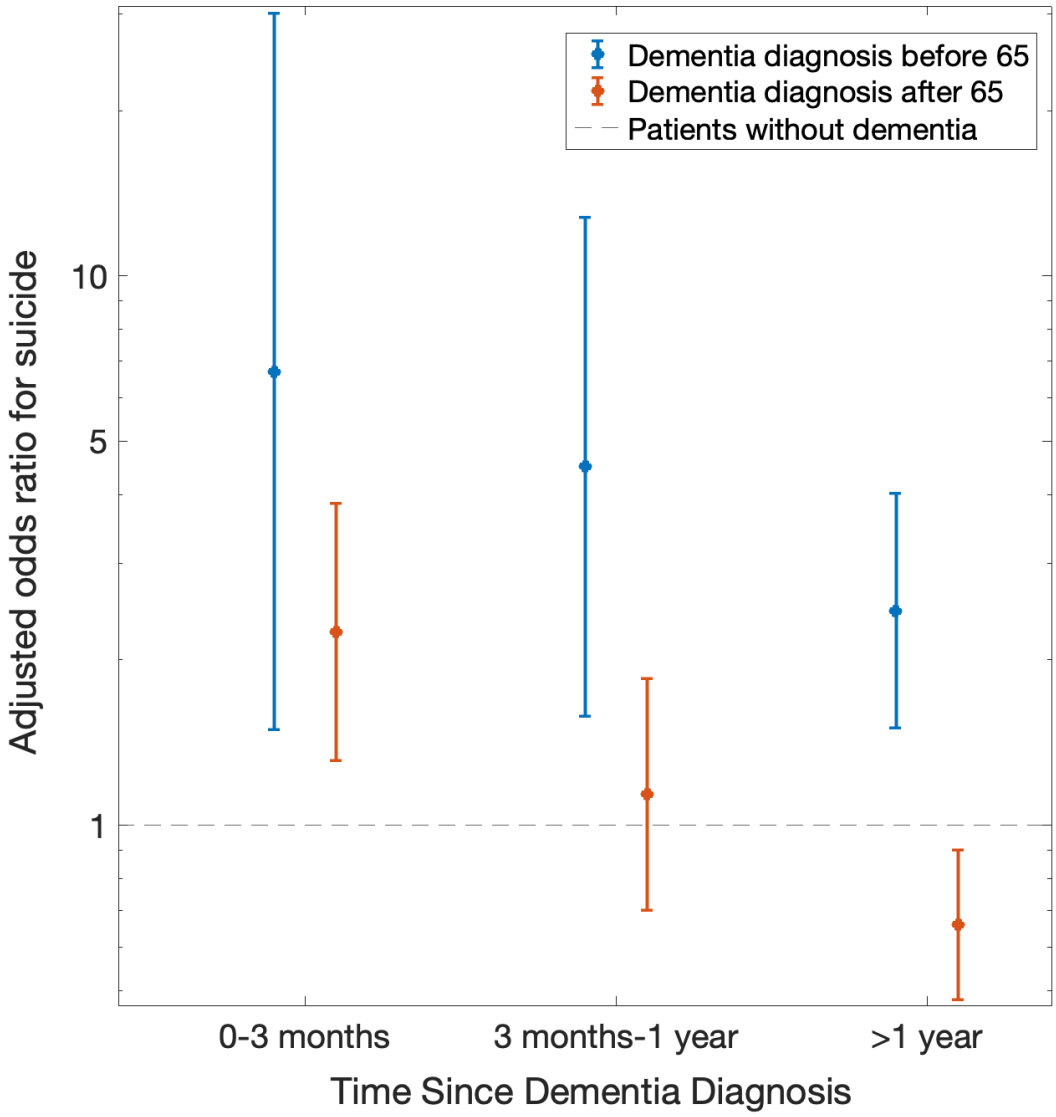
[a] adjusted for gender and age (at death date for suicide cases and at index date for controls).
P values across categories were tested using the likelihood ratio test.

Figure 1: Flow chart demonstrating the sampling process using both CPRD GOLD and Aurum



Abbreviations:
CPRD: Clinical Practice Research datalink
HES: Hospital Episode Statistics
ONS: Office for National Statistics

Figure 2: Risk of suicide following dementia diagnosis, stratified by age at diagnosis



The figure shows odds ratios for suicide adjusted for gender and age at suicide/index date separately for those diagnosed with dementia before and after the age of 65 relative to those without dementia in three epochs following diagnosis. The y-axis is displayed on a log scale. Error bars represent 95% confidence intervals.

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Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Data availability

The data used for this work were obtained under license from CPRD. This license does not permit further sharing. However, anyone wishing to access the data can obtain it direct from CPRD subject to their licensing requirements.

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