Introduction

Lower cognitive function in dementia is a predictor of mortality [1–3], although this has primarily been described in severe impairment, and effects of milder dysfunction remain controversial [4–10]. Lower cognitive function in older people without dementia has also been found to be associated with higher mortality, although this again remains inconclusive [8,11–17] and evidence on interventions to prevent mortality remains limited [18]. A better understanding is therefore needed of factors influencing prognosis in older people with and without dementia to aid care planning and clinical decision making [8,18,19].

Depression is commonly comorbid with dementia, and associated itself with worse outcome [10,16,20], although the relationship between the two may be complex, with depression potentially a cause of dementia, a consequence, a prodromal symptom, and/or a condition with shared risk factors [20,21]. Some research has suggested that depression is an independent risk factor for mortality in people without dementia [10,22], although others have not found this [16], and the diagnosis of depressive disorder itself is recognised to be associated with elevated mortality risk particularly in older people [23].

In the study described here, we analysed data from a retrospective cohort aged 65 years and above, using information from a large secondary mental healthcare provider in southeast London. We hypothesised that lower cognitive function assessed by Mini-Mental State Examination (MMSE) would be an independent risk factor for mortality in those with dementia, depression and those with a psychiatric diagnosis other than dementia.
Methods

Study setting

The South London and Maudsley NHS Foundation Trust (SLAM) Case Register has been described in detail previously [24]. In brief, the Clinical Record Interactive Search (CRIS) program allows researchers to access full but anonymised data from a large electronic mental health records dataset [25]. Within the UK National Health Service, secondary mental health care is provided according to defined geographic catchment areas. SLAM is one of the largest mental health providers in Europe, delivering comprehensive secondary mental health services to a population of approximately 1.23 million residents in four London boroughs (Lewisham, Lambeth, Southwark, and Croydon), including outpatient/community, inpatient, and general hospital liaison services. Currently, there are records on over 220,000 cases accessed by CRIS and this database has been extensively utilised [26–28]. The SLAM Case Register has been approved as an anonymised data resource for secondary analyses by Oxfordshire Research Ethics Committee C (08/H0606/71+5) and governance is provided for all projects by a patient-led oversight committee.

Analysed sample

All cases with at least one MMSE score recorded during the period between 1st Jan 2007 and 31st Dec 2010 were first identified. This sample was restricted to cases aged at least 65 years.

Figure 1. Diagram of sample selection and diagnosis subgroups. doi:10.1371/journal.pone.0105312.g001
**Table 1.** Distribution of baseline covariates among clients of a secondary mental health service provider aged 65 years old or more and by psychiatric diagnoses.

| Risk factors                        | Number (%)/mean ± SD |
|-------------------------------------|----------------------|
|                                     | All (N = 6,704)      | Dementia (n = 3,368) | Depression (n = 1,129) | Others (n = 2,207) |
| Age at MMSE assessment              | 80.24 ± 7.69         | 82.04 ± 7.00         | 77.97 ± 7.64           | 78.64 ± 8.06        |
| Gender                              |                      |                      |                        |                    |
| Female                              | 4,116 (61.4%)        | 2,111 (62.7%)        | 717 (63.5%)            | 1,288 (58.4%)       |
| Male                                | 2,587 (38.6%)        | 1,256 (37.3%)        | 412 (36.5%)            | 919 (41.6%)         |
| Ethnic group                        |                      |                      |                        |                    |
| White                               | 5,341 (79.7%)        | 2,715 (80.6%)        | 958 (84.9%)            | 1,668 (75.6%)       |
| Black                               | 757 (11.3%)          | 392 (11.6%)          | 83 (7.4%)              | 282 (12.8%)         |
| East Asia                           | 96 (1.4%)            | 41 (1.2%)            | 18 (1.6%)              | 37 (1.7%)           |
| South Asia                          | 165 (2.5%)           | 79 (2.4%)            | 23 (2.0%)              | 63 (2.9%)           |
| Unknown/Mixed/Others                | 345 (5.1%)           | 141 (4.2%)           | 47 (4.2%)              | 157 (7.1%)          |
| Marital status                      |                      |                      |                        |                    |
| Married/Civil partner/Cohabitig     | 1,970 (29.4%)        | 1,056 (31.4%)        | 312 (27.7%)            | 602 (27.3%)         |
| Single                              | 954 (14.2%)          | 403 (12.0%)          | 161 (14.3%)            | 390 (17.7%)         |
| Separated/Divorced                  | 629 (9.4%)           | 249 (7.4%)           | 119 (10.6%)            | 261 (11.8%)         |
| Widowed                             | 2,530 (37.7%)        | 1,378 (40.9%)        | 446 (39.5%)            | 706 (32.0%)         |
| Unknown                             | 621 (9.3%)           | 282 (8.4%)           | 91 (8.1%)              | 248 (11.2%)         |
| Area-level deprivation score        |                      |                      |                        |                    |
| 1<sup>st</sup> tertile (1.63–22.16, the least deprived group) | 2,202 (32.8%) | 1,143 (34.0%) | 329 (29.1%) | 730 (33.1%) |
| 2<sup>nd</sup> tertile (22.17–35.25) | 2,137 (31.9%) | 1,061 (31.5%) | 362 (32.1%) | 714 (32.4%) |
| 3<sup>rd</sup> tertile (35.26–65.53, the most deprived group) | 2,167 (32.3%) | 1,075 (31.9%) | 392 (35.7%) | 700 (31.7%) |
| Missing                             | 198 (3.0%)           | 89 (2.6%)            | 46 (4.1%)              | 63 (2.9%)           |
| Cognitive function                  |                      |                      |                        |                    |
| Non-impairment (MMSE: 30-25)       | 2,565 (38.3%)        | 530 (15.7%)          | 749 (66.3%)            | 1,286 (58.3%)       |
| Impairment (MMSE: 24-0)            | 4,139 (61.7%)        | 2,838 (84.3%)        | 380 (33.7%)            | 921 (41.7%)         |
| MMSE score in quintiles             |                      |                      |                        |                    |
| 1<sup>st</sup> quintile (30-28)     | 1,259 (18.8%)        | 131 (3.9%)           | 445 (39.4%)            | 683 (31.0%)         |
| 2<sup>nd</sup> quintile (27-25)     | 1,306 (19.5%)        | 399 (11.9%)          | 304 (26.9%)            | 603 (27.3%)         |
| 3<sup>rd</sup> quintile (24-21)     | 1,454 (21.7%)        | 812 (24.1%)          | 202 (17.9%)            | 440 (19.9%)         |
| 4<sup>th</sup> quintile (20-16)     | 1,395 (20.8%)        | 1,003 (29.8%)        | 115 (10.2%)            | 277 (12.6%)         |
| 5<sup>th</sup> quintile (15-0)      | 1,290 (19.2%)        | 1,023 (30.4%)        | 63 (5.6%)              | 204 (9.2%)          |

doi:10.1371/journal.pone.0105312.t001
Table 2. Effect of baseline covariates and associations with mortality assessed by Cox regressions (N = 6,704).

| Risk factors | Death (%) | Hazard Ratio (95% Confidence Interval) |
|--------------|-----------|----------------------------------------|
|              | Crude     | Adjusted                               |
| Age at MMSE assessment | – | 1.05 (1.05, 1.06)* – |
| Gender       |           |                                        |
| Female       | 22.79     | Ref                                    |
| Male         | 28.64     | 1.35 (1.22, 1.48)*                    |
| Ethnic group |           |                                        |
| White        | 27.20     | Ref                                    |
| Black        | 15.06     | 0.52 (0.43, 0.62)* 0.61 (0.50, 0.74)* |
| East Asia    | 14.58     | 0.51 (0.30, 0.86) 0.66 (0.39, 1.12)   |
| South Asia   | 13.94     | 0.49 (0.33, 0.75)* 0.59 (0.39, 0.90)  |
| Unknown/Mixed/Others | 21.74 | 0.87 (0.69, 1.09) 0.94 (0.70, 1.11) |
| Marital status |          |                                        |
| Married/Civil partner/Cohabiting | 21.12 | Ref Refa |
| Single       | 26.42     | 1.30 (1.11, 1.52)* 1.33 (1.13, 1.55)* |
| Separated/Divorced | 16.69 | 0.77 (0.62, 0.95) 0.93 (0.75, 1.16)  |
| Widowed      | 27.47     | 1.35 (1.20, 1.53)* 1.30 (1.14, 1.48)* |
| Unknown      | 33.98     | 1.59 (1.35, 1.88)* 1.50 (1.27, 1.78)* |
| Area-level deprivation score |          |                                        |
| 1st tertile (1.63–22.16, the least deprived group) | 22.84 | Ref Refb |
| 2nd tertile (22.17–35.25) | 26.16 | 1.11 (0.98, 1.25) 1.14 (1.02, 1.29)* |
| 3rd tertile (35.26–65.53, the most deprived group) | 26.81 | 1.20 (1.06, 1.35)* 1.26 (1.11, 1.42)* |
| Missing      | 18.18     | 0.78 (0.55, 1.09) 0.79 (0.66, 1.10)   |
| Diagnosis of dementia |          |                                        |
| No           | 22.12     | Ref                                    |
| Yes          | 27.94     | 1.28 (1.16, 1.41)* 1.08 (0.98, 1.19)  |
| Diagnosis of depression |          |                                        |
| No           | 24.57     | Ref                                    |
| Yes          | 26.39     | 1.11 (0.99, 1.25) 1.32 (1.17, 1.74)* |
| Cognitive function |          |                                        |
| Normal (MMSE: 30-25) | 19.10 | Ref Refb |
| Impaired (MMSE: 24-0) | 28.73 | 1.62 (1.46, 1.80)* 1.42 (1.28, 1.58)* |
| MMSE score   | –         | 0.96 (0.95, 0.96) 0.96 (0.96, 0.97)*  |
| MMSE score in quintiles |          |                                        |
| 1st quintile (30-28) | 17.39 | Ref Refb |
| 2nd quintile (27-25) | 20.75 | 1.20 (1.01, 1.44) 1.08 (0.90, 1.29)  |
| 3rd quintile (24-21) | 32.31 | 1.38 (1.17, 1.64)* 1.23 (1.03, 1.46)  |
| 4th quintile (20-16) | 29.32 | 1.84 (1.56, 2.17)* 1.54 (1.30, 1.83)* |
| 5th quintile (15-0) | 34.19 | 2.24 (1.90, 2.63)* 1.90 (1.60, 2.25)* |

*aAge and gender adjusted.

1Adjusted for age at assessment, gender, ethnicity group, marital status, and index of deprivation score; HR = 1.23 (95% CI: 1.18, 1.28) for each quintile increment.

* P-value<0.01,

p-value<0.05.

1P-value of test for linear trend <0.001.
doi:10.1371/journal.pone.0105312.t002

old at the date of this MMSE record, and excluded those with a recorded delirium diagnosis (ICD-10 code: F05) within three months before or after the date of the MMSE assessment. MMSE scores recorded during routine clinical care were derived from dedicated structured fields on the electronic health record, supplemented by a specific information extraction application developed using Generalised Architecture for Text Engineering (GATE) software: a natural language processing architecture which takes into account the linguistic context of a word or phrase of interest, thus allowing structured data to be obtained from open-text fields. The specific GATE applications were developed by programmers and validated against human raters to extract and code MMSE scores and associated dates of assessment with a recall (sensitivity) of 97% and precision (positive predictive value)
Covariates and analysis subgroups

Mental disorder diagnoses are categorised in structured fields on the source clinical record according to World Health Organization International Classification of Diseases 10th edition (ICD-10) codes. In addition, a further GATE information extraction application identifies text strings associated with a diagnosis statement in correspondence fields, and this was used for additional searches on predefined diagnostic terms. The following groups were defined for analysis: 1) a group with dementia was defined on the basis of a diagnosis (ICD-10 codes F00–F03) recorded anywhere before or up to six months after the index MMSE assessment; 2) within the non-dementia group, a group with depression (F32–F33) anytime before or up to six months after the MMSE assessment was specified for analysis; 3) the remainder within the non-dementia group consisted of elders with other diagnoses before the MMSE assessment, including schizophrenia and related psychotic disorders (F20–F29), anxiety spectrum and stress-related disorders (F40–F48), bipolar affective disorder (F30–F31), and others. Demographic data included age (defined at the index MMSE) and gender. Ethnic group was classified from a structured field in the record as: i) white British and other white background; ii) African, Caribbean and other black background; iii) east Asian; iv) south Asian; and v) mixed, unknown, or others. Marital status was categorised from a structured field into: i) married, civil partner, or cohabiting; ii) single; iii) separated or divorced; iv) widowed; and v) unknown. Area-level socioeconomic status was estimated from an index of multiple deprivation applied to the UK Census lower super output area (standard geographic areas with an average 1,500 residents). This index is defined by seven domains assessed in the national Census: employment, income, education, health, barriers to housing and services, crime and the living environment. Indices were calculated from 2001 Census output and were divided by tertiles for this analysis.

Mortality outcome

The outcome of interest in this analysis was all-cause mortality occurring from January 2007 to the end of July 2011. Information about each death was collected through a nationwide mortality tracing linked to the SLAM database on a monthly routine basis. In UK, all death certifications are linked by NHS number (a unique identifier for each UK NHS service user) to all healthcare providers, keeping these records up to date.

Results

A total of 9,683 subjects were identified with at least one MMSE score during the period of 01/01/2007 to 31/12/2010. Of these, 230 with an MMSE denominator less than 25, 2,257 aged less than 65 years old, and 492 with diagnoses of delirium were excluded (Figure 1). Of the remaining 6,704 subjects in the analysed sample, the mean (SD) index MMSE score was 21.2 (6.6), and 1,679 (25.0%) died prior to the end of the follow-up (31/07/2011). Around half (n = 3,368; 50.2%) had a diagnosis of dementia, and in those without dementia (n = 3,336), depression was the most common primary diagnosis (n = 1,129; 33.8%) followed by 30.8% with schizophrenia and related psychotic disorders, 17.1% with anxiety spectrum and stress-related disorders, and 6.8% with bipolar affective disorder.

The mean (SD) follow-up period was 26.5 (14.8) months. Figure 2 illustrates Kaplan-Meier survival curves comparing groups with and without cognitive impairment stratified by diagnosis subgroups (dementia, depression, and others). In all three subgroups, the difference between MMSE groups was statistically significant (p < 0.001).
Cognitive Function and Mortality

Table 1 revealed the basic characteristics of the study subjects. In Table 2, the unadjusted analyses showed that older age and male gender were associated with lower survival. After adjustment for age and gender, mortality was significantly raised in those with a diagnosis of depression, but did not differ significantly between those with/without dementia. Mortality risk was significantly lower in black and south Asian compared to white groups, and was higher in single and widowed compared to married/cohabiting subjects. Higher deprivation score was associated with increased risk of mortality with a significant linear trend (p-value<0.001). A fully adjusted hazard ratio (HR) of 1.42 (95% CI: 1.28, 1.58) was identified for MMSE score<25. When MMSE score was divided into quintiles, a significant linear trend was evident for all subjects with a fully adjusted HR of 1.23 (95% CI: 1.18, 1.28) for each unit increment in quintiles of MMSE estimated (Table 2), as well as in those with dementia (Figure 3 left; fully adjusted HR 1.25, 95% CI: 1.18–1.33), without dementia (adjusted HR 1.18, 95% CI: 1.12–1.25) with depression but no dementia (Figure 3 middle; 1.21, 1.10–1.33), and with other non-dementia diagnoses but no depression or dementia (Figure 3 right; 1.19, 1.11–1.28).

Discussion

In total, 6,704 older subjects were included for analyses, with 61.4% for females, 3,368 of them diagnosed as dementia and 3,336 of them as depression or other mental disorders. No matter if a dementia diagnosis was given, people with impaired cognitive function (MMSE score<25) showed worse survival with statistical significance. Linear trends of MMSE in quintiles were found for the groups of dementia and other non-dementia diagnoses. Cognitive impairment has been suggested to be associated with increased mortality in community samples [29–32], but this relationship between cognitive impairment and mortality in clinical samples has not been clear. Using a large anonymised electronic database containing mental health records for a geographic catchment of approximately 1.23 million residents, we investigated the relationship between cognitive function and mortality risk in older people within a mean period of over 2 years. We found that MMSE score was a substantial predictor of mortality, regardless of diagnosis. However, although linear trends were found for the quintiles of MMSE scores for different diagnosis subgroups, there still appeared to be individual dose-response patterns in terms of their effects on mortality.

People with dementia are known to have higher mortality rates than general population, and increasing severity of dementia is also associated with increased risk of mortality [33]. As cognitive impairment itself is a core construct in dementia, cognitive impairment is unsurprisingly a predictor of mortality in dementia [1–3]. Our analysis supported this, in that lower MMSE scores strongly predicted subsequent mortality in people with a dementia diagnosis (Figure 2 left). However, the effect was noted to be similar in people without a dementia diagnosis (Figure 2 middle & right), as has also been suggested [34]. Several studies have found that people with severe mental disorders (schizophrenia, depression, schizoaffective disorder, and bipolar disorder) have a higher mortality rate and a shortened life expectancy, comparing to the general population [35–38], an association which was not statistically significant on log-rank tests (p-value<0.001) with similar patterns.

Reference patterns in terms of their effects on mortality.

Author Contributions

Conceived and designed the experiments: YPS CKC RS. Performed the experiments: YPS CKC GP MB DT. Analyzed the data: YPS CKC. Contributed reagents/materials/analysis tools: RDH MB DT MH. Wrote the paper: YPS CKC MH RS.

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