Cognitive Trajectories in Comorbid Dementia With Schizophrenia or Bipolar Disorder: The South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Case Register

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ABSTRACT

Objectives: We aimed to compare trajectories of cognitive performance in individuals diagnosed with dementia with and without severe mental illness (SMI).

Design: Retrospective cohort study.

Setting: We used data from a large longitudinal mental healthcare case register, the Clinical Record Interactive Search (CRIS), at the South London and Maudsley NHS Foundation Trust (SLaM) which provides mental health services to four south London boroughs.

Participants: Our sample (N = 4718) consisted of any individual who had a primary or secondary diagnosis of dementia from 2007 to 2018, was 50 years old or over at first diagnosis of dementia and had at least 3 recorded Mini-Mental State Examination (MMSE) scores.

Measurements: Cognitive performance was measured using MMSE. Linear mixed models were fitted to explore whether MMSE trajectories differed between individuals with or without prior/current SMI diagnoses. Models were adjusted by socio-demographics, cardiovascular risk, smoking, and medication.

Results and conclusions: Our results showed differences in the rate of change, where individuals with comorbid SMI had a faster decline when compared with those that have dementia without comorbid...
SMI. However, this association was partially attenuated when adjusted by socio-demographics, smoking and cardiovascular risk factors; and more substantially attenuated when medication was included in models. Additional analyses showed that this accelerated decline might be more evident in individuals with bipolar disorders. Future research to detangle the potential biological underlying mechanisms of these associations is needed. (Am J Geriatr Psychiatry 2020; ■■:■■−■■)

INTRODUCTION

Most research on cognitive decline in individuals with dementia does not include individuals with comorbid severe mental illness (SMI; e.g., schizophrenia and bipolar disorder). This is because individuals with comorbidities in general, and mental health illness in particular, are traditionally excluded from large population studies or their numbers are very small. In recent decades, there has been a growing interest to include these under-represented subpopulations. As a result, most studies have explored cognitive performance in individuals diagnosed with SMI but not dementia. Most of these studies have explored cross-sectional differences between individuals with bipolar disorders and schizophrenia\(^1\) and their results tend to show similar cognitive profiles for both.\(^2,3\) However, some studies have suggested that differences might be arise when exploring this association in longitudinal settings.\(^4\)

To date, most longitudinal studies have not found differences between cognitive trajectories in individuals with schizophrenia and bipolar disorders.\(^5−7\) For example, Gildengers et al.\(^5\) compared the trajectories of cognitive performance in outpatients with bipolar disorder with healthy controls over 2 years and they found that although individuals with SMI had overall lower cognitive performance, their rates of change did not differ. Other studies also compared cognitive performance and trajectories between individuals with bipolar disorder and schizophrenia and found no relevant differences.\(^6,7\) A recent review highlighted that most of longitudinal studies have small sample sizes and they might be underpowered to detect subtle cognitive changes over time or to reveal differences between schizophrenia and bipolar disorders.\(^1\) Therefore, further research with larger sample sizes and longer follow ups are needed.

It has been suggested that the short term cognitive impairments associated with acute exacerbations of mental disorders do not result in an accelerated cognitive decline,\(^5\) other studies have suggested that psychosis could be a risk factor for the development of dementia\(^8,9\) and subsequent cognitive decline in individuals with other comorbidities such as Parkinson disease.\(^10\) Potential shared biological mechanisms could be associated with alterations of hypothalamic–pituitary–adrenal axis, mitochondrial dysfunction/oxidative stress, glutamatergic abnormalities found in bipolar disorders and dementia\(^11,12\) and/or with common cardiovascular risk factors which are independently associated with antipsychotic medication intake\(^12\) and with dementia risk.\(^8,9\) However, some authors do not find that these play a role in the increased risk for dementia in individuals with bipolar disorders.\(^13\) Less is known about the potential shared links between schizophrenia and dementia. Schizophrenia is considered a neurodevelopmental disorder with its distinct underlying biological mechanisms such as aberrant pruning of synapses\(^14\) and although previous research has discussed potential shared mechanisms with dementia,\(^15−17\) evidence remains scarce and inconclusive.

Given this context, there is an ongoing debate on the nature of the progression of cognitive changes in schizophrenia and bipolar disorders and it is yet not clear whether these are associated with a neurodevelopmental or neurodegenerative process such as dementia. Understanding the underlying biological mechanisms between SMI such as schizophrenia or bipolar disorders and dementia could contribute to improve healthcare and reveal potential new therapeutic targets. Therefore, there is a need for research to disentangle the complex inter-relationships between SMI and dementia, especially given that individuals with this comorbidity pattern are at increased risk of psychiatric hospitalizations and
higher levels of health care utilization12,18 and may share common determinants such as health behaviors or cardiovascular risk factors.18,19 The main aim of this study was to compare trajectories of cognitive performance in individuals diagnosed with dementia with and without SMI diagnosis using data from a large longitudinal mental healthcare case register, and to investigate associations with sociodemographic status, health behaviors, cardiovascular risk factors, and medication. In addition, we investigate whether different SMI diagnosis (schizophrenia and bipolar disorders) showed different cognitive trajectories when compared with individuals with only dementia.

METHODS

Setting and Sample

Data were extracted from the South London and Maudsley NHS Foundation Trust (SLaM) Clinical Record Interactive Search (CRIS). SLaM provides mental health services to a defined geographic catchment area of four south London boroughs (Lambeth, Southwark, Lewisham, and Croydon), with populations comparable overall with those of London as a whole in terms of age, gender, education and socioeconomic status distributions.20 CRIS provides researcher access to deidentified data from SLaM’s electronic health record which has been used across all services since 2006 and which has been substantially enhanced through a range of natural language processing (NLP) algorithms, as described in detail in an open-access catalogue (https://www.maudsleybrc.nihr.ac.uk/facilities/clinical-record-interactive-search-cris/cris-natural-language-processing/). The sample (N = 4718) consisted of any individual who had a primary or secondary diagnosis of dementia from 2007 to 2018, 50 years old or over at first diagnosis of dementia and at least three recorded MMSE scores, following Singer and Willet21 guideline. These individuals were similar for most of the relevant variables included in our study to those that were less than 50 years old at first diagnosis of dementia and those with at least one MMSE score but less than 3 MMSE measures (n = 10023). Within included individuals we found slightly higher percentages of Black Caribbean and married or cohabiting individuals and higher levels of education. Diagnoses are recorded in SLaM according to the International Classification of Mental and Behavioural Disorders-10 (ICD-10). Dementia was defined based on codes F00, F01, F02, F03, or F04; SMI included schizophrenia-spectrum disorders, bipolar affective disorders and manic episodes (codes F20-29, F30-31).

Variables

Cognitive performance. Cognitive performance was measured using extracted scores from the Mini-Mental State Examination (MMSE).22 The MMSE consists of 21 questions on orientation, immediate and delayed recall, naming, spelling, and simple arithmetic and constructional praxis. Higher scores indicate better cognitive performance. We used data from structured fields, and when these were not available, we extracted data from unstructured text fields, using NLP algorithms as in;23 13% of scores were derived from structured fields, and 87% using NLP.

Covariates. Socio-demographic covariates included age at baseline (i.e., when first MMSE was recorded), sex, education, ethnicity, marital status, deprivation index and English as first language. Education was derived from records as a binary variable with two levels, primary or lower education and secondary or higher education (i.e., at least GSCE or equivalent), and extracted using NLP algorithms.24 Ethnicity was grouped into White, Black African, Black Caribbean, Indian, mixed or other. Marital status was grouped in two categories: married/cohabiting and single/separated/divorced/widowed. Neighborhood deprivation was measured at Lower Super Output Area level (a standard UK residence unit with a mean population size of 1,500 residents) using the address recorded current or most recent at the index date, linked to the Index of Multiple Deprivation (IMD) score for that neighborhood, extracted from 2011 national Census data (Department for Communities and Local Government, 2015). IMD scores were then categorized as deciles with lower deciles were indicative of higher deprivation. Smoking status extracted using an NLP algorithm25 and individuals were categorized as never, current, and former smokers. Cardiovascular risk factors such as obesity, diabetes and hypertension were combined in an index which was used to classify individuals as normal or at risk. Data was extracted using a combination of
structured data when available and NLP techniques. Normal status was defined as a BMI between 18.5 and 25 (National, Clinical Guideline Centre UK, 2014), a systolic/diastolic blood pressure ratio up to 120/80 (National High Blood Pressure Education Program, 2003) and plasma glucose level lower than 5.5 (National Institute for Health and Care Excellence, 2012) Individuals were considered at cardiovascular risk when at least one of these indicators was not within clinically normal ranges.

Medication was extracted using a combination of structured and NLP derived data, identifying mentions or not of prescribed medications in three categories for this analysis: antipsychotic, antidepressant, and dementia-treatment agents (list provided in Supplemental Appendix 1).

Statistical Analyses

Preliminary analyses were performed to describe the characteristics of the sample and compare these between individuals diagnosed with SMI or not. To examine group differences in cognitive trajectories and investigate associations with covariates, we used linear mixed models with random coefficients. The main advantage of using linear mixed models is that they allow us to account for between and within individual variability. Linear and quadratic unconditional models were examined. Chronological age measured in 6-month intervals as the time metric. Intraclass coefficients (ICC) for unconditional models were estimated as a measure of variation. ICCs of between 0.20 and 0.80 are suggestive of between- and within-individual variations (i.e., differences between individuals and change over time). In order to investigate the independence of the association of interest, we first ran an unadjusted model (model 1), then a model adjusted by socio-demographic factors (model 2), followed by additional cumulative adjustments for smoking (model 3), cardiovascular risk factors (model 4), and medication (model 5). The fit of the models was compared using the Bayesian Information Criterion (BIC), which is an index that combines information on a model’s goodness of fit and parsimony. Lowest BIC is an indicator of better fit. Effect sizes for slopes were estimated using standardized regression coefficients. Missing values in some of our covariates was larger than 30% (ethnicity [n = 21, 0.44%], marital status [n = 51, 1.08%], IMD [n = 976, 20.68%], smoking status [n = 492, 10.42%], CVD risk [n = 1533, 32.49%] and first language [n = 1,995, 42.28%]), thus our models included a unknown category for these variables. Sensitivity analyses were performed to compare these models with cases with complete data for all covariates (n = 1,453). In addition, further sensitivity analyses were performed to ensure the robustness of our results considering attrition due to death or potential variance heterogeneity associated to age at diagnoses. In order to examine whether there could be any potential bias associated to the premature mortality in individuals with SMI we replicated our analyses restricting the sample to the individuals who were still alive at 2019 (n = 1766) and compared the results.

RESULTS

As can be seen in Table 1, individuals with dementia and SMI had slightly higher MMSE scores than those individuals with dementia alone [t(20826) = −8.71; p <0.001]. For all other variables exact Chi-square were performed. Individuals with dementia and comorbid SMI were also more likely to be younger [t (20826) = 26.16; p<0.001], from a minority ethnic group [χ² (4) = 127.31; p <0.001], not married [χ²(1) = 63.48; p<0.001], have higher education [χ²(1) = 248.42; p <0.001], be more socially deprived [χ²(4) = 51.89; p <0.001], at higher CVD risk [χ² (1) = 27.21; p <0.001], currently smoking [χ² (2) = 147.04; p <0.001] and taking antipsychotics [χ²(1) = 697.25; p <0.001] and antidepressants [χ²(1) = 106.56; p <0.001] (and less likely to be taking dementia-treatment agents [χ²(1) = 21.33; p <0.001]) when compared with those without comorbid SMI at first MMSE recorded. Within the group of individuals with dementia and SMI (Table 2), we examined whether there were differences related to the SMI diagnoses (bipolar versus schizophrenia) and we found that individuals with dementia and bipolar disorders had slightly higher MMSE scores than those individuals with dementia and schizophrenia [t(2640) = −1.39; p <0.001] and those with bipolar were disorders were more likely to be younger [t(2640) = 3.44; p <0.001]. Individuals with schizophrenia were more likely to be from a minority ethnic group [χ² (4) = 63.52; p <0.001], single or separated [χ²(1) = 25.27; p <0.001], have lower levels of education [χ²(1) = 3.05; p = 0.081], higher levels of social deprivation [χ²(4) = 18.26; p < 0.001] and less likely to be taking antidepressant medication.
There were no significant differences for gender, first language, smoking, CVD risk and other medication intake. Fisher exact Chi-square tests were additionally performed to explore the potential association between CVD risk and antipsychotic and no significant associations were found ($p = 0.33$ and $p = 0.79$, respectively).

| TABLE 1. Descriptive Statistics at Baseline for Maximal Sample Available (N = 4718) and Individuals With Dementia Alone and Individuals With Comorbid SMI |
|---------------------------------|--------------------------------|--------------------------------|
| **Total Sample (N = 4,718)**    | **Dementia Alone (n = 4,162)** | **Dementia and SMI (n = 556)** |
| **n**                           | **Mean (SD)**                  | **n**                           | **Mean (SD)**                  | **N**                           | **Mean (SD)**                  |
| MMSE***                         | 4718                           | 19.8(6.2)                       | 4162                           | 19.7(6.2)                       | 556                            | 20.8(6.3)                      |
| Age at Baseline***              | 4718                           | 77(7.3)                         | 4162                           | 77(6.8)                         | 556                            | 72(8.3)                        |
| Gender                          |                                  |                                 |                                |                                 |                                |                                 |
| Female                          | 2878                           | 61                              | 2552                           | 61.3                            | 326                            | 58.6                            |
| Male                            | 1840                           | 39                              | 1610                           | 38.7                            | 230                            | 41.4                            |
| Ethnicity***                    |                                  |                                 |                                |                                 |                                |                                 |
| White                           | 3399                           | 72                              | 3075                           | 73.9                            | 324                            | 58.3                            |
| Black African                   | 155                            | 3                               | 127                            | 3.1                             | 28                             | 5                                |
| Black Caribbean                 | 712                            | 15                              | 573                            | 13.8                            | 139                            | 25                               |
| Indian                          | 176                            | 4                               | 156                            | 3.7                             | 20                             | 3.6                               |
| Mixed/Other                     | 255                            | 5                               | 211                            | 5.1                             | 44                             | 7.9                               |
| Unknown                         | 21                             | 20                              | 20                             | 0.5                             | 1                              | 0.2                               |
| Marital Status***               |                                  |                                 |                                |                                 |                                |                                 |
| Single/Separated                | 2905                           | 62.0                            | 2480                           | 59.6                            | 425                            | 76.4                            |
| Married/Cohabiting              | 1762                           | 37.0                            | 1633                           | 39.2                            | 129                            | 25.2                            |
| Unknown                         | 51                             | 1                               | 49                             | 1.2                             | 2                              | 0.4                               |
| Education***                    |                                  |                                 |                                |                                 |                                |                                 |
| Gcse+                           | 1629                           | 35                              | 1308                           | 31.4                            | 321                            | 57.7                            |
| Primary/Lower                   | 3089                           | 65                              | 2854                           | 68.6                            | 235                            | 42.3                            |
| Language                        |                                  |                                 |                                |                                 |                                |                                 |
| English                         | 2544                           | 54                              | 2178                           | 52.3                            | 366                            | 65.8                            |
| Not English                     | 179                            | 4                               | 157                            | 3.8                             | 22                             | 4.0                               |
| Unknown                         | 1995                           | 42                              | 1827                           | 43.9                            | 168                            | 30.2                            |
| IMD***                          |                                  |                                 |                                |                                 |                                |                                 |
| [0–10]                          | 451                            | 9.0                             | 412                            | 9.9                             | 19                             | 3.4                               |
| [10–20]                         | 785                            | 17.0                            | 715                            | 17.2                            | 70                             | 12.6                              |
| [20–30]                         | 1038                           | 22.0                            | 893                            | 21.5                            | 145                            | 26.1                              |
| [30–40]                         | 1027                           | 22.0                            | 895                            | 21.5                            | 132                            | 23.7                              |
| [40–60]                         | 461                            | 10.0                            | 392                            | 9.4                             | 69                             | 12.4                              |
| Unknown                         | 976                            | 21.0                            | 855                            | 20.5                            | 121                            | 21.8                              |
| Smoking***                      |                                  |                                 |                                |                                 |                                |                                 |
| No                              | 2429                           | 51.0                            | 2195                           | 52.7                            | 234                            | 42.1                              |
| Current                         | 1303                           | 28.0                            | 1041                           | 25.0                            | 262                            | 47.1                              |
| Past                            | 494                            | 10.0                            | 460                            | 11.1                            | 34                             | 6.1                               |
| Unknown                         | 492                            | 10.0                            | 466                            | 11.2                            | 26                             | 4.7                               |
| CVD Risk***                     |                                  |                                 |                                |                                 |                                |                                 |
| Normal                          | 586                            | 12.0                            | 532                            | 12.8                            | 54                             | 9.7                               |
| At Risk                         | 2599                           | 55.0                            | 2174                           | 52.2                            | 425                            | 76.4                              |
| Unknown                         | 1533                           | 32.0                            | 1456                           | 35.0                            | 77                             | 13.8                              |
| Antidementia***                 |                                  |                                 |                                |                                 |                                |                                 |
| No                              | 4453                           | 96.9                            | 3904                           | 96.7                            | 549                            | 99.2                              |
| Yes                             | 265                            | 3.1                             | 258                            | 3.3                             | 7                              | 0.8                               |
| Antipsychotics***               |                                  |                                 |                                |                                 |                                |                                 |
| No                              | 4596                           | 99.4                            | 4134                           | 99.9                            | 462                            | 93.7                              |
| Yes                             | 122                            | 0.6                             | 28                             | 0.1                             | 94                             | 6.3                               |
| Antidepressant***               |                                  |                                 |                                |                                 |                                |                                 |
| No                              | 4625                           | 99.6                            | 4112                           | 99.8                            | 513                            | 97.4                              |
| Yes                             | 93                             | 0.4                             | 50                             | 0.2                             | 43                             | 2.6                               |

GCSE+: qualification at least General Certificate of Secondary Education, or equivalent; IMD: index of multiple deprivation.

*** $p < .05$. 

$[\chi^2(1) = 4.71; p = 0.029]$ compared to those with bipolar disorders. There were no significant differences for gender, first language, smoking, CVD risk and other medication intake. Fisher exact Chi-square tests were additionally performed to explore the potential association between CVD risk and antipsychotic and no significant associations were found ($p = 0.33$ and $p = 0.79$, respectively).
Linear Mixed Models

When we investigated MMSE trajectories for this sample, we found that linear models showed a better fit than quadratic models (linear BIC 107342 versus quadratic BIC: 108301). The ICC for the unconditional model was 0.75, indicating significant between- and within-individual variability. At intercept level...
TABLE 3. Estimates for the Fully Adjusted Linear Mixed Model for MMSE Trajectories (n = 4,718, 20,828 Observations)

| Intercept | Slope |
|-----------|-------|
| **Estimate (SE)** | **CI 95%** | **Estimate (SE)** | **CI 95%** |
| Intercept | 26.21 (1.45) | [23.369, 29.052] | -0.377 (0.235) | [-0.837, 0.083] |
| Slope linear | | | | |
| Diagnoses | | | | |
| Dementia + SMI | 0.97 (0.389) | [0.208, 1.732] | -0.133 (0.061) | [-0.252, -0.014] |
| Age | 0.019 (0.018) | [-0.016, 0.053] | 0.01 (0.003) | [0.004, 0.015] |
| Gender (ref: Female) | | | | |
| Male | 0.253 (0.259) | [-0.254, 0.76] | -0.037 (0.042) | [-0.119, 0.044] |
| Ethnicity (ref: White) | | | | |
| Black African | -2.732 (0.736) | [-4.175, -1.289] | -0.285 (0.114) | [-0.509, -0.062] |
| Black Caribbean | -1.788 (0.351) | [-2.476, -1.1] | -0.104 (0.055) | [-0.212, 0.005] |
| Indian | -0.024 (0.664) | [-1.325, 1.277] | -0.134 (0.101) | [-0.352, 0.065] |
| Mixed/other | -0.156 (0.577) | [-1.287, 0.975] | -0.097 (0.087) | [-0.268, 0.074] |
| Unknown | -1.227 (3.431) | [-7.951, 5.498] | -0.243 (0.398) | [-1.023, 0.536] |
| Marital status (ref: Married) | | | | |
| Single or separated | -0.465 (0.265) | [-0.984, 0.054] | -0.066 (0.043) | [-0.115, 0.018] |
| Unknown | -3.585 (1.536) | [-6.596, -0.575] | -0.668 (0.212) | [-1.084, -0.252] |
| Education (ref: GSCE+) | | | | |
| Primary or lower | -0.916 (0.261) | [-1.429, -0.403] | -0.03 (0.042) | [-0.113, 0.052] |
| First language (ref: English) | | | | |
| Not English | -3.962 (0.637) | [-5.212, -2.713] | -0.148 (0.105) | [-0.354, 0.057] |
| Unknown | 0.483 (0.255) | [-0.016, 0.981] | -0.029 (0.041) | [-0.109, 0.052] |
| IMD (ref: [0–10]) | | | | |
| [10–20] | -0.3 (0.482) | [-1.245, 0.646] | 0.1 (0.08) | [0.057, 0.257] |
| [20–30] | -0.823 (0.464) | [-1.732, 0.085] | 0.071 (0.077) | [-0.08, 0.223] |
| [30–40] | -1.495 (0.475) | [-2.417, -0.574] | 0.039 (0.078) | [-0.114, 0.193] |
| [40–60] | -1.316 (0.556) | [-2.406, -0.226] | 0.061 (0.091) | [-0.117, 0.239] |
| Unknown | -2.079 (0.472) | [-3.005, -1.154] | -0.027 (0.079) | [-0.181, 0.128] |
| Smoking (ref: No) | | | | |
| Current | -1.018 (0.287) | [-1.582, -0.455] | -0.11 (0.046) | [-0.201, -0.019] |
| Former | 0.34 (0.422) | [-0.486, 1.167] | 0.029 (0.067) | [-0.103, 0.161] |
| Unknown | -1.167 (0.404) | [-1.96, -0.375] | 0.059 (0.073) | [-0.083, 0.201] |
| CVD risk (ref: No) | | | | |
| Yes | -2.067 (0.409) | [-2.868, -1.266] | -0.382 (0.068) | [-0.515, -0.249] |
| Unknown | -0.738 (0.378) | [-1.478, 0.003] | -0.136 (0.062) | [-0.257, -0.014] |
| Antidepressant | -2.163 (0.446) | [-3.037, -1.289] | 0.439 (0.086) | [0.271, 0.606] |
| Antipsychotic | -3.39 (0.745) | [-4.849, -1.931] | -0.275 (0.127) | [-0.523, -0.026] |
| Antimanic | 1.437 (0.79) | [-0.11, 2.985] | 0.274 (0.144) | [-0.008, 0.555] |

Variances

| Intercept | Slope |
|-----------|-------|
| Residual | 28.816 (5.368) | 0.609 (0.781) | 11.601 (3.406) |

Fit statistics for linear models

| BIC | -2LL |
|-----|------|
| 123788.715 | -61625.868 |

*p < 0.05.

*p < 0.01.

*p < 0.001.

(Table 3), we found that individuals with dementia and SMI had higher MMSE scores than those with dementia alone. Lower MMSE scores were found in individuals from a minority background (Black African and Caribbean), those with lower levels of education and those whose first language was not English, and with higher levels of social deprivation. Current smokers, individuals classified at CVD risk or those to be taking dementia or antipsychotic medication were also found to have lower MMSE scores when compared with those that never smoked, were not classified at CVD risk and not taking dementia or antipsychotic medication. At slope level (Table 4 and Fig. 1), we found that although individuals with
dementia and SMI showed an accelerated decline in their MMSE scores when compared to those with only dementia in unadjusted (model 1 in Table 4). Effect sizes for slopes were of 0.20 for differences between dementia only and dementia with comorbid SMI. These estimates are common in these studies and considered meaningful.27 When adjustments were considered (model 2, 3, and 4 in Table 4); this association was partially attenuated when models were additionally adjusted by socio-demographics, smoking, CVD risk factors and further attenuated when adjusted by medication (model 5 in Table 4). When the association of each specific type of medication was examined, our results showed that this attenuation is associated with dementia, antipsychotics, and antidepressants independently (models 5a, 5b, and 5c in Table 4).

When we further investigated whether different SMI diagnosis (schizophrenia and bipolar disorders) additionally adjusted by socio-demographics, smoking, CVD risk factors and further attenuated when adjusted by medication (model 5 in Table 4). When the association of each specific type of medication was examined, our results showed that this attenuation is associated with dementia, antipsychotics, and antidepressants independently (models 5a, 5b, and 5c in Table 4).

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When we further investigated whether different SMI diagnosis (schizophrenia and bipolar disorders)
showed different cognitive trajectories when compared with individuals with only dementia (Table 5), we found that, at intercept level, individuals with schizophrenia and bipolar disorders had higher MMSE scores at intercept level when compared with individuals without comorbid SMI, even after adjusting for relevant covariates. However, post hoc analyses did not reveal significant differences between those with schizophrenia and bipolar disorders at this level. At slope level (Table 5), our results showed differences between the trajectories of individuals with schizophrenia and bipolar disorders, before and after relevant adjustments. An acceleration in cognitive decline was found in individuals with bipolar disorders compared to those with only dementia, while the trajectories with schizophrenia did not seem to be different from those that had dementia without comorbid SMI. Post hoc analyses confirmed the differences between the trajectories of those with bipolar disorders and those with schizophrenia and effect sizes for slopes were equal to 0.17 (although relatively moderate these can still be considered meaningful\(^2\)).

When sensitivity analyses included age at diagnoses similar trends were found. When we compared results with only complete cases for all covariates (n = 1453) and only those individuals that were still alive in 2019 (n = 1766) we found similar trends as slope estimates were reduced but in the same direction for fully adjusted models even considering the different length of follow up between both groups (individuals with dementia and SMI had longer follow ups (M = 4.7; SD = 2.7) compared to those that had only dementia (M = 3.1; SD = 2.01).

### Table 5. Intercept and Slope Estimates for Individuals With Dementia and SMI (Split into Bipolar and Schizophrenia) (Reference Category: Only Dementia) for MMSE Trajectories Unadjusted and Adjusted Models (n = 4,718, 20,828 Observations)

| Intercept for Fully Adjusted Model | M (SE) | 95% CI |
|-----------------------------------|--------|--------|
| **Diagnoses (ref: Dementia only)** |        |        |
| Dementia + bipolar                 | 0.871 (0.801) | [−0.699, 2.442] |
| Dementia + schizophrenia           | 2.337 (0.478)  | [1.4, 3.274] |

| Slope | M (SE) | 95% CI |
|-------|--------|--------|
| Model 1: unadjusted |        |        |
| Dementia + bipolar     | −0.343 (0.121) | [−0.58, −0.107] |
| Dementia + schizophrenia | −0.036 (0.071) | [−0.175, 0.102] |
| Model 2: adjusted by socio-demographics |        |        |
| Dementia + bipolar     | −0.357 (0.12)  | [−0.593, −0.121] |
| Dementia + schizophrenia | −0.005 (0.072) | [−0.146, 0.135] |
| Model 3: additionally adjusted by smoking |        |        |
| Dementia + bipolar     | −0.342 (0.121) | [−0.578, −0.106] |
| Dementia + schizophrenia | 0.014 (0.072)  | [−0.127, 0.155] |
| Model 4: additionally adjusted by CVD risk |        |        |
| Dementia + bipolar     | −0.361 (0.12)  | [−0.597, −0.126] |
| Dementia + schizophrenia | −0.012 (0.072) | [−0.153, 0.13] |
| Model 5: additionally adjusted by medication |        |        |
| Dementia + bipolar     | −0.296 (0.121) | [−0.554, −0.059] |
| Dementia + schizophrenia | −0.063 (0.075) | [−0.084, 0.209] |

**Models with adjustments for medication groups**

| Model 5a: Model 4 with only antidementia |        |        |
| Dementia + bipolar     | −0.347 (0.119) | [−0.58, −0.114] |
| Dementia + schizophrenia | 0.0 (0.071)   | [−0.14, 0.14] |
| Model 5b: Model 4 with only antipsychotic |        |        |
| Dementia + bipolar     | −0.296 (0.123) | [−0.536, −0.056] |
| Dementia + schizophrenia | −0.047 (0.075) | [−0.101, 0.194] |
| Model 5c: Model 4 with only antidepressant |        |        |
| Dementia + bipolar     | −0.377 (0.121) | [−0.615, −0.14] |
| Dementia + schizophrenia | −0.015 (0.072) | [−0.157, 0.127] |

\(^{a} p < 0.05.\)
\(^{b} p < 0.01.\)
\(^{c} p < 0.001.\)
DISCUSSION

This study examined trajectories of cognitive performance in individuals diagnosed with dementia, comparing those with and without a comorbid SMI diagnosis. This study used data from a large longitudinal mental healthcare case register, and considered sociodemographic factors, health behaviors, cardiovascular risk factors, and medication as covariates.

Our primary finding was that individuals with dementia with SMI diagnoses had a faster cognitive decline when compared with those without comorbid SMI. However, this association was partially explained by socio-demographic, health behaviors and CVD risk factors; and more substantially attenuated when medication was considered. Associations of socio-demographic and health-related factors with cognitive trajectories are broadly consistent with previous research in British ageing cohorts.28 Higher educated individuals had higher intercept coefficients, in line with cognitive reserve hypotheses,29 but no difference in rate of decline which is consistent with findings of Davis et al.28 Moreover, individuals who were current smokers and showed higher number of CVD risk factors were more likely to have a faster decline as found in previous studies.26 People with SMI are also known to be more likely to be smokers and have higher CVD risk.30 Given that these factors accounted for a reasonable proportion of the overall association between SMI and faster decline, future research on interventions in this population should explore further the beneficial cognitive effects of smoking cessation and physical activity interventions and whether public health strategies for dementia prevention could be adapted for individuals with SMI. Given the impact of health behaviors and CVD risk factors on cognitive trajectories, especially in older adults, it is important that our health care pathway addressed these at the onset of the illness, bringing primary/general medical care into the psychiatric clinic early on.

When we explored whether there were differences between those individuals with schizophrenia and bipolar disorders compared to those with dementia without comorbid SMI, we found that there those with dementia with comorbid SMI had higher MMSE scores at intercept level, even after adjusting for age. However, no differences were found between those individuals with schizophrenia and bipolar disorders. Although our findings are not directly comparable with previous research in individuals without dementia, they are consistent with previous cross-sectional studies which found similar profiles.2,3 Furthermore, the differences found at slope level in our study provides some evidence in line with those studies that suggested that differences might be arise when exploring this association in longitudinal settings but differs from those that found no differences between cognitive trajectories in individuals with schizophrenia and bipolar disorders.5–7 This could be associated to the fact that previous research had smaller sample sizes and they might have been underpowered to detect subtle cognitive changes over time or to reveal differences between disorders or the fact that our study, and therefore, cohort is restricted to individuals with comorbid dementia. Future research should explore whether these differences might be associated to the different underlying biological mechanisms of schizophrenia and bipolar disorders or with the potentially shared mechanisms between disorders and dementia.

With regards to medication, adjustment for dementia, antipsychotic, and antidepressant medications strongly impacted the association of interest even after accounting for the other covariates considered such as CVD risk. When we examined the role of each medication independently, we found that this impact was clear for dementia and antidepressants, the estimates suggest that there could be a greater and potentially protective impact for antipsychotics medication in the case of bipolar disorders.

Besides the strengths of our study associated with the large sample from a traditionally underrepresented population in cognitive decline studies and the richness of the longitudinal nature of the data, some limitations should be acknowledged. First, data on health behaviors was limited to smoking status, and we could not include important potential predictors such as alcohol consumption or physical activity in our models. Future studies are therefore needed to understand further the role of lifestyle and health when understanding cognitive decline in individuals with these comorbidities. Second, dementia was ascertained using routine clinical diagnoses rather than research instruments and we did not explore differences between diagnostic subgroups due to their limited sample sizes and the difficulty to distinguish
those clinical diagnoses that are often recorded to facilitate and speed the patient/s patient’s journey through the different healthcare pathways. Third, there could be some potential selection bias associated to the fact that: our sample was limited to those with at least three MMSE scores available (following methodological guidelines), dementia can go undiagnosed in SMI and our population has an increased risk of premature mortality. Although the direction of our results were robust when performing sensitivity analyses restricted to only those that were still alive at the end of the study period, the attenuation of the estimate suggests that individuals closer to their death were more likely to exhibit an accelerated decline. These findings are consistent with the terminal cognitive decline hypotheses and future research should explore further the potential drivers of mortality in this population. Finally, this data only had a global measure of cognition such as MMSE which is well known and used for comparative purposes; however, some research has highlighted that there could be a different impact for different cognitive domains as a function of SMI.

To conclude, our findings showed that individuals with comorbid SMI show a faster cognitive decline when compared with those that have dementia without comorbid SMI. This accelerated decline seems to be more evident in individuals with bipolar disorders when compared with individuals with dementia only and it is only partially explained by relevant confounders. Further research is needed to detangle the biological explanatory pathways. Clinical and public health interventions should monitor medication regimes and promote healthy lifestyles in individuals diagnosed with dementia and SMI to reduce the potential risk of accelerated cognitive decline in this population.

**AUTHORS CONTRIBUTIONS**

RB conceived the idea, designed the study and the analytical plan. AM extracted, preprocessed, and analyzed the data. RS provided clinical input and all authors contributed to the interpretation of the results. RB drafted the manuscript and all authors made substantial contributions, revised this work critically and approved final version to be published.

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SUPPLEMENTARY MATERIALS

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References

1. Bora E, Özdemir A: Meta-analysis of longitudinal studies of cognition in bipolar disorder: comparison with healthy controls and schizophrenia. Psychol Med 2017; 47:2753
2. Krabbendam L, Arts B, van Os J, et al: Cognitive functioning in patients with schizophrenia and bipolar disorder: a quantitative review. Schizophr Res 2005; 80:137–149
3. Bora E, Yucel M, Pantelis C: Cognitive functioning in schizophrenia, schizoaffective disorder and affective psychoses: meta-analytic study. Br J Psychiatr 2009; 195:475–482
4. Demjaha A, MacCabe JH, Murray RM: How genes and environmental factors determine the different neurodevelopmental trajectories of schizophrenia and bipolar disorder. Schizophr Bull 2012; 38:209–214
5. Gildengers AG, Chisholm D, Butters MA, et al: Two-year course of cognitive function and instrumental activities of daily living in older adults with bipolar disorder: evidence for neuroprogression? Psychol Med 2015; 43:801–811
6. Depp CA, Maushach BT, Harmell AL, et al: Meta-analysis of the association between cognitive abilities and everyday functioning in bipolar disorder. Bipolar Disord 2012; 14:217–226
7. Dickerson FB, Sommerville J, Origoni AE, et al: Outpatients with schizophrenia and bipolar I disorder: do they differ in their cognitive and social functioning? Psychiatr Res 2001; 102:21–27
8. Diniz AL, Teixeira F, Cao C, et al: History of bipolar disorder and the risk of dementia: a systematic review and meta-analysis. Am J Geriatr Psychiatr 2017; 25:357–362
9. Rise JM, Haro B: Clinical features, comorbidity, and cognitive impairment in elderly bipolar patients. Neuropsychiatr Dis Treat 2016; 12:1203–1213
10. Lee AH, Weintraub D: Psychosis in Parkinson’s disease without dementia: common and comorbid with other non-motor symptoms. Mov Disord 2012; 7:858–863
11. Nascimento C, Nunes PV, Rodrigues RD, et al: A review on shared clinical and molecular mechanisms between bipolar disorder and frontotemporal dementia. Prog Neuropsychopharmacol Biol Psychiatr 2019; 93:269–283
12. Soreca I, Frank E, Kupfer DJ: The phenomenology of bipolar disorder: what drives the high rate of medical burden and determines long-term prognosis? Depress Anxiety 2009; 26:73–82
13. Kessing LV, Nilsson FM: Increased risk of developing dementia in patients with major affective disorders compared to patients with other medical illnesses. J Affect Disord 2003; 75:261–269
14. Feinberg I: Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? J Psychiatr Res 1982; 17:519–534
15. Keshavan M, Lizzano P, Prasad K: The synaptic pruning hypothesis of schizophrenia: promises and challenges. World Psychiatry 2020; 19:110
16. Chan HM, Stolwyk R, Kelso W, et al: Comparing neurocognition in severe chronic schizophrenia and frontotemporal dementia. Aust N Z J Psychiatry 2014; 48:828–837
17. Harciarek M, Malaspina D, Sun T, Goldberg E: Schizophrenia and frontotemporal dementia: Shared causation? Int Rev Psychiatry 2013; 25:168–177
18. Tuppin P, Kusnik-Joinville O, Weill A, et al: Primary health care use and reasons for hospital admissions in dementia patients in France: database study for 2007. Dement Geriatr Cogn Disord 2009; 28:225–232
19. Kivipelto M, Ngandu T, Fratiglioni L, et al: Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol 2005; 62:1556–1560
20. Stewart R, Soremekun M, Perera G, et al: The South London and Maudsley NHS foundation trust biomedical research centre (SLAM BRC) case register: development and descriptive data. BMC Psychiatry 2009; 9:1–12
21. Singer JD, Willett JB: Applied Longitudinal Data Analysis: Modeling Change and Event Occurrence. Oxford University Press, 2003
22. Folstein MF, Robins LN, Helzer JE: The mini-mental state examination. Arch Gen Psychiatry 1983; 40, 812-812
23. Perera G, Khondoker M, Broadbent M, et al: Factors associated with response to acetylcholinesterase inhibition in dementia: a cohort study from a secondary mental health care case register in London. PloS One 2014; 9:e109484
24. Perera G, Broadbent M, Callard F, et al: Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Case Register: current status and recent enhancement of an electronic mental health record-derived data resource. BMJ Open 2016; 6
25. Wu CY, Chang CK, Robson D, et al: Evaluation of smoking status identification using electronic health records and open-text information in a large mental health case register. PloS One 2013; 8:e74262
26. Baguley T: Standardized or simple effect size: what should be reported? Br J Psychol 2009; 100:603–617
27. Adachi P, Willoughby T: Interpreting effect sizes when controlling for stability effects in longitudinal autoregressive models: implications for psychological science. Eur J Dev Psychol 2015; 12:116–128
28. Davis D, Bendayan R, Terrera GM, et al: Decline in search speed and verbal memory over 26 years of midlife in a British birth cohort. Neuroepidemiology 2017; 49:121–128
29. Stern Y: Cognitive reserve in ageing and Alzheimer’s disease. Lancet Neurol 2012; 11:1006–1012
30. Osborn DP, Nazareth I, King MB: Risk for coronary heart disease in people with severe mental illness: cross-sectional comparative study in primary care. Br J Psychiatr 2006; 188:271–277
31. Hayes JF, Marston L, Walters K, et al: Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000–2014. Br J Psychiatr 2017; 211:175–181
32. Riegel KF, Riegel RM: Development, drop, and death. Dev Psychol 1972; 6, -306
33. Bendayan R, Piccinin AM, Hofer SM, et al: Decline in memory, visuospatial ability, and crystalized cognitive abilities in older adults: normative aging or terminal decline? J Aging Res 2017: 1-17

34. Millan MJ, Agid Y, Brüne M, et al: Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. Nature Reviews Drug Discov 2012; 11:141-168