Are symptoms of serious mental health illness in the two years before pregnancy a good predictor for relapse in the perinatal period?

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Introduction

For women who suffer with, or are susceptible, to serious mental illness (SMI), perinatal period can be a particularly difficult time. It can have potentially serious implications on the mother, such as suicidal thoughts and attempts, discordant bonding with her child, and, rarely, infanticide.

Women with bipolar are at a high risk for relapse in the perinatal period and this risk ranges from 9-23% in pregnancy and 9-27% postpartum, based on hospital admissions [1,2,3,4]. Similarly, relapse rates for women with schizophrenia ranges from 13 to 39% in pregnancy and 21-22% postpartum [3, 4, 5, 6, 7, 8]. However, due to high heterogeneity in study designs and time period and type of relapse, comparison between studies is difficult. Studies have shown a higher risk of relapse in women with schizophrenia during pregnancy, and higher risk of relapse postpartum for bipolar disorder based on hospitalisation [6, 9]. Predictors of relapse in SMI include discontinuing medication, younger onset, longer duration of illness and increased recurrences, suicide attempt, primiparity, being unmarried and unplanned pregnancy[10, 11, 12, 13].

In clinical practice, symptoms are seen as a more useful indicator for mental health disorders than clinician-attributed diagnoses and potentially predictors of relapses. Negative symptoms in schizophrenia are associated with increased likelihood of hospital admissions and increased likelihood of readmission following discharge[14]. This shows symptoms can influence relapse rates in schizophrenic patients overall, however, whether symptoms can influence perinatal relapse rates in women with SMIs is unknown and the extent of their prediction is equally unknown. Positive symptoms are common in patients with schizophrenia, with relapses being more common during pregnancy. Bipolar disorder patients have manic and depressive symptom profiles, and relapses are more likely postpartum.

In our study, we will be looking at symptom profiles as a predictor for relapse in pregnant women with serious mental illness. Our aim is to see how the predominance of particular symptom domains, in SMI's affects the relapse risk during the perinatal period.

Methods

Data source

Data was gathered from the South London and Maudsley Biomedical Research Centre (SLaM BRC) Clinical Record Interactive Search (CRIS) system and Hospital Episode Statistics (HES). Data extraction was carried out using text mining and natural language processing programs, such as General Architecture for Text Engineering (GATE) software and TextHunter. The data used were from women who were patients at the SLaM NHS Foundation Trust. SLaM is a mental health care Trust, which provides secondary mental healthcare for the four London boroughs of Lambeth, Southwark, Lewisham and Croydon. It has adopted Electronic Healthcare Records (EHRs) for all its services during 2006 [15]. CRIS creates a research database formed of a pseudonymised version of SLaM's EHR system where it currently contains over 250000 de-identified patient records and above 3.5 million documents in word-processed formats. Fernandes et al has published CRIS de-identification performance and security protocols and, since 2008, the Oxfordshire Research Ethics Committee C (08/H0606/71+5) has approved CRIS as a source of secondary data for research [16]. Hospital Episode Statistics provide national statistical data on all NHS hospital care in England, including hospital admissions, outpatient appointments, A&E attendances and NHS maternity data. CRIS data is linked with HES and is stored by the Clinical Data Linkage Service (CDLS) within the SlaM firewall and has approved governance and security [17].

Natural language processing

CRIS has free text data with a vast amount of clinical information available for research purposes. Natural language processing applications for CRIS have now been developed to make this task easier for researchers using GATE software. Structured data is derived from free text fields using natural language processing which takes into account the textual context of words or phrases of interest in order to identify constructs of interest (for example, the presence or not of a reported symptom).

Study design

A retrospective cohort of pregnant women with a history of SMI was assembled using CRIS and HES for previous studies [18]. The inclusion criteria involved women who had been pregnant from 2007 to 2011 (identified using HES delivery episodes which established the end of pregnancy), active SLAM patients at any point from 6 months before to 3 months after the HES episode identifying the end of pregnancy and SMI diagnosis (established from CRIS). As part of inclusion criteria, women with SMI were identified in CRIS if they had ever had the following ICD-10 (World Health Organization, 1992) diagnoses recorded: schizophrenia, acute and transient psychotic disorders, schizoaffective disorders, non-organic psychotic disorders, manic episode, bipolar affective disorder, psychotic depression, puerperal psychosis. For previous studies, correspondence and case note text fields were read around two years before pregnancy for all women identified only with ICD-10 diagnostic codes F53 (mental and behavioral disorders associated with puerperium) or F53.1 (severe mental and behavioural disorders associated with the puerperium not elsewhere classified) in order to establish SMI as these codes do not necessarily indicate SMI. To ensure the onset of SMI pre-dated the pregnancies identified, structured fields containing SMI diagnosis from any point in a woman's SLaM referral and GATE diagnosis application (which returns text strings associated with diagnostic statements in clinical notes and correspondence) were extracted at or before 9 months before delivery date.

The linkage with HES was used to identify instances of pregnancy within the study period. Delivery episodes were identified from hospital episode statistics which identify live births and stillbirths at greater than 24 weeks gestation. We will be analysing each woman with the first pregnancy they have had in the study period. The exclusion criteria excluded women who did not have history of SMI before the index pregnancy, and women with SMI diagnoses secondary to an organic disorder.

Exposure variables

Our main exposure variables were mental health symptoms that a patient experienced for a period of two years up until the beginning of pregnancy. For the purpose of this study, we extracted 50 symptoms using the NLP applications for the 2 years before pregnancy. The symptoms extracted using the NLP applications were categorized into

six groups: positive, negative, disorganization, manic, catatonic and depressive subgroups, allowing some symptoms relevant to more than one dimension (for example, anhedonia to both negative and depressive dimensions) to be duplicated.

Table 1: Grouping of symptoms apps into categories

Symptom profiles	Symptoms included
Positive symptoms	Abstract thinking, Aggression, Agitation, Delusion, Hallucination, Hostility, Paranoia, Persecution
Negative symptoms	Anergia, Anhedonia, Blunted flat affect, Poor motivation, Poverty of Speech, Poverty of Though, Social Withdrawal
Disorganisation symptoms	Circumstantial speech, Coherence, Derailment of speech, Flight of ideas, Formal thought disorder, Tangential speech
Manic symptoms	Disturbed sleep, Elation, Elevated mood, Grandiosity, Insomnia, Irritability, Pressurised speech
Catatonia symptoms	Catatonic syndrome, Echolalia, Echopraxia, Immobility, Mannerism, Mutism, Perseverance, Posturing, Stereotype, Stupor, Waxy flexibility
Depression symptoms	Anergia, Anhedonia, Appetite, Blunted flat affect, Concentration, Disturbed sleep, Guilt, Helpless, Hopeless, Insomnia, Low mood, Poor motivation, Psychomotor, Worthless

Detailed information of performance and prevalence has been described in a study for fifty symptoms of severe mental illness (schizophrenia and bipolar disorder) [19]. The precision and recall metrics of each modeled symptom for individuals with an SMI diagnosis range between 66% to 97%, for precision, and 56% to 100% for recall.

Outcome variables

The outcome variables were severe relapse during pregnancy or postpartum. This was defined as an admission to acute mental health care during pregnancy. Relapse during postpartum was defined as an admission to acute mental health care in the first three months after the delivery date. The postpartum relapses were inclusive of relapses during the pregnancy period as well. Acute mental health care comprised of admission to an inpatient ward or home treatment.

Covariates

Covariates used were selected from data already extracted for a PhD thesis that used the same cohort as in this study [18, 20]. Data containing information about ethnicity and maternal age was extracted from CRIS structured fields. Smoking in pregnancy was extracted from free text using terms used for a GATE natural language processing smoking application that was in development at the time of data extraction. CRIS structured data and the GATE diagnosis application was used to extract data about the women's baseline mental health diagnoses before their index pregnancy. The baseline diagnoses were derived from ICD-10 codes and included 'bipolar disorder or mania', 'schizophrenia', 'acute and transient psychosis', 'psychotic depression', 'schizoaffective', 'psychosis NOS' and 'puerperal psychosis'.

Relationship status during the index pregnancy was established using manual CRIS searches and search terms were used (see Appendix). If a partner or husband was referred to during pregnancy or immediately after childbirth then 'partner present' status was assigned. In free text searches of patient admissions, discharge summaries or referral correspondence, search terms were used to establish number of children before the index pregnancy. From free text searches of summaries and referral documents, search terms were used to see mentions of the disorder and family member (see Appendix). Family history of psychosis was coded if schizophrenia, bipolar disorder, or psychotic depression were recorded. Ethnicity was extracted from CRIS and split into three categories: 'White British and other White', 'Black African and other Black' and 'Asian/Mixed/Other'. As patients have a varying amount of clinical records, the number of documents in the 2 years before pregnancy was extracted from CRIS data.

Analysis

Analysis was conducted using the software STATA Version 12. Descriptive analysis was carried out to describe the baseline socio-demographic and clinical characteristics of the cohort and their symptoms recorded in the 2 years before their index pregnancy. The symptoms were grouped together to construct symptom profiles, their distributions were inspected then the symptom profiles were categorized and split into

three or four even categories. Pearson's chi squared was calculated for associations of symptom profiles and socio-demographic characteristics with relapse rates during the pregnancy and postpartum period. A t-test was used to calculate the association between maternal ages and relapse rates during the two time periods.

The primary inferential analysis was the multivariable analyses that was conducted using logistic regression to model the associations between symptom profiles and the presence of relapse, during pregnancy and postpartum, with symptom categories entered as an ordinal independent variable (on one degree of freedom). A secondary, additional analysis was the multivariable analyses, which were carried out using logistic regression to produce odds ratios for associations between symptom profiles and socio-demographic characteristics and relapse rates, with symptoms as categorical variables and compared to a reference of 'no symptoms' category. The models were first adjusted for age and ethnicity and then partner during pregnancy, primiparity, smoking, family history of psychosis were added to them model and finally number of documents in CRIS.

Results

The final cohort contained 399 women with SMI, with 399 index pregnancies for each woman during the study period 2007-2011 (mean age = 31.7, SD = 6.0). 76 women relapsed during pregnancy (19.0%) and 107 (27.0%) women relapsed postpartum.

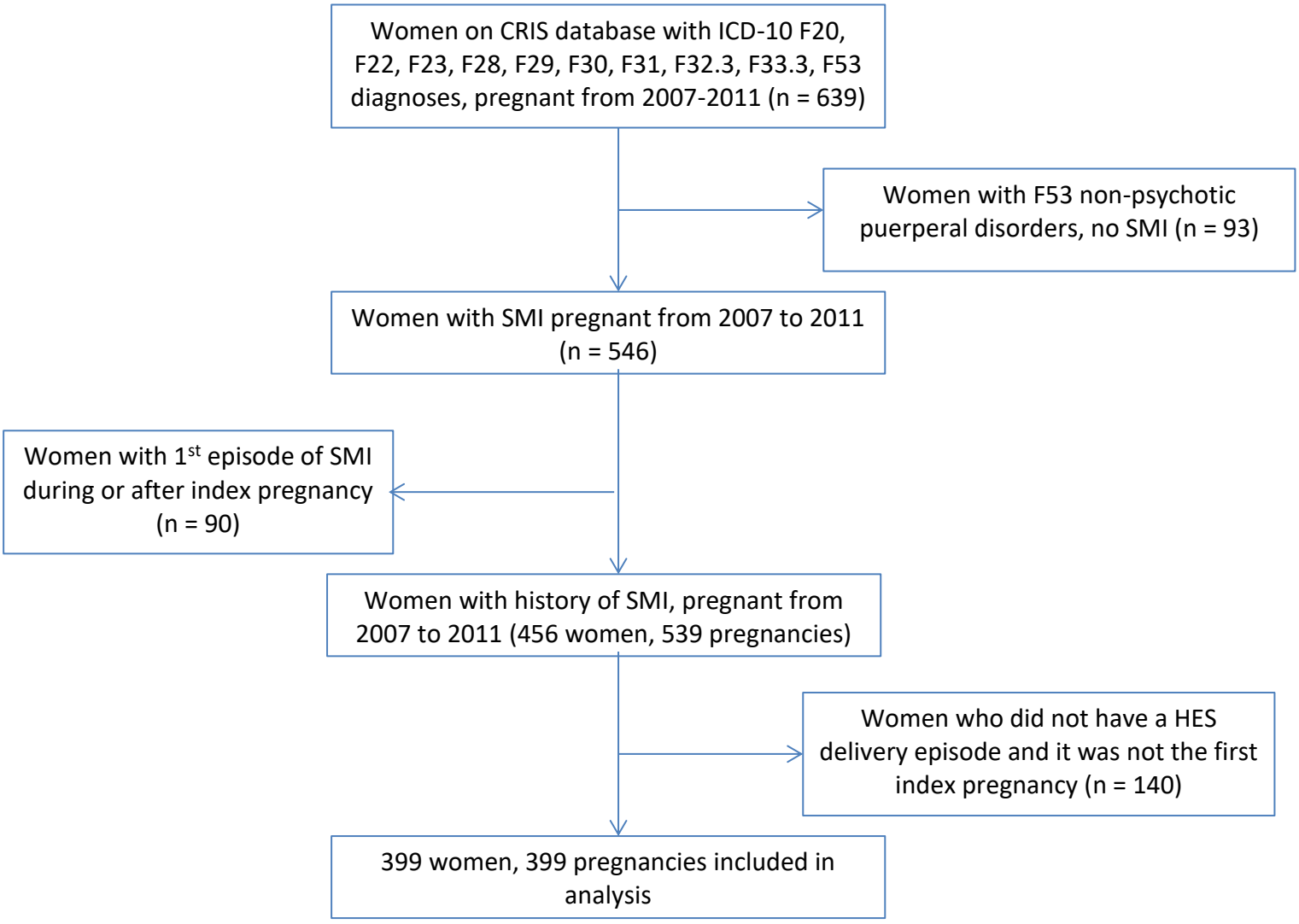

Figure 1: Cohort of women with SMI used

The most common diagnosis was bipolar affective disorder, 145 women (36.3%), and the least common was puerperal psychosis, with 7 patients (1.8%) (Table 2). The

most common ethnicity was Black African or other black ethnicity, 190 patients (47.6%). 190 (47.6%) women were primiparous at the first recorded pregnancy in the database and 271 women (67.9%) had a partner throughout their pregnancy. 56 women (14.0%) had a family history of psychosis and 75 women (18.8%) were recorded as smoking during pregnancy.

Table 2: Socio-demographic and clinical characteristics of 399 pregnant women with severe mental illness

	N=399
Diagnosis at beginning of pregnancy, N (%)	
BPAD/Mania	145 (36.3)
Schizophrenia	112 (28.1)
Acute and transient psychosis	47 (11.8)
Psychotic depression	44 (11.0)
Schizoaffective	26 (6.5)
Psychosis NOS	18 (4.5)
Puerperal psychosis	7 (1.8)
Ethnicity, N (%)	
White British & other White	135 (33.8)
Black African & other Black	190 (47.6)
Asian/ Mixed/ Other	74 (18.6)
Maternal age at 1st index delivery, mean (SD)	31.7 (6.0)
Partner during 1st index pregnancy	271 (67.9)
Primiparity	190 (47.6)
Family history of psychosis	56 (14.0)
Smoking in pregnancy	75 (18.8)
No. of documents in the 2 years before pregnancy	
0	93 (23.3)
1 – 42	108 (27.1)
43 – 127	99 (24.8)
129 – 1131	99 (24.8)

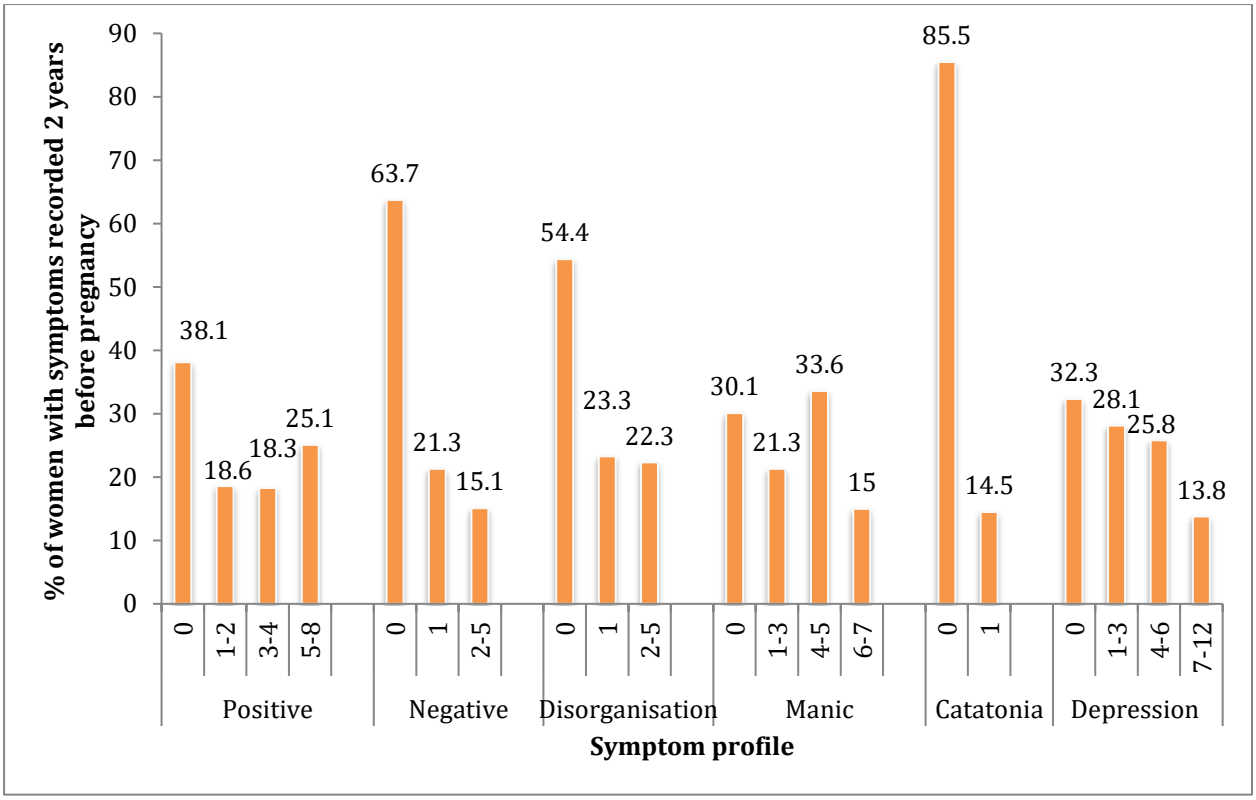

Figure 2: Symptom profiles of women with SMI recorded in the 2 years before the start of pregnancy, based on Table 2 in the Appendix.

Figure 2 shows the most common symptom profiles extracted in the 2 years before the pregnancy and postpartum period were manic symptoms (69.9%), depression symptoms (67.7%) and positive symptoms (62.0%). The least common symptom profile was catatonic symptoms (14.5%). Table 3 shows significant associations found between positive symptoms, disorganisation symptoms, manic symptoms and catatonic symptoms and relapses during pregnancy. The percentages show non-linear, U-shaped trends where significant findings are high in the zero group as well as in those with most symptoms.

Table 3: Association between symptom profiles and relapse during pregnancy

Symptom profiles	Number (%) of admissions in pregnancy	Chi squared value (Degrees of freedom)	p-value

Positive symptoms		**12.08 (3)**	**0.007****
0	24 (15.8)		
1-2	8 (10.8)		
3-4	14 (19.2)		
5-8	30 (30.0)		
Test for trend		**7.99**	**0.005***
Negative symptoms		0.87 (2)	0.647
0	47 (18.5)		
1	19 (22.4)		
2-5	10 (16.7)		
Test for trend		0.00	0.994
Disorganisation symptoms		**11.30 (2)**	**0.003***
0	30 (13.8)		
1	19 (20.4)		
2-5	27 (30.3)		
Test for trend		**11.16**	**0.001****
Manic symptoms		**16.20 (3)**	**0.001****
0	22 (18.3)		
1-3	6 (7.1)		
4-5	28 (20.1)		
6-7	20 (33.3)		
Test for trend		**6.04**	**0.014***
Catatonia symptoms		**4.64 (1)**	**0.031***
0	59 (17.3)		
1	17 (29.3)		
Depression symptoms		1.07 (3)	0.785
0	22 (17.1)		
1-3	20 (17.9)		
4-6	22 (21.4)		
7-12	12 (21.8)		
Test for trend		0.95	0.329

*** p< 0.05**

**** p < 0.001**

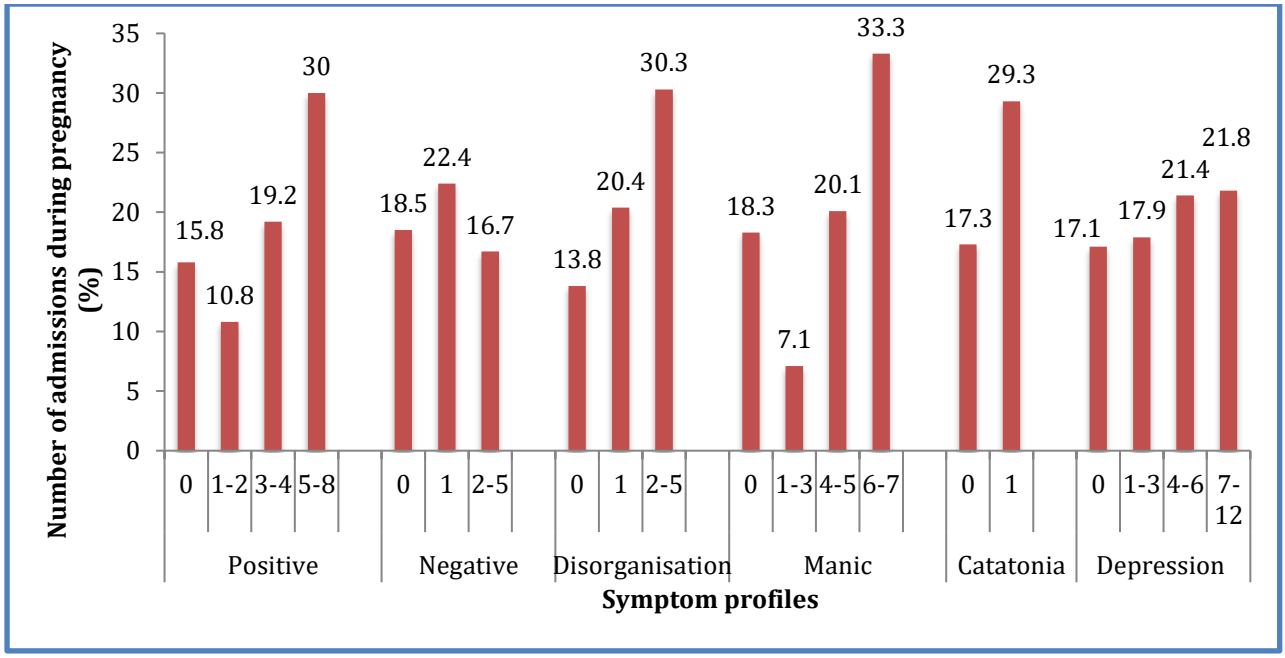

Figure 3: A graph to show the associations between symptom profiles and relapse during pregnancy

During postpartum period, significant associations were found between positive symptoms, disorganisation symptoms, manic symptoms, depression symptoms and relapse rates (see Table 4). No significant linear trends were found between the number of symptoms and relapse rate; however, the percentages show a non-linear (U-shaped) trend between the number of symptoms and relapses.

Table 4: Association between symptom profiles and relapse during postpartum period

Symptom profiles	**Number (%) of admissions in postpartum period**	**Chi squared value (Degrees of freedom)**	**p-value**
Positive symptoms		**10.55 (3)**	**0.014***
0	48 (31.6)		
1-2	11 (14.9)		
3-4	15 (20.6)		
5-8	33 (33.0)		
Test for trend		0.00	0.959
Negative symptoms		1.93 (2)	0.381
0	74 (29.1)		

1	19 (22.4)		
2-5	14 (23.3)		
Test for trend		1.47	0.225
Disorganisation symptoms		**7.24 (2)**	**0.027***
0	58 (26.7)		
1	17 (18.3)		
2-5	32 (36.0)		
Test for trend		1.33	0.249
Manic symptoms		**11.32 (3)**	**0.010***
0	41 (34.2)		
1-3	17 (20.0)		
4-5	27 (20.2)		
6-7	22 (36.7)		
Test for trend		0.40	0.528
Catatonia symptoms		1.22 (1)	0.269
0	88 (25.8)		
1	19 (32.8)		
Depression symptoms		**8.47 (3)**	**0.037***
0	46 (35.7)		
1-3	22 (19.6)		
4-6	25 (24.3)		
7-12	14 (25.5)		
Test for trend		2.82	0.093

*** p< 0.05**

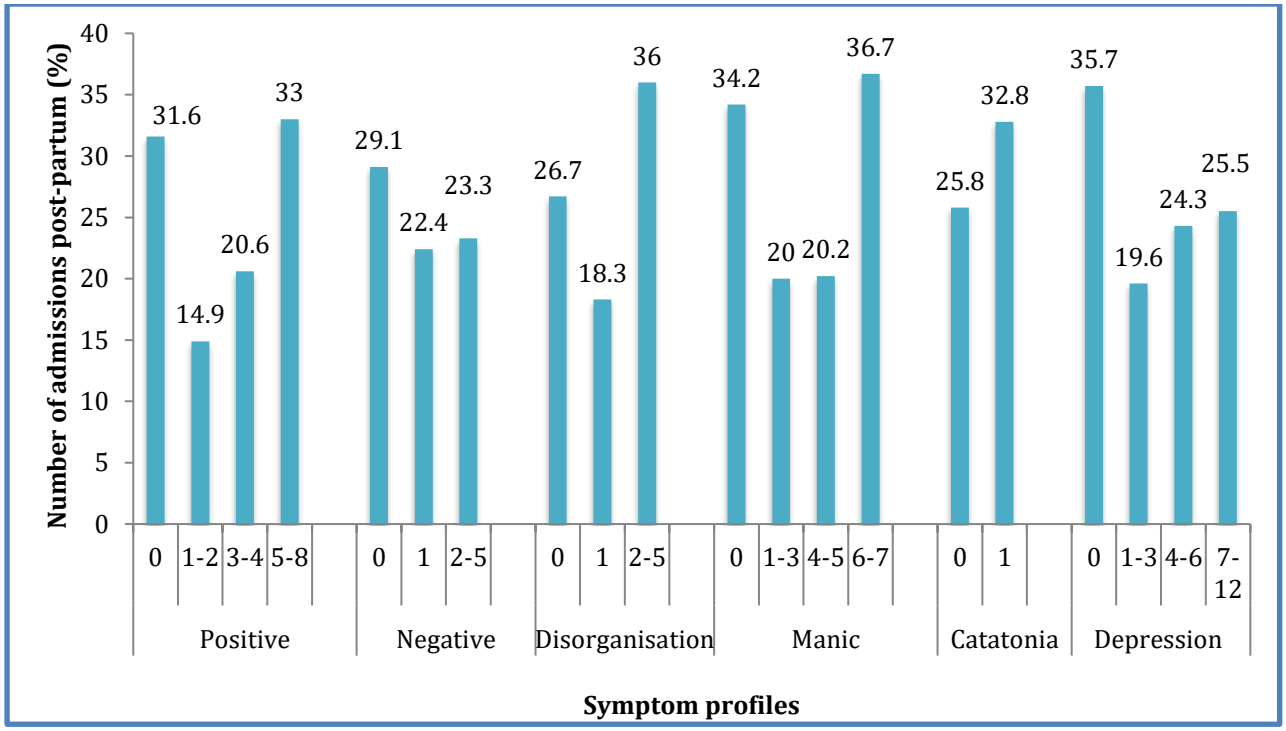

Figure 4: A graph to show the association of symptom profiles and relapse postpartum

Mean age of women who relapsed during pregnancy was younger (M = 30.1, SD = 6.0) than mean age of women who did not relapse during pregnancy 32.1 (SD = 6.0), t = 2.6, p = 0.010. Table 5 shows ethnicity was significantly associated with relapse during pregnancy but not postpartum. Smoking during pregnancy was associated with relapse during pregnancy and post partum.

Table 5: Association between socio-demographic characteristics and relapse during pregnancy and postpartum

	Percentage of women who relapsed during pregnancy	**Chi-squared value (Degrees of freedom)**	**p-value**	**Percentage of women who relapsed postpartum**	**Chi-squared value (Degrees of freedom)**	**p-value**
Ethnicity, N(%)		**15.5 (2)**	**P<0.001**		2.18 (2)	0.336
White British & other White	8.9			25.2		
Black African & other	26.3			30.0		

Black Asian/ Mixed/ Other	18.9			21.6		
Partner during 1st index pregnancy		2.36 (1)	0.125		0.10 (1)	0.748
Yes	17.0			27.3		
No	23.4			25.8		
Primiparity		0.95 (1)	0.331		0.84 (1)	0.360
Yes	21.1			29.0		
No	17.2			24.9		
Smoking in pregnancy		**26.30 (1)**	**P < 0.001**		**8.18 (1)**	**0.004**
Yes	40.0			40.0		
No	14.2			23.8		
Family history of Psychosis		0.24 (1)	0.625		0.43 (1)	0.51
Yes	21.4			23.2		
No	18.7			27.4		

Table 6 shows multivariable analysis, where symptom categories were entered as ordinal variables to look at linear trends, show that only disorganisation symptoms were positively associated with relapse during pregnancy, when adjusted for age and ethnicity. However, after adjusting for all other variables in the other models, disorganisation symptoms were not significantly associated with relapse anymore. Multivariable analyses were then repeated with '0 symptoms' as a reference category and categorical rather than ordinal independent variables. Results show that after adjusting for age and ethnicity, women who had 2-5 disorganisation symptoms before pregnancy and the lower number of manic symptoms had significantly higher likelihood of relapse during pregnancy compared with those who had no recorded disorganisation or manic symptoms (Table 7). After adjusting for all the other variables, the lower number of manic symptoms remained significantly associated with relapse during pregnancy.

Table 6: Multivariable analysis of predictors of relapse in pregnancy

	Relapse in pregnancy, Odds ratios* (95% CI), p-value; N=399, n=76 relapses			
	Unadjusted	**Model 1**	**Model 2**	**Model 3**
Positive symptoms	**1.34 (0.09, 1.65), 0.005**	1.21 (0.98, 1.50), 0.082	1.09 (0.87, 1.37), 0.462	1.04 (0.72, 1.51), 0.830
Negative symptoms	1.00 (0.71, 1.40), 0.993	0.92 (0.65, 1.31), 0.660	0.85 (0.58, 1.23), 0.380	0.70 (0.44, 1.09), 0.116
Disorganisation symptoms	**1.65 (1.22, 2.21), 0.001**	**1.51 (1.12, 2.05), 0.008**	1.36 (0.99, 1.87), 0.060	1.50 (0.97, 2.33), 0.069
Manic symptoms	**1.35 (1.06, 1.72), 0.015**	1.25 (0.98, 1.61), 0.074	1.09 (0.84, 1.42), 0.523	1.00 (0.62, 1.61), 0.991
Catatonia symptoms	**1.98 (1.05, 3.73), 0.034**	1.51 (0.78, 2.89), 0.219	1.24 (0.62, 2.47), 0.546	1.14 (0.55, 2.39), 0.722
Depression symptoms	1.13 (0.89, 1.43), 0.329	1.05 (0.82, 1.35), 0.686	0.97 (0.74, 1.26), 0.814	0.77 (0.51, 1.16), 0.219

Model 1 = adjusted for age and ethnicity
Model 2 = adjusted for age, ethnicity, partner present during pregnancy, primiparity, smoking, family history of psychosis
Model 3 = adjusted for age, ethnicity, partner present during pregnancy, primiparity, smoking, family history of psychosis and number of documents
*****Odds ratio reflects incremental changes in odds ratio per category

Table 7: Multivariable analysis of predictors of relapse in pregnancy

	Relapse in pregnancy, Odds ratios (95% CI), p-value; N=399, n=76 relapses			
	Unadjusted	**Model 1**	**Model 2**	**Model 3**
Positive symptoms				
0	Ref	Ref	Ref	Ref
1-2	0.65 (0.28, 1.52), 0.316	0.54 (0.22, 1.29), 0.162	0.52 (0.21, 1.28), 0.154	0.45 (0.16, 1.23), 0.118

3-4	1.27 (0.61,2.62), 0.526	1.12 (0.53, 2.37), 0.759	0.90 (0.41, 1.96), 0.604	0.72 (0.26, 2.01), 0.532
5-8	**2.29 (1.24, 4.21), 0.008**	1.61 (0.84, 3.07), 0.150	1.20 (0.60, 2.38), 0.604	0.88 (0.28, 2.77), 0.833
Negative symptoms				
0	Ref	Ref	Ref	Ref
1	1.27 (0.70, 2.31), 0.439	1.16 (0.62, 2.15), 0.648	0.98 (0.51, 1.90), 0.957	0.75 (0.36, 0.60), 0.460
2-5	0.88 (0.42, 1.86), 0.740	0.76 (0.35, 1.65), 0.486	0.66 (0.29, 1.50), 0.320	0.47 (0.19, 1.20), 0.115
Disorganisation symptoms				
0	Ref	Ref	Ref	Ref
1	1.60 (0.85, 3.02), 0.146	1.51 (0.79, 2.89), 0.214	1.30 (0.66, 2.59), 0.449	1.50 (0.67, 3.36), 0.328
2-5	**2.71 (1.50, 4.92), 0.001**	**2.29 (1.24, 4.22), 0.008**	1.86 (0.98, 3.53), 0.058	2.26 (0.94, 5.43), 0.069
Manic symptoms				
0	Ref	Ref	Ref	Ref
1-3	**0.34 (0.13, 0.87), 0.025**	**0.30(0.11, 0.79), 0.015**	**0.29 (0.11, 0.79), 0.016**	**0.22 (0.069, 0.68), 0.009**
4-5	1.18 (0.63, 2.19), 0.608	0.95 (0.50, 1.81), 0.871	0.76 (0.39, 1.50), 0.428	0.45 (0.14, 1.47), 0.186
6-7	**2.23 (1.10, 4.52), 0.027**	1.85 (0.89, 3.86), 0.102	1.29 (0.58, 2.85), 0.534	0.67 (0.16, 2.82), 0.582
Catatonia symptoms				
0	Ref	Ref	Ref	Ref
1	**0.98 (1.05, 3.73), 0.034**	1.51 (0.78, 2.89), 0.219	1.24 (0.62, 2.47), 0.546)	1.14 (0.55, 2.39), 0.722
Depression symptoms				
0	Ref	Ref	Ref	Ref
1-3	1.06 (0.54, 2.06), 0.870	0.87 (0.44, 1.75), 0.702	0.72 (0.35, 1.49), 0.375	0.41 (0.16, 1.06), 0.067
4-6	1.32 (0.68, 2.55), 0.407	1.13 (0.57, 2.23), 0.724	0.87 (0.43, 1.78), 0.705	0.39 (0.13, 1.20), 0.101
7-12	1.36 (0.62, 2.98), 0.447	1.08 (0.48, 2.44), 0.852	0.88 (0.37, 2.08), 0.762	0.35 (0.10, 1.29), 0.115

Multivariable analysis, with symptoms as ordinal variables, showed no significant associations with any of the symptoms and relapses postpartum (Table 8). Multivariable analysis, with symptoms as categorical variables, shows that the lower 'present' category of positive symptoms (1-2 symptoms), manic symptoms (1-3, 4-5 symptoms) and depression symptoms (1-3, 4-6, 7-12 symptoms) are significantly associated with lower relapse postpartum, after adjusting for all the variables, with reference to 'no symptoms' category (Table 9). The highest category of depression symptoms (7-12 symptoms) was also significantly negatively associated with relapse rates postpartum, after adjusting for all variables. With depression symptoms, the patients with zero symptoms were more likely to relapse than higher category symptoms as the lower category (1-3 symptoms) had a higher relapse risk than the highest category (7-12 symptoms). There were similar findings noted for positive symptoms and manic symptoms.

Table 8: Multivariable analysis of predictors of relapse during the postpartum period

	Relapse during postpartum period, Odds ratios* (95% CI), p-value; N=399, n=107 relapses			
	Unadjusted	**Model 1**	**Model 2**	**Model 3**
Positive symptoms	1.00 (0.84, 1.21), 0.959	0.97 (0.81, 0.18), 0.779	0.93 (0.76, 1.13), 0.445	1.08 (0.79, 1.48), 0.635
Negative symptoms	0.82 (0.60, 1.13), 0.226	0.81 (0.59, 1.11), 0.190	0.78 (0.57,1.08), 0.139	0.84 (0.57, 0.24), 0.383
Disorganisation symptoms	1.17 (0.90, 1.53), 0.249	1.15 (0.87,1.50), 0.323	1.08 (0.81, 1.42), 0.603	1.45 (0.99, 2.13), 0.057
Manic symptoms	0.93 (0.76, 1.15), 0.527	0.91 (0.73, 1.12), 0.380	0.85 (0.68, 1.06), 0.151	0.89 (0.60, 1.34), 0.588
Catatonia symptoms	1.40 (0.77, 2.55), 0.271	1.24 (0.72, 2.47), 0.353	1.19 (0.64, 2.23), 0.586	1.47 (0.74, 2.90), 0.268
Depression symptoms	0.83 (0.67, 1.03), 0.094	0.81 (0.65, 1.01), 0.062	**0.78 (0.62, 0.98), 0.032**	0.73 (0.51, 1.04), 0.082

Model 1 = adjusted for age and ethnicity

Model 2 = adjusted for age, ethnicity, partner present during pregnancy, primiparity, smoking, family history of psychosis
Model 3 = adjusted for age, ethnicity, partner present during pregnancy, primiparity, smoking, family history of psychosis and number of documents
*****Odds ratio reflects incremental changes in odds ratio per category

Table 9: Multivariable analyses of predictors of relapse during the postpartum period

	Relapse during postpartum period, Odds ratios (95% CI), p-value; N=399, n=107 relapses			
	Unadjusted	**Model 1**	**Model 2**	**Model 3**
Positive symptoms				
0	Ref	Ref	Ref	Ref
1-2	**0.38 (0.18, 0.78), 0.009**	**0.36 (0.17, 0.74), 0.006**	**0.36 (0.17, 0.76), 0.007**	**0.41 (0.18, 0.94), 0.035**
3-4	0.56 (0.29,1.09), 0.087	0.54 (0.28, 1.06), 0.071	**0.49 (0.25, 0.97), 0.040**	0.59 (0.25, 1.41), 0.235
5-8	1.07 (0.62, 1.83), 0.813	0.96 (0.54, 1.69), 0.878	0.84 (0.46, 1.52), 0.564	1.10 (0.42, 2.87), 0.849
Negative symptoms				
0	Ref	Ref	Ref	Ref
1	0.70 (0.39, 1.25), 0.227	0.69 (0.38, 1.23), 0.204	0.63 (0.35, 1.14), 0.123	0.67 (0.35, 1.32), 0.248
2-5	0.74 (0.38, 1.43), 0.369	0.71 (0.37, 1.39), 0.323	0.69 (0.35, 1.36), 0.282	0.76 (0.34, 1.68), 0.496
Disorganisation symptoms				
0	Ref	Ref	Ref	Ref
1	0.61 (0.33, 1.12), 0.114	0.62 (0.34, 1.14), 0.121	0.59 (0.31, 1.10), 0.098	0.83 (0.20, 1.73), 0.628
2-5	1.54 (0.91, 2.61), 0.109	1.47 (0.86, 2.51), 0.157	1.29 (0.74, 2.23), 0.371	2.09 (0.98, 4.45), 0.056

Manic symptoms				
0	Ref	Ref	Ref	Ref
1-3	**0.48 (0.25, 0.92), 0.028**	**0.47 (0.24, 0.90), 0.024**	**0.47 (0.24, 0.92), 0.027**	**0.42 (0.18, 0.95), 0.036**
4-5	**0.49 (0.28, 0.86), 0.013**	**0.45 (0.25, 0.80), 0.006**	**0.40 (0.22, 0.73), 0.003**	**0.32 (0.12, 0.89), 0.030**
6-7	1.12 (0.58, 2.13), 0.740	1.04 (0.54, 2.00), 0.914	0.86 (0.43, 1.71), 0.670	0.66 (0.19, 2.26), 0.507
Catatonia symptoms				
0	Ref	Ref	Ref	Ref
1	1.40 (0.77, 2.55), 0.271	1.34 (0.72, 2.47), 0.353	1.19 (0.32, 2.23), 0.586	1.47 (0.74, 2.90), 0.268
Depression symptoms				
0	Ref	Ref	Ref	Ref
1-3	**0.44 (0.24, 0.79), 0.006**	**0.40 (0.22, 0.74), 0.003**	**0.37 (0.20, 0.69), 0.002**	**0.25 (0.11, 0.56), 0.001**
4-6	0.58 (0.32, 1.03), 0.063	**0.54 (0.30, 0.98), 0.041**	**0.49 (0.27, 0.89), 0.020**	**0.28 (0.11, 0.73), 0.009**
7-12	0.62 (0.30, 1.25), 0.179	0.56 (0.27, 1.15), 0.114	0.50 (0.24, 1.05), 0.069	**0.26 (0.08, 0.81), 0.020**

Model 1 = adjusted for age and ethnicity

Model 2 = adjusted for age, ethnicity, partner present during pregnancy, primiparity, smoking, family history of psychosis

Model 3 = adjusted for age, ethnicity, partner present during pregnancy, primiparity, smoking, family history of psychosis and number of documents

Discussion

Overall, this study found mostly negative findings in terms of symptom profiles being independent predictors for relapse rates. In the unadjusted model with symptoms as ordinal variables, positive, disorganisation, manic and catatonic symptoms were positively associated with relapse during pregnancy (Table 6). After adjusting for age and ethnicity, disorganisation symptoms were positively associated with relapse during pregnancy and the trend continued, close to statistically significance, after adjusting for all the variables. This implies that disorganisation symptoms are a potential risk factor for relapse and we may not have detected effects due to lack of power. Depressive symptoms showed a negative trend with relapse rates postpartum, and were close to statistical significance; the association indicates that women with less depressive symptoms are more likely to relapse. During secondary analysis, the study found significant associations between positive symptoms, manic symptoms, depression symptoms and relapse post-partum, when symptoms were entered as categorical variables, with reference to a zero symptom category, in the unadjusted and fully adjusted model (Table 8). The associations found were U-shaped and with higher likelihood of relapse for most symptom scales in those with either zero or highest scores.

In our primary analysis, the unadjusted and adjusted models' showing no associations between manic symptoms and depression symptoms with relapse postpartum disagrees with the bipolar disorder literature. Patients of bipolar disorder usually present in the postpartum period but our results suggest that manic or depressive symptoms were not associated with the postpartum period. Our secondary analysis found that in the depressive, positive and manic symptoms groups postpartum, women with no symptoms were more likely to relapse than women with some symptoms. This could be because the no symptom group was the largest group overall and since the category included women who were admitted to SLAM with a new relapse, it is possible that some women had no previous data on symptom profiles in SLAM, they were inactive patients or were generally a stable group that happened to relapse during the perinatal period.

This is a unique study seeing as no other study has explored associations between symptoms as predictors of relapses or risk factors associated with relapses, in the perinatal SMI cohort. The finding of disorganisation symptoms being associated with relapse during pregnancy and postpartum is interesting and is supported by other work in this cohort where non-affective disorders (schizophrenia and related psychotic disorders) were associated with relapses during pregnancy and postpartum[20]. Disorganisation symptoms are most commonly found in non-affective disorders, and although they are more common in schizophrenia they are also present in bipolar disorder hence increasing the difficulty of establishing which diagnostic group is more prone to relapse [6, 9]. Our study utilises an alternative classification of mental health disorders involving symptom profiles and less reliance on diagnostic classifications in the clinical setting. It could be that the number of symptoms themselves do not predict relapse but further research exploring symptom profiles in SMI is needed.

A key strength of this study is the size and generalizability of our sample. The data was from a large representative sample of pregnant women with SMI in the perinatal period, in an ethnically diverse population, due to the mental health provider (South London and Maudsley NHS Foundation Trust). Uniquely this source enabled access to data for a particularly hard-to-reach population for recruitment into clinical studies, who tend to be underrepresented in studies. In comparison with the rest of the country, the SLAM catchment areas have increased residents of ethnic minorities, greater unemployment rates, residents with higher levels of education and a more dynamic movement into and out of the area[16]. The use of CRIS and HES database in combination, with HES having full coverage of England, allowed follow-up for detecting relapses in women who moved away from the area or were discharged. The linkage to maternity data contributes to a robust method of identifying pregnancies, and is not dependent on using mental health notes to record pregnancy or delivery.

Limitations include our sample being generalizable to only women in secondary care and maternity information is not always complete and can have systematic errors in its transfers. Also, CRIS data was not primarily collected for research purposes and there are obvious differences in information that is clinically important to record

versus data systematically obtained for research; this increases the chances of under-reporting and missing information from CRIS and HES data. Another major limitation is the inaccuracy of symptom profiles as a determinant of mental health issues. Symptoms are subjective measures based on a clinician's or healthcare professional's interpretation of a patient experience. The routine clinical care staff may not be specifically trained in symptom profile assessment, and certain symptom profiles such as negative symptoms are difficult to detect and assess, and may be less documented than the more obvious positive symptom profile.

Conclusion

In consideration of clinical implications, the use of innovative methodology using secondary mental healthcare data for cohorts who are difficult to recruit in large numbers for research purposes has potential to be used for further research in identifying predictors of relapse. Also, the use of data linkage with hospital episode statistics and CRIS to identify pregnancy in women is a robust method, and should be employed more in the future. In light of the study's negative findings, a larger cohort may yield more statistically significant results between symptom profiles and relapse rates, however, the use of symptoms as predictors for relapse rates needs further research. Future research could look at including medication as a covariate, removing the zero symptoms category or removing women without previous SLAM documents before their relapse.

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Appendix

Table 1: Free text searches used for CRIS searches in the patient notes

Variable	Search terms
Partner in index pregnancy	'partner', 'husband', 'father', 'relationship'
Number of children	'obstetric history', 'family composition', 'personal circumstances', 'children'
Smoking in pregnancy	'smoke', 'smoking', 'smoker', 'tobacco' ,'cigarette', 'cigarettes', 'cigarette', 'cigarettes', 'cigar', 'cigars', 'cigs', 'cigarette', 'cigerettes', 'fag', 'roll-up', 'rollup', 'nicotine', 'nicorette', 'Smoke', 'Smoking', 'Smoker', 'Tobacco', 'Cigarette', 'Cigarettes', 'Cigarette', 'Cigarettes', 'Cigar', 'Cigars', 'Cigs', 'Cigarette', 'Cigerettes', 'Fag', 'Roll-up', 'Rollup', 'Nicotine', 'Nicorette'
Family history of mental disorder	'History', 'Family', 'Background', 'Family history', 'Family psychiatric history', 'Family psych history', 'Family psych hx', 'HX'

Table 2: Symptom profiles of women with SMI recorded in the 2 years before pregnancy and postpartum period

	N=399
Positive symptoms	
0	152 (38.1)
1-2	74 (18.6)
3-4	73 (18.3)
5-8	100 (25.1)
Negative symptoms	
0	254 (63.7)
1	85 (21.3)
2-5	60 (15.1)
Disorganisation symptoms	
0	217 (54.4)
1	93 (23.3)
2-5	89 (22.3)
Manic symptoms	
0	120 (30.1)

1-3	85 (21.3)
4-5	134 (33.6)
6-7	60 (15.0)
Catatonia symptoms	
0	341 (85.5)
1	58 (14.5)
Depression symptoms	
0	129(32.3)
1-3	112 (28.1)
4-6	103 (25.8)
7-12	55 (13.8)