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Title:
Association of physical health multimorbidity with mortality in people with schizophrenia spectrum disorders: Using a novel semantic search system that captures physical diseases in electronic patient records

Running title:
Physical multimorbidity and mortality in schizophrenia

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Abstract

Objective:

Single physical comorbidities have been associated with the premature mortality in people with schizophrenia-spectrum disorders (SSD). We investigated the association of physical multimorbidity (≥two physical health conditions) with mortality in people with SSD.

Methods:

A retrospective cohort study between 2013 and 2017. All people with a diagnosis of SSD (ICD-10: F20-F29), who had contact with secondary mental healthcare within South London during 2011-2012 were included. A novel semantic search system captured conditions from electronic mental health records, and all-cause mortality were retrieved. Hazard ratios (HRs) and population attributable fractions (PAFs) were calculated for associations between physical multimorbidity and all-cause mortality.

Results:

Among the 9775 people with SSD (mean (SD) age, 45.9 (15.4); males, 59.3%), 6262 (64%) had physical multimorbidity, and 880 (9%) died during the 5-year follow-up. The top three physical multimorbidity combinations with highest mortality were cardiovascular-respiratory (HR: 2.23; 95% CI, 1.49-3.32), respiratory-skin (HR: 2.06; 95% CI, 1.31-3.24), and respiratory-digestive (HR: 1.88; 95% CI, 1.14-3.11), when adjusted for age, gender, and all other physical disease systems. Combinations of physical diseases with highest PAFs were cardiovascular-respiratory (PAF: 35.7%), neurologic-respiratory (PAF: 32.7%), as well as respiratory-skin (PAF: 29.8%).

Conclusions:

Approximately 2/3 of patients with SSD had physical multimorbidity and the risk of mortality in these patients was further increased compared to those with none or single physical conditions. These findings suggest that in order to reduce the physical health burden and subsequent mortality in

people with SSD, proactive coordinated prevention and management efforts are required and should extend beyond the current focus on single physical comorbidities.

Keywords: Schizophrenia, severe mental illness, mortality, somatic, comorbidity

1. Introduction

People with schizophrenia have life expectancies up to 20 years shorter than those in the general population (Chang et al., 2011; Walker, McGee, & Druss, 2015). The majority of early deaths (70%) are explained by physical health conditions, such as cardiovascular, respiratory and neoplastic diseases (Correll, Solmi, et al., 2017; Jayatilleke et al., 2017). Despite the established worse physical health morbidity in people with schizophrenia (Oud & Meyboom-de Jong, 2009; Razzano et al., 2015), most research to date has focused on single physical health conditions such as cardiovascular, respiratory disease, and diabetes (Schoepf et al., 2012; Vancampfort et al., 2016). However, in populations with poor physical health outcomes such as schizophrenia (DE Hert et al., 2011; Smith, Langan, McLean, Guthrie, & Mercer, 2013), people are often affected by two or more physical health conditions, termed physical health multimorbidity (Stubbs et al., 2016).

In the general population, the number of people with physical multimorbidity has increased in most countries around the world and is becoming one of the main challenges for health care systems (Dhalwani et al., 2016). A large-scale systematic review of more than 70 million people from the general population across 12 different countries suggested that the prevalence of multimorbidity was 13% in people aged 18 years and older, and a positive association between age and prevalence of multimorbidity (Violan et al., 2014). Multimorbidity is a concern, with data from the general population demonstrating that people affected are more likely to have functional decline (A. Ryan, Wallace, O'Hara, & Smith, 2015), worse quality of life (Fortin et al., 2004), increased risk of premature mortality (Di Angelantonio et al., 2015) and higher healthcare costs (Lehnert et al., 2011).

Whilst there have been concerted efforts to understand poor physical health in schizophrenia, little is known about the impact of physical health multimorbidity on mortality in these patients. However, recent evidence indicates a higher risk of physical health multimorbidity compared to the general population (Gabilondo, Alonso-Moran, Nuño-Solinis, Orueta, & Iruin, 2017; Stubbs et al., 2016), and a recent large multinational study in low- and middle-income countries, concluded that

psychosis was associated with an increased odds ratio of 4.1 for physical multimorbidity, compared to controls (Stubbs et al., 2016). Stubbs et al. reported that psychosis patients had high levels of asthma combined with diabetes, angina pectoris or tuberculosis, and arthritis combined with angina pectoris, and hearing problems combined with visual impairment or edentulism (Stubbs et al., 2016). The study by Gabilondo et al. showed that physical disease clusters of neuropsychiatric conditions (Parkinson, dyspepsia, cerebrovascular disease) as well as cardiovascular and respiratory disease clusters were most common (Gabilondo et al., 2017). Even though such combinations show that physical morbidities co-occur frequently in patients with SSD, no studies have to date investigated the impact of such combinations to mortality, which is necessary in order to understand and possibly reduce the premature mortality in patients with SSD.

Clearly, an improved evidence base is important to identify at risk groups, develop interventions, and address the premature mortality. Since SSD is a heterogeneous condition (Os & Kapur, 2009), which is associated with premature mortality (Walker et al., 2015) and greatly increased single physical health comorbidities, we aimed to investigate the prevalence of physical health multimorbidity in people with SSD. Secondly, we assessed which physical health conditions and clusters (i.e. combinations of physical disease systems) are likely to be associated with increased mortality rates in patients with SSD using data from a large electronic health record (EHR) platform.

2. Methods

2.1 Study design

A retrospective cohort study using data from electronic mental health records linked to national mortality surveillance with a five-year follow-up period.

2.2 Study period

Cohort selection and characterisation used data from 2011-2012. Follow-up ran from January 1, 2013 to December 31, 2017.

2.3 Data source

Data were derived from the Clinical Record Interactive Search (CRIS); a case register system that contains de-identified electronic health record (EHR) data from the South London and Maudsley (SLaM) National Health Service Foundation Trust. SLaM is one of the largest mental healthcare services in Europe, providing comprehensive mental health care to a catchment of approximately 1.3 million residents in south London (Croydon, Lambeth, Lewisham, and Southwark). EHRs have been used across all SLaM services since 2006, and CRIS was established with funding from the National Institute of Health Research (NIHR) as a 'live' resource, commencing with imported legacy data in 2008 and accumulating information on the full SLaM caseload since that time (Perera et al., 2016). CRIS data are accessed and used within a robust governance model, and CRIS has received research ethics approval as a data resource for secondary analysis (Oxford REC C, reference 18/SC/0372).

2.4 Study population

The cohort included all individuals aged 18 years or older with a diagnosis of SSD (ICD-10: F20-F29) and had at least one face to face contact with SLaM during the period between 1st January 2011 and 31st December 2012, and who were alive on 1st January 2013 (set up in this way to allow all cases to have at least 5 year follow-up). In recognition of the heterogeneous nature of schizophrenia, we included the spectrum of schizophrenia (SSD) as in accordance with previous research papers (Chang et al., 2010; Stubbs, Mueller, et al., 2018). We used primary and secondary diagnoses of F20-29 within the structured ICD-10 codes that were recorded routinely in the source EHR. Physical health conditions were ascertained, using natural language processing (NLP) as described below, from data reported in CRIS at any time before index date (1st January 2013). We defined physical health multimorbidity as combination of two- or more physical health disease categories within one person at any given time before index date (Stubbs et al., 2016; Violan et al., 2014). These physical diseases were then grouped into the letter-based chapters from ICD-10 version 16 (World Health Organisation, 2016).

2.5 Semantic computing and learning system to capture physical health comorbidities on electronic patient records

To identify patients' physical health conditions from these clinical notes, we used SemEHR – an open source toolkit that integrates text mining and semantic computing for identifying mentions of UMLS (Unified Medical Language System) concepts from clinical documents (Wu et al., 2018). To identify mentions of a broad range of physical diseases (ICD-10; A00-N99), we mapped each top level ICD code (3-character code, e.g. A00) to a corresponding UMLS concept CUI (e.g. C0008354) using the mappings available at BioPortal (http://sparql.bioontology.org/) by querying its SPARQL Endpoint. The first benefit of using UMLS concepts instead of ICD-10 terms is that UMLS provides extensive synonyms for each concept, which helps identifying as many variants of disease mentions as possible. The second benefit comes from the comprehensive concept relations provided by UMLS, which helps the disambiguation in NLP and the identification of more disease subtypes.

To optimise performance for identifying physical condition mentions, we used SemEHR's continuous learning functionality to iteratively improve its text-mining model on these conditions. Briefly, each iteration includes sampling (random selection of a fixed number of mentions for each top-level condition), validation (manual assessment of samples on a specific browser-based user interface) and learning (validation results learnt by the system to improve the model). Based on previous studies on SLaM data, the recall (sensitivity) of SemEHR is generally very good (96-98%) for physical conditions at document level (Wu et al., 2018). The accuracy achieved for affirmed, recent and patient-suffered conditions was 83% ± 0.13(precision) - over 50 codes (2,960 instances) - at document level. The most comparable processing resource is CRIS-CODE (Jackson et al., 2017), which validated 46 mental health symptoms on CRIS with 85% precision. The SemEHR classification were found to have continued poor performance despite training for some physical disease systems, namely; bacterial infection (chapter A), neoplasm (chapter C), diseases of the blood and blood-forming organs (chapter D), and eye and ear (chapter H). These were therefore not included in the

multimorbidity algorithm used for analyses described here, which instead ascertained viral infection (chapter B, e.g. HIV, mycoses, hepatitis.), endocrine (chapter E, e.g. diabetes mellitus, cystic fibrosis, obesity), neurologic (chapter G, e.g. Parkinson disease, epilepsy, Huntington disease), cardiovascular (chapter I, e.g. stroke, heart failure, myocardial infarction), respiratory (chapter J, e.g. asthma, bronchitis, chronic obstructive pulmonary disease), digestive (chapter K, e.g. liver diseases, gastric ulcer, irritable bowel syndrome), skin (chapter L, e.g. psoriasis, eczema, dermatitis), musculoskeletal (chapter M, e.g. systemic lupus, arthrosis, dorsopathies) and urogenital (chapter N, e.g. renal failure, endometriosis, diseases of genital (male/female) organs) systems. The precision at chapter level after removing poor-performing chapters is 86% ± 0.11. The source of validation data was generated in the study by two annotators (P.K. and R.S.) via 16 rounds of iterations. The precision at chapter-level was estimated by manual assessments on sampled documents (80 documents per chapter of the last rounds). It needs to be noted that reported performances in this section are not for asserting conditions at patient-level, i.e. decide whether a patient had a physical condition or not. Instead, they were evaluated for the ability to identify whether a sequence of words is a contextualised condition mention (phenotype identification task). To translate phenotype task results to patient-level condition asserting, our previous study (Wu et al., 2018) on SLaM CRIS showed that a model with 85-87% precision at phenotype identification tasks on free-text can achieve 93-99% F-measure at patient-level for Hepatitis C and HIV diseases. The SemEHR has also been recently used and validated against other machine learning tools on Radiology Reports in Scotland (Gorinski et al., 2019).

2.6 Outcomes and measures

The index date for characterisation of the cohort and commencement of follow-up was defined as 1st January 2013, and the sample was thus restricted to all individuals who were alive at this time. The follow-up began on 1st January 2013 and ended on 31st December 2017, or at the day of death, whichever came first. The date of death of each deceased patient was obtained from CRIS, using a

linkage between SLaM's EHR and the national mortality spine updated on at least a monthly basis and complete for the entirety of the follow-up period.

2.7 Covariates

We obtained sociodemographic data for the cohort in relation to the index date, including age (18-39, 40-59, >60), sex (male, female), ethnicity (White, Black/Caribbean, others/mixed/unknown), and marital status (married/cohabiting, divorced, single), using structured EHR data accessed via CRIS. In the United Kingdom, mental health services have completed the Health of the Nation Outcome Scales (HONOS) among all patients. The HONOS is also widely used in Australia and New Zealand and is a validated measure with robust psychometric properties to routinely assess outcomes in mental health service users (Bebbington, Brugha, Hill, Marsden, & Window, 1999; Pirkis et al., 2005). We used five subscales from the routine HoNOS within the EHR, and these were obtained based on their specific relevance for this particular patient group, including agitated/aggressive behaviour, self-injury, substance use, cognitive problems and depression scores. Each score was divided into three categories of not present (HoNOS subscale score 0), minimal or questionable (score 1) or significant (scores 2-4); these were based on the closest HoNOS recorded within a year prior to, or up to 3 months after index date (1st January 2013).

The address recorded as current or most recent at the index date was linked to the Index of Multiple Deprivation (IMD) score for that neighbourhood, derived from 2011 national Census data, and providing a measure of neighbourhood-level socioeconomic status (Department for Communities and Local Government, 2015).

2.8 Statistical analysis

Descriptive statistics for all variables were calculated as frequencies and percentages. The baseline characteristics included information on age (bands), sex, ethnicity, marital status, HoNOS, and deprivation score (divided in quantiles). In addition, the numbers of physical disease systems affected were grouped into categories from 0-6.

First, prevalence (percentage) of physical multimorbidity was calculated by combining two disease systems affected. The prevalence estimates of physical multimorbidity were demonstrated by ranking the most frequency occurring individual disease systems, and were expressed into categories of ≥10%, 5-9%, and <5%.

Second, a Cox proportional hazards regression analysis was performed to study the relationship between physical multimorbidity and mortality for all possible disease combinations compared to those people with schizophrenia who had no recorded physical diseases. We adjusted for age at index and sex in the first adjusted model and then further adjusted for all other disease systems to account for an increased mortality driven by other disease systems than those combinations investigated. We calculated crude and adjusted HRs and their 95%CIs by using patients with SSD who had no recorded physical diseases as reference..

Finally, the population attributable fraction (PAF) for mortality was calculated to assess the effect of different physical disease combinations on mortality. The PAF (expressed as a percentage) is a measure of proportion of deaths that might hypothetically be prevented if the disease combinations were not present. PAF calculations were carried out using STATA package "punafcc" for the adjusted cox regression model according to methods previously described (Spiegelman, Hertzmark, & Wand, 2007). Statistically significance were defined as $p < 0.05$. All analyses were conducted using STATA version 14.

3. Results

A total of 9775 people with SSD were assembled for the analysed cohort, with a mean (SD) age of 45.9 (15.4) on the index date; 59.3% were males. Most of the sample were single (74.6%), and of black African/Caribbean (44.4%) or white (40.8%) ethnicity. The first column of Table 1 describes the characteristics of the total cohort.

-Insert Table 1 here-

3.1 Prevalence of physical disease in patients with SSD

Among the 9775 people with SSD, 1798 (18.4%) did not have any recorded physical disease systems affected, 1715 (17.5%) had one disease system affected, 1639 (16.8%) had two disease systems affected, and 1403 (14.4%) had three disease systems affected. The prevalence of people with physical multimorbidity was 6,262 (64.1%). The most common disease systems affected were neurological (49.7%), endocrine (42.4%), and respiratory (36.9%), see table 1. Figure 1 shows that the most frequently observed two-way disease combinations were neurologic-endocrine system (27.9%), followed by neurologic-respiratory system (25.2%) and neurologic-viral infection (24.9%).

-Insert Figure 1 here-

3.2 The association between baseline variables and mortality

A total of 880 (9.0%) people with SSD died during the 5-year follow up period. As described in table 1, in models including age and sex, the demographic variables that remained associated with increased mortality were increased age and male sex. Black compared to white ethnic group was associated with significant lower mortality. Of clinical characteristics, aggressive behaviour, self-injury and substance abuse were all associated with increased mortality. Compared to people without physical disease, all specific physical disease systems had significantly increased mortality. People with SSD, who had two physical diseases or more, had increased mortality, compared to those without physical diseases. When comparing individuals with physical multimorbidity versus those with ≤2 physical disease systems, we observed a significant increased mortality in the multimorbidity group (HR: 1.23; 95% CI, 1.07-1.43).

3.3 The association between physical health multimorbidity and mortality

Table 2 displays Cox regression analyses of the associations between two-disease combinations and mortality. Among people with physical multimorbidity, most of the two-way combinations were associated with significantly increased mortality. Compared with the reference group, the highest age- and sex adjusted HR for mortality was 2.07 (95% CI, 1.42-3.02) for people with digestive-urogenital diseases, 2.05 (95% CI, 1.45-2.88) for people with skin-urogenital diseases and 2.00 (95%

CI, 1.48-2.72) for people with respiratory-urogenital diseases. However, these specific combinations fell below statistical significance levels after further adjustment for other physical disease groups.

In the final adjusted model, only respiratory diseases combined with other disease systems remained significantly increased, with the highest mortality observed in cardiovascular-respiratory diseases (HR: 2.23; 95% CI, 1.49-3.32), followed by respiratory-skin (HR: 2.06; 95% CI, 1.31-3.24) and respiratory-digestive (HR: 1.88; 95% CI, 1.14-3.11). Having respiratory disease alone compared to those without any physical disease did not significantly increase mortality, but only when respiratory diseases were combined with other disease systems, we observed an increased mortality. The only single physical disease system that alone increased mortality was cardiovascular disease (HR: 1.97; 95% CI, 1.24-3.12), all others were insignificant, but the number of people who only had one disease systems affected were generally low.

-Insert Table 2 here-

3.4 Population attributable fractions of physical multimorbidity and mortality

The top five highest PAFs are shown in table 3. The cardiovascular-respiratory disease combination had the highest PAF of 35.7%, followed by neurologic-respiratory (PAF: 32.7%) and respiratory-skin (PAF: 29.8%).

-Insert Table 3 here-

4. Discussion

To the best of our knowledge, the current study is the first to investigate the association between physical multimorbidity and mortality in people with SSD. In this retrospective cohort study of 9,775 patients with SSD with a mean age of 46 years, we found that 64% had physical health multimorbidity. The most frequently observed disease combinations were neurologic-endocrine system (28%), neurologic-respiratory system (25%), and viral infection-neurologic system (25%). Cardiovascular disease combined with respiratory disease had highest mortality rate (HR: 2.23; 95% CI, 1.49-3.32) and at the same time showed highest PAF (35.7%), but also respiratory-neurologic (HR:

1.84; 95% CI, 1.35-2.52, PAF: 32.7%) and respiratory-skin (HR: 2.06; 95% CI, 1.31-3.24, PAF: 29.8%) were associated with excess mortality in people with SSD, compared to those without physical diseases.

Previous studies have reported increased risk of physical health multimorbidity in people with schizophrenia (Gabilondo et al., 2017; Stubbs et al., 2016). Our study is the first to include a large scale of physical diseases to explore the most frequently co-occurring physical disease systems in people with SSD. Previous findings have reported prevalence of physical multimorbidity of 29% (Gabilondo et al., 2017), 33% (Smith et al., 2013), 36% (Stubbs et al., 2016) and 39% (Correll, Ng-Mak, et al., 2017), in people with schizophrenia. Our prevalence rate of 64% with physical multimorbidity is higher than the prevalence rates observed in those studies, but given the differences in the inclusion criteria of physical diseases, it is not surprising that we found higher prevalence rates than those who only included specific physical diseases. The most common physical disease systems affected were neurologic, endocrine, and respiratory systems, although we cannot determine whether they are higher than expected due to the lack of a non-schizophrenia comparison group. However, neurologic diseases, especially epilepsy and migraine, have been previously linked to psychosis (Clancy, Clarke, Connor, Cannon, & Cotter, 2014). It has also previously been suggested that there might be similar genetic pathways between schizophrenia and neurologic conditions (Ferentinos & Dikeos, 2012). On the other hand, the increased prevalence of neurologic diseases observed in this population may also be explained by the side effects of first-generation antipsychotics, as many patients will experience extrapyramidal side effects (Miller et al., 2008). Endocrine diseases, including diabetes mellitus, obesity, and thyroid diseases are increased in patients with schizophrenia compared to the general population (Pillinger, Beck, Stubbs, & Howes, 2017; M. C. M. Ryan, Collins, & Thakore, 2003). This can partly be explained by unhealthy lifestyle risk behaviors (Vancampfort, Firth, et al., 2017), side effects from second-generation antipsychotics (Manu et al., 2015), as well as common genetic pathways between psychosis and metabolic disorders (Tandon, Keshavan, & Nasrallah, 2008). Most studies regarding physical multimorbidity in

the general population have focused on populations above the age of 60 years (Guisado-Clavero et al., 2018; Schäfer et al., 2010), making comparison between people with SSD and the general population much more challenging. However, high smoking rates, substance abuse, unhealthy dietary behaviours (Firth et al., 2018) as well as less physical activity (Stubbs, Vancampfort, et al., 2018) are important risk factors for physical multimorbidity in people with psychosis (Laursen et al., 2013; Ringen, Engh, Birkenaes, Dieset, & Andreassen, 2014; Vancampfort, Koyanagi, et al., 2017), and might also explain the increased prevalence of respiratory diseases. Future studies are needed to explore the main contributing factors that predict development of co-occurring physical diseases, as well as the effectiveness of early screening and intervention to reduce the likelihood of developing physical multimorbidity in people with SSD.

Our data clearly demonstrate that physical health multimorbidty is an important contributor to the excess mortality in people with SSD. Previous research in people with physical multimorbidity from the general population has demonstrated that the number of physical comorbidities are associated with increased mortality (Ferrer, Formiga, Sanz, Almeda, & Padrós, 2017). No other studies have investigated the PAF of physical diseases for mortality in people with schizophrenia, so comparisons are difficult, since previous studies have only focused on single comorbid diseases. In the current study, we showed that a single disease was not associated with an increased mortality (however it reached almost significance), but patients who had two or more physical diseases were associated with increased mortality. The risk of premature mortality in patients suffering from two-way disease combinations was further increased compared to those with none or single physical disease condition. This could indicate that the excess mortality observed in people with SSD is not driven by the presence of a single disease system but is associated with the presence of physical multimorbidity. The finding that respiratory, cardiovascular and neurologic disease combinations had the highest impact on mortality adds impetus to further study the underlying aetiology of the impact of these disease combinations on the excess mortality in people with SSD. Patients with physical multimorbidity may find that one physical disorder creates difficulty in the management of

another, which could affect compliance with medical treatment for their health condition, and thereby possibly explain some of the increased mortality. Smoking is an important confounder that affects multiple organ systems, but especially cardiovascular and respiratory systems (Yanbaeva, Dentener, Creutzberg, Wesseling, & Wouters, 2007), and we cannot quantify the possible effect of this or other confounders on the excess mortality observed. Whether these disease systems affected are the same relative increase in mortality in patients with SSD as compared to the general population remain unanswered, as we did not have any data on a psychiatric healthy population. However, more research is required to unravel the findings of the current study, which should be given high priority because of this excess mortality.

4.1 Limitations

Whilst our data provide novel insights into this neglected area, some limitations need to be addressed. First, we were only able to follow patients for 5 years, and there are potentially large differences in short-term and long-term outcome for different physical disease systems. Second, we did not have information regarding the specific time-point of the recorded physical disease, as some might have had the diagnosis for several years, while others might just have received the diagnosis, which may have led to differences in the estimated mortality rates. Third, we did not assess the severity of the physical condition, and we are aware that within each disease system investigated there are large variations between physical conditions in terms of importance for mortality. Fourth, we had incomplete disorder systems captured by the SemEHR, since we did not develop sufficient accuracy for cancer (mainly due to feared entity) as well as bacterial infections (because some vaccinations were captured here). Fifth, the NLP and its performance needs to be further developed in terms of accuracy, but any inaccuracy would reduce rather than exaggerate associations with mortality. Nevertheless, our findings are showing good predictive validity and a novel multimorbidity measure that could be routinely applied to EHRs for health monitoring and risk stratification. Sixth, there is an issue as to whether physical health conditions are recorded at all in a mental health record, and it might even be possible that physical conditions are more likely to be recorded in

people with more severe mental disorders or risk states, but we were unable to adjust for this in the current data. On the other hand, when a physical health disorder is recorded, it means that it is recognized, so there could also be an obscuring effect of recognition and relatively better outcomes. The increased risk of suicide mortality in these patients challenges the findings observed in the current study, as many patients die early without having the chance to develop somatic diseases (competing risk). This is often considered as a major limitation is observations studies. It is also a major limitation that the current data did not include information on important confounders, such as smoking and alcohol consumption as well as levels of physical activity and intake of healthy diet, which are important variables in morbidity and mortality outcomes. For example, the finding that respiratory system is a strong contributor for morbidity and mortality in patients with SSD could be confounded by the excessive rates of smokers in patients with SSD, and we would have expected to reduce some of the respiratory mortality if we were able to include smoking as a variable in our regression model. On the other hand, smoking cessation is very difficult to implement in patients with SSD, and some patients even use smoking as self-medication to handle negative and cognitive symptoms (Winterer, 2010), which again challenges the use of such adjustment in our analysis. Lastly, when considering the generalisability of the cohort, we included people with SSD known to mental healthcare, so it is not possible to generalize these findings to those people with undiagnosed disorders or those treated in primary care alone, which might include people with better prognosis of mental disorders.

5. Conclusion

In a large representative sample, we identified that approximately two thirds of people with schizophrenia had physical multimorbdity. The current data is the first to address physical multimorbidity and its association to mortality in people with SSD, and suggest that cardiovascular-respiratory, neurologic-respiratory, and respiratory-skin disease combinations had the highest impact on mortality rates. Our data indicate that current treatment models for improving physical

health and reducing premature mortality in SSD need to acquire a more coordinated approach and move beyond the consideration of single disease systems.

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Table 1. Baseline characteristics and their association to death in people with SSD.

	Schizophrenia Spectrum Disorders, N=9775	
Variables	n (%)	Adjusted HR (95% CI)*
Age, n (%)		
18-39	3707 (37.9)	Reference
40-59	4377 (44.8)	2.59 (2.06-3.25)
≥60	1691 (17.3)	13.37 (10.73-16.65)
Gender, n (%)		
Females	3983 (40.7)	Reference
Males	5792 (59.3)	1.37 (1.20-1.58)
Marital status, n (%)		
Married/cohabiting	1096 (11.2)	Reference
Divorced/widowed	1267 (13.0)	1.14 (0.90-1.44)
Single	7293 (74.6)	1.14 (0.92-1.41)
Unknown	119 (1.2)	0.69 (0.28-1.69)
Ethnicity, n (%)		
White	3990 (40.8)	Reference
Black African/Caribbean	4339 (44.4)	0.73 (0.63-0.85)
Other/unknown	1445 (14.8)	0.84 (0.68-1.04)
Social deprivation index (quintiles), n (%)		
1 (Least deprived)	1957 (20.0)	Reference
2	1953 (20.0)	0.90 (0.73-1.11)
3	1979 (20.3)	0.91 (0.74-1.13)
4	1939 (19.8)	1.06 (0.86-1.30)
5 (Most deprived)	1947 (19.9)	1.06 (0.86-1.30)
HoNOS domain score		
Agitated/aggressive behaviour, n (%)		
0	7356 (75.2)	Reference
1	1327 (13.6)	1.02 (0.81-1.28)
2-4	1073 (11.0)	1.29 (1.02-1.62)
Missing	19 (0.2)	
Self-injury, n (%)		
0	9145 (93.6)	Reference
1	373 (3.8)	1.21 (0.82-1.78)
2-4	236 (2.4)	1.60 (1.02-2.49)
Missing	21 (0.2)	
Substance abuse, n (%)		
0	8012 (82.0)	Reference
1	634 (6.5)	1.18 (0.86-1.62)
2-4	1078 (11.0)	1.56 (1.22-1.98)
Missing	51 (0.5)	
Cognitive problems, n (%)		
0	7151 (73.2)	Reference
1	1488 (15.2)	1.10 (0.90-1.34)
2-4	1115 (11.4)	1.09 (0.87-1.35)
Missing	21 (0.2)	
Depression, n (%)		
0	6434 (65.8)	Reference
1	1980 (20.3)	1.16 (0.96-1.40)
2-4	1333 (13.6)	1.09 (0.86-1.38)
Missing	28 (0.3)	
Number of physical disease systems affected, n (%)		
0	1798 (18.4)	Reference
1	1715 (17.5)	1.26 (0.99-1.62)
2	1639 (16.8)	1.30 (1.02-1.66)
3	1403 (14.4)	1.34 (1.04-1.72)
4	1185 (12.1)	1.41 (1.09-1.83)
5	846 (8.7)	1.62 (1.23-2.13)
6+	1189 (12.2)	1.43 (1.11-1.85)
Disease systems affected, n (%)		

No disorder	1798 (18.4)	Reference
Viral infection	3758 (38.5)	1.38 (1.11-1.71)
Endocrine	4141 (42.4)	1.30 (1.06-1.61)
Neurologic	4859 (49.7)	1.33 (1.08-1.64)
Cardiovascular	2621 (26.8)	1.47 (1.19-1.83)
Respiratory	3609 (36.9)	1.70 (1.38-2.10)
Digestive	1822 (18.6)	1.53 (1.22-1.93)
Skin	2144 (21.9)	1.44 (1.15-1.80)
Musculoskeletal	2447 (25.0)	1.27 (1.01-1.59)
Urogenital	711 (7.3)	1.77 (1.35-2.32)

*Adjusted for age and gender

Figure 1. Prevalence rates of two-way disease system combinations presented as percentages.

Table 2. Cox proportional hazards regression of physical disease combinations and their association to death.

Physical disease combinations	Crude HR (95% CI)	Adjusted HR (95% CI)*	Adjusted HR (95% CI)†	p
No physical disease	1.0 (Ref.)	1.0 (Ref.)	1.0 (Ref.)	
Viral infection only	1.11 (0.67-1.82)	1.31 (0.80-2.17)	N/A	ns
Viral infection + Endocrine	1.39 (1.10-1.76)	1.33 (1.05-1.69)	1.19 (0.79-1.77)	ns
Viral infection + Neurologic	1.37 (1.08-1.72)	1.34 (1.06-1.69)	0.92 (0.62-1.37)	ns
Viral infection + Cardiovascular	1.75 (1.37-2.23)	1.44 (1.13-1.84)	1.06 (0.64-1.77)	ns
Viral infection + Respiratory	1.74 (1.38-2.18)	1.64 (1.31-2.06)	**1.65 (1.17-2.33)**	**<0.01**
Viral infection + Digestive	1.84 (1.42-2.38)	1.59 (1.23-2.07)	1.08 (0.61-1.90)	ns
Viral infection + Skin	1.57 (1.22-2.03)	1.35 (1.04-1.74)	0.96 (0.57-1.63)	ns
Viral infection + Musculoskeletal	1.55 (1.20-1.99)	1.39 (1.08-1.79)	1.06 (0.64-1.77)	ns
Viral infection + Urogenital	2.00 (1.42-2.80)	1.65 (1.18-2.32)	0.75 (0.26-2.18)	ns
Endocrine only	1.50 (1.01-2.22)	1.23 (0.83-1.82)	N/A	ns
Endocrine + Neurologic	1.34 (1.07-1.69)	1.23 (0.98-1.54)	0.80 (0.56-1.14)	ns
Endocrine + Cardiovascular	1.69 (1.33-2.15)	1.29 (1.01-1.64)	0.83 (0.52-1.30)	ns
Endocrine + Respiratory	1.72 (1.37-2.16)	1.62 (1.29-2.04)	**1.72 (1.18-2.49)**	**<0.01**
Endocrine + Digestive	1.58 (1.21-2.07)	1.42 (1.09-1.86)	1.11 (0.63-1.94)	ns
Endocrine + Skin	1.63 (1.26-2.09)	1.41 (1.09-1.82)	1.51 (0.95-2.42)	ns
Endocrine + Musculoskeletal	1.39 (1.08-1.79)	1.21 (0.93-1.56)	0.94 (0.59-1.50)	ns
Endocrine + Urogenital	2.09 (1.53-2.86)	1.66 (1.22-2.28)	0.80 (0.36-1.75)	ns
Neurologic only	1.09 (0.73-1.63)	1.20 (0.80-1.79)	N/A	ns
Neurologic + Cardiovascular	1.85 (1.47-2.33)	1.46 (1.16-1.83)	1.22 (0.84-1.77)	ns
Neurologic + Respiratory	1.86 (1.49-2.32)	1.71 (1.38-2.14)	**1.84 (1.35-2.52)**	**<0.001**
Neurologic + Digestive	1.78 (1.39-2.28)	1.58 (1.24-2.03)	1.19 (0.76-1.87)	ns
Neurologic + Skin	1.73 (1.36-2.20)	1.46 (1.15-1.86)	1.31 (0.83-2.05)	ns
Neurologic + Musculoskeletal	1.45 (1.14-1.86)	1.29 (1.01-1.66)	0.67 (0.41-1.10)	ns
Neurologic + Urogenital	2.25 (1.68-3.03)	1.83 (1.36-2.46)	1.08 (0.52-2.31)	ns
Cardiovascular only	3.04 (1.92-4.81)	1.97 (1.24-3.12)	N/A	
Cardiovascular + Respiratory	2.34 (1.86-2.95)	1.78 (1.41-2.25)	**2.23 (1.49-3.32)**	**<0.001**
Cardiovascular + Digestive	1.93 (1.47-2.54)	1.51 (1.15-2.00)	1.33 (0.65-2.71)	ns
Cardiovascular + Skin	2.00 (1.54-2.60)	1.46 (1.13-1.90)	1.07 (0.57-2.00)	ns
Cardiovascular + Musculoskeletal	1.72 (1.32-2.25)	1.30 (0.99-1.69)	0.71 (0.37-1.37)	ns
Cardiovascular + Urogenital	2.64 (1.92-3.65)	1.81 (1.31-2.50)	0.71 (0.26-1.93)	ns
Respiratory only	1.16 (0.67-2.03)	1.12 (0.64-1.95)	N/A	ns
Respiratory + Digestive	2.23 (1.74-2.86)	1.88 (1.47-2.41)	**1.88 (1.14-3.11)**	**<0.05**
Respiratory + Skin	2.04 (1.60-2.60)	1.75 (1.37-2.24)	**2.06 (1.31-3.24)**	**<0.01**
Respiratory + Musculoskeletal	1.88 (1.47-2.40)	1.62 (1.27-2.07)	**1.57 (1.01-2.44)**	**<0.05**
Respiratory + Urogenital	2.73 (2.02-3.70)	2.00 (1.48-2.72)	1.39 (0.65-2.96)	ns
Digestive only	1.34 (0.59-3.06)	1.13 (0.49-2.58)	N/A	ns
Digestive + Skin	1.92 (1.45-2.55)	1.59 (1.20-2.12)	0.96 (0.44-2.08)	ns
Digestive + Musculoskeletal	1.80 (1.36-2.38)	1.54 (1.16-2.04)	0.71 (0.33-1.54)	ns
Digestive + Urogenital	2.65 (1.82-3.86)	2.07 (1.42-3.02)	1.97 (0.63-6.15)	ns
Skin only	1.35 (0.66-2.77)	1.03 (0.50-2.12)	N/A	ns
Skin + Musculoskeletal	1.75 (1.33-2.29)	1.41 (1.07-1.85)	0.68 (0.35-1.31)	ns
Skin + Urogenital	2.70 (1.92-3.79)	2.05 (1.45-2.88)	1.39 (0.45-4.28)	ns
Musculoskeletal only	0.9 (0.42-1.94)	0.88 (0.41-1.88)	N/A	ns
Musculoskeletal + Urogenital	2.42 (1.71-3.41)	1.85 (1.31-2.61)	0.70 (0.25-1.97)	ns
Urogenital only	3.68 (1.50-9.02)	1.87 (0.76-4.61)	N/A	ns

* Adjusted for age and gender

† Adjusted for age, gender, and all other physical disease systems (chapter B-N)

N/A, not applicable

Significance testing for the final adjusted model only (†)

Table 3. Top five highest population attributable fractions (PAFs) for 5-year mortality associated with physical multimorbidity combinations as well as single diseases in patients with SSD

Physical disease combinations and single diseases ranked by PAF	PAF estimate (%, 95%CI)	p
No physical disease	Ref.	Ref.
Physical multimorbidity		
Cardiovascular + Respiratory	35.7 (23.0-46.3)	<0.001
Neurologic + Respiratory	32.7 (19.3-43.8)	<0.001
Respiratory + Skin	29.8 (15.8-41.5)	<0.001
Endocrine + Respiratory	27.5 (11.7-40.5)	<0.001
Respiratory + Digestive	26.4 (9.4-40.3)	<0.001
Single diseases		
Cardiovascular alone	8.1 (4.2-9.6)	<0.001
Neurologic alone	3.6 (-3.9-10.6)	ns
Endocrine alone	4.2 (-3.2-11.1)	ns
Respiratory alone	1.2 (-4.6-6.6)	ns
Skin alone	0.2 (-4.5-4.8)	ns
Digestive alone	0.6 (-3.3-4.3)	ns

PAF calculated by an adjusted cox regression analysis adjusted for age, gender, and all other physical disease systems.
Abbreviations: PAF, population attributable fraction