Risk of acute pancreatitis among people with severe mental illness

Mathew Vithayathil MBBS,[a] Chin-Kuo Chang, PhD,[a,b] Hitesh Shetty MSc,[c]

Robert Stewart. MD.[a,c]

[a] Department of Psychological Medicine, King's College London (Institute of Ps ychiatry, Psychology, and Neuroscience), London, UK

[b] Department of Health and Wellbeing, University of Taipei, Taipei City, Taiwan

[c] South London and Maudsley NHS Foundation Trust, London, UK

e-mail: mathew.vithayathil@doctors.org.uk for MV ckchang@utaipei.edu.tw for C-KC, and robert.stewart@kcl.ac.uk for RS

Corresponding Author: Dr. Chin-Kuo Chang, Department of Health and Wellbeing, University of Taipei (Teinmu Campus), 111 Shilin District, Taipei City, Taiwan. e-mail: ckchang@utaipei.edu.tw; TEL: +886 228718288 ext 4091;

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Introduction

Severe mental illness (SMI) encompasses schizophrenia, schizoaffective disorder, and bipolar affective disorder, and is recognised to be associated with higher risks of physical morbidity and mortality(Chang et al., 2011). Mortality in this group has been found to be 2-3 fold higher than general population estimates, including both natural and unnatural causes of death(Brown et al., 2010), resulting in a substantial reduction of 15-20 years in life expectancy. Increased risk of physical co-morbidities in people with SMI has been described for cardiovascular, respiratory and gastrointestinal diseases(Carney and Jones, 2006, Carney et al., 2006). However, most research interest has been focused on cardiovascular and metabolic disorders(Taylor and MacQueen, 2006), and there is a pressing need for further characterisation of health risks in order to develop and target prevention strategies against adverse health outcomes(Chang, 2012).

Acute pancreatitis is the leading cause of gastroenterological hospitalisations. In the UK, the hospitalisation rate for acute pancreatitis is 9·8 per 100,000 per year(Goldacre and Roberts, 2004), and is associated itself with significant morbidity and mortality(Dervenis et al., 1999). Patients with acute pancreatitis have an increased risk of further reoccurrence, with 10% progressing to chronic pancreatitis(Yadav et al., 2012).

The most common risk factors for acute pancreatitis are gallstones and acute excessive alcohol intake, with idiosyncratic drug reactions to multiple medications also described(Jones et al., 2015). Furthermore, aging and Afro-Caribbean ethnicity group are risk factors for the disease(Yadav and Lowenfels, 2013). Alcohol excess is the second most common cause of acute pancreatitis after gallstones(Yadav and Lowenfels, 2006). People with SMI have been found to have an increased risk of alcohol use disorder (AUD), demonstrated both in schizophrenia and bipolar affective disorder (Carney and Jones, 2006, Carney et al., 2006). However to date no study has investigated the risk of acute pancreatitis in people with SMI. Through a large retrospective cohort analysis and a nested case-control study we therefore sought to characterise the risk of hospitalisation with acute pancreatitis in people with SMI, with particular focus on the influence of co-morbid AUD.

Materials and Methods

Study Setting

The study cohort was obtained from the South London and Maudsley NHS Foundation Trust (SLaM) case register, which covers all secondary mental healthcare across four Southeast London boroughs (i.e. Lambeth, Southwark, Lewisham and Croydon) with an estimated population of 1·36 million residents (2011 UK Census data). SLaM provides a full range of secondary mental healthcare services across all age groups, including community, inpatient, and forensic services, liaison to local acute hospitals, and also national tertiary mental health services(Perera et al., 2016). Since 2008, the Clinical Record Interactive Search (CRIS) resource has allowed search and retrieval of anonymised data from the electronic clinical records of all SLaM service users for research purposes(Perera et al., 2016, Stewart et al., 2009). The CRIS database received approval for secondary data analysis by the Oxfordshire Research Ethics Committee C (reference: 08/H0606/71+5).

Sample Selection

All people with SMI were identified from CRIS based on a recorded diagnosis of schizophrenia (ICD-10 code: F20), schizoaffective disorder (F25) or bipolar affective disorder (F31) from structured fields, and were restricted to those who received SLaM services within the observation window of 1st January 2007 to 31st March 2016. All cases included in the study were aged 20 years or older at their first diagnosis anywhere in the records for those with pre-existing diagnoses or at the midpoint of the observation window for the newly diagnosed cases. CRIS data has been linked with the Hospital Episode Statistics (HES) for England: a database which contains nationally extracted data on all hospitalisation episodes accompanied by all assigned discharge diagnoses. These linked data were utilised to ascertain admissions with a primary diagnosis of acute pancreatitis (ICD-10 code: K85) after the diagnosis of SMI. In order to estimate the standardised admission ratios of acute pancreatitis among people with SMI, HES data for all residents of SLaM's geographic catchment were used as the standard.

The second stage of investigation comprised a nested case-control study on the association between AUD and acute pancreatitis admission among people with SMI. The 'case group' consisted of all 80 people with SMI who had experienced hospitalisation with acute pancreatitis as a primary diagnosis within the observation period, identified through the linkage to HES. Controls were randomly selected from the SMI cohort from members who had not been recorded as having any admission with acute pancreatitis in the same period, matched by age, gender and SMI diagnosis (i.e. schizophrenia, schizoaffective disorder and bipolar affective disorder) at a ratio of 4:1 controls per case. For controls, the date of first pancreatitis admission for their matched case was used as the index date of the analysis.

Measurements

In the case-control study, ethnicity and relationship status, derived from routine structured fields in the record, were considered as potential confounders in multivariate analyses for the effect of AUD. The presence of a diagnosis of AUD (ICD-10 code F10) prior to the first admission of acute pancreatitis was determined in the case group. Ethnicity categories were white, black and others (including "mixed" and "unknown"). Relationship status categories were "married/cohabiting", "single, separated/divorced" and "others" (including widowed and unknown).

Statistical analysis

In the first stage of analysis, the study cohort of people with SMI were compared to the local general population with respect to general hospital admissions caused by acute pancreatitis during the observation period. Age- and gender-standardised admission ratios (SARs) were calculated using the following age strata: 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85-89, and 90+ years old. Cohort and gender-specific SARs were calculated first for all admission events, and then for any admission event (i.e. excluding repeat admissions) for more conservative estimations. To further characterise the effect of co-morbid AUD, SARs were calculated for a cohort of SMI without a diagnosis

of AUD, with the same age strata, and specific for gender and all admissions and excluding repeat admissions.

Population attributable fraction (PAF) for acute pancreatitis was calculated for co-morbid AUD in patients with SMI. The numerator was calculated by subtracting the incidence of acute pancreatitis in SMI patients without a diagnosis of AUD from the incidence of acute pancreatitis in all patients with SMI. The denominator was the incidence of acute pancreatitis in all patients with SMI.

AUD was further characterised. For the case-control study, univariate and multivariate analyses using conditional logistic regression models were conducted to estimate odds ratios (ORs) for acute pancreatitis admission. Statistical significance level (alpha level) was set at 0·05 and Stata 14·1 SE software (StataCorp, College Station, Texas, USA) was used for all the statistical analysis.

Role of Funding Source

This study was funded by the National Institute for Health Research (NIHR) Biomedical Research Centre and Dementia Biomedical Research Unit at South London and Maudsley NHS Foundation Trust and King's College London. There were no additional external sponsors for the study.

Results

Cohort characteristics and standardised admission ratios (SARs) for acute pancreatitis

Figure 1 summaries the process of study sample selection involved in analysis. Over the 9+ year observation period, 22,337 people with a diagnosis of SMI were ascertained. In this period, there were 148 admission events for acute pancreatitis identified in 80 individuals. Considering all admission events for acute pancreatitis, the SAR for the cohort was significantly higher than the general population (2·33; 95% confidence intervals: 1·97, 2·74; n=148) as a whole, and for females (2·06; 1·54, 2·70; n=52) and males (2·52; 2·04, 3·07; n=96), separately. Considering the presence of any admission event, excluding re-admissions in the same year, SARs were 1·75 (1·39, 2·17; n=80) for the total cohort, 1·42 (0·94, 2·05; n=28) for females, and 2·00 (1·49, 2·62; n=52) for males. Standardised admission ratios are summarised in Table 1.

There remained an increased risk of admission remained in SMI patients without a diagnosis of AUD, though SARs were reduced. In 21,030 cohort members without co-morbid AUD, there were 92 acute pancreatitis admission events in 54 individuals. For all admission events, the SAR for acute pancreatitis was less than seen in all SMI patients, though still significantly higher than the general population, in the total cohort (1·55; 1·25-1·90; n=92), and in females (1·52; 1·07-2·10; n=37) and males (1·56; 1·18-2·03; n=55) (Table 2). Excluding re-admission events, SARs were increased, but did not show significance.

To further investigate the impact of co-morbid AUD Population attributable fraction (PAF) was calculated for all admission events, stratified by SMI diagnosis and gender (Table 3). For all admission events, the PAF for AUD was 33·97%. The PAF for patients with

Schizophrenia and Bipolar Affective Disorder were similar (36·98% and 36·90%) but lower for Schizoaffective Disorder (21·80%). PAF was higher in males with SMI (38·14%) compared to females (25·84%).

Nested case-control study

The 80 cases and 308 matched controls are compared in Table 4. Over one-third of SMI patients with acute pancreatitis had a co-morbid diagnosis of AUD (33·75%) compared to only 3·57% in those without pancreatitis. In summary, a high unadjusted odds ratio (OR) of 18·11 (95% CI: 6·93, 47·34) was found for the exposure of AUD. In multivariable analysis, further adjusting for ethnicity and relationship status, AUD remained relatively unaltered with an odds ratio of 16·10 (5·92, 43·79).

Discussion

Summary

To our knowledge, ours is the first study to investigate acute pancreatitis hospitalisations in people with severe mental illness. The cohort study revealed that adults with a diagnosis of bipolar affective disorder, schizophrenia or schizoaffective disorder had over a two-fold increased risk of admission for acute pancreatitis, standardised by age and gender. There remained an increased risk of acute pancreatitis in SMI patients without a concurrent diagnosis of alcohol use disorder, though this risk was reduced. The population attributable fraction of co-morbid AUD for acute pancreatitis in SMI patients was approximately one third. Further analysis in the nested and matched case-control study identified AUD as a strong independent risk factor for acute pancreatitis in people with SMI.

Acute pancreatitis is associated with significant mortality and morbidity(Dervenis et al., 1999). The most common risk factors for acute pancreatitis are gallstones and acute alcohol intake, with idiosyncratic drug reactions to multiple medications described(Jones et al., 2015). Furthermore, aging and Afro-Caribbean ethnicity group are risk factors for the disease(Yadav and Lowenfels, 2013). To our best knowledge, this is the first study to disclose an increased risk of acute pancreatitis admission in people with severe mental illness. Two previous studies reported an association between chronic pancreatitis and severe mental illness, based on a total of 1,074 people with schizophrenia or schizoaffective disorder(Carney et al., 2006) and 3,557 with bipolar disorder(Carney and Jones, 2006). Schizophrenia patients and bipolar patients showed a 4.00 and 2.53 fold increased risk for chronic pancreatitis respectively, although risk factors such as AUD, smoking or antipsychotic medications were not adjusted for. Though pancreatic damage is common to both acute and chronic pancreatitis, the pathophysiology between the diseases is different, with chronic pancreatitis characterised by progressive fibrotic destruction(Brock et al., 2013) and acute pancreatitis mediated by enzyme autophagy(Clemens et al., 2016).

Excessive consumption of alcohol and risk of acute pancreatitis

Alcohol consumption is a well-established risk factor for acute pancreatitis(Yadav and Lowenfels, 2006). The proposed biochemical mechanisms for alcohol-related pancreatitis include impairment of enzyme autophagy, raised levels of intracellular calcium and

mitochondrial dysfunction(Clemens et al., 2016). Given that only a small proportion of heavy alcohol drinkers develop pancreatitis, it is suggested that alcohol consumption alone does not directly cause acute pancreatitis, but forms part of a "two-hit" model, where other environmental, metabolic and genetic factors are also involved(Apte et al., 2010). The metabolism of alcohol through two biochemical pathways, oxidative and non-oxidative, leads to generation of acetaldehyde and fatty acid ethyl esters by-products, which damage pancreatic tissue in a variety of ways(Shalbueva et al., 2013). These by-products stimulate inositol trisphosphate receptors to release intracellular calcium, which is reported to be the key mediator in pancreatic cell death(Criddle et al., 2006). Increased intracellular calcium stimulates mitochondrial induced cell apoptosis(Gukovskaya and Gukovsky, 2011) and impairment of normal lysosomal degeneration of damaged organelles(Mareninova et al., 2009). *In vitro* studies exposing acinar cells to ethanol have demonstrated that alcohol sensitises acinar cells to the neural and humoral mediators in inflammatory response through activation of protein kinase C(Satoh et al., 2006). All these findings suggest alcohol consumption might predispose individuals to acute pancreatitis.

Our study shows the diagnosis of AUD significantly raised the risk of acute pancreatitis in people with SMI. In addition, individuals with SMI are recognised to have a higher risk of AUD with adjusted odds ratios of 13 and 20 in schizophrenia(Carney et al., 2006) and bipolar I disorder(Carney and Jones, 2006), respectively.

An increased risk of acute pancreatitis hospitalisation remained in SMI without co-morbid AUD, though SARs were reduced. The attributable fraction of AUD was 33˙97% for acute pancreatitis in the SMI population. These results suggest that AUD is proportionally a major contributor to acute pancreatitis in patients with SMI. The PAF of acute pancreatitis due to alcohol exposure was higher in males compared to females, which is consistent with a higher prevalence of AUD amongst males in the SMI cohort. (7˙39% in males, 4˙06% in females, data not shown). However, it does not account for all cases of acute pancreatitis in the SMI population. This may be due to the full effects of alcohol intake not being accounted for by a diagnosis of AUD. There may be other factors in this population, such as medication use. Drug-induced acute pancreatitis is rare (0˙1-2%) among all cases of acute pancreatitis in community populations, and includes medications such as non-steroid anti-inflammatory drugs and corticosteroids(Jones et al., 2015). However, medications commonly used in SMI have also been highlighted, including several case reports of acute pancreatitis in relation to atypical antipsychotic agents(Koller et al., 2003), particularly olanzapine(Kerr et al., 2007) and clozapine(Frankenburg and Kando, 1992), as well as sodium valproate implicated in 90 separate case reports(Gerstner et al., 2007). Further studies with more detailed information on medication exposure would clearly be useful.

The increased risk of acute pancreatitis admission associated with AUD in people with SMI supports taking active steps to reduce problematic alcoholic intake in this population. Though there are recommendations for monitoring physical health in patients with SMI, these guidelines have been described as insufficient and inconsistent(Citrome and Yeomans, 2005). There has been a call for people with SMI to be designated as a “Health Disparity Population”, such is the high risk of physical illness in this population(De Hert et al., 2011). The National Institute for Clinical Excellence has incorporated cardiac and metabolic risk assessments into the Commissioning for Quality and Innovation (CQUIN) targets for patients with SMI as part of a strategy to improve physical health outcomes(*Commissioning for Quality and Innovation Guidance for 2015/16* 2015). However, currently, there is no recommendation for AUD prevention strategies, despite findings that almost one quarter of

people with SMI in acute psychiatric services reported excessive alcohol intake(Barry et al., 2006). Given the findings of our study, early identification and engagement with drug and alcohol services would aid in reducing the range of disorders associated with AUD including severe outcomes such as acute pancreatitis.

Strengths and Limitations

Our study has several strengths. The South London and the Maudsley (SLaM) provides almost full coverage of secondary mental healthcare use in its catchment, and is one of the largest single providers of mental healthcare in Europe. The CRIS database allowed a very large cohort of over 22,000 patients with SMI to be assembled and linkage with HES allowed all outcomes occurring in England to be ascertained, and a temporal association between SMI and acute pancreatitis to be established. Limitations of routine data, however, need to be considered. While missed diagnosis of SMI and non-ascertained acute pancreatitis are unlikely, given the clinical severity of the conditions, the diagnosis of AUD might well be an underestimate of wider problematic consumption; this would in turn underestimate the contribution of alcohol use to the outcome of interest. In addition, information was insufficient on other risk factors for acute pancreatitis such as antipsychotic medication use, presence of gallstones, smoking or hyperlipidaemia(Yadav and Lowenfels, 2013), which would need more specific evaluation.

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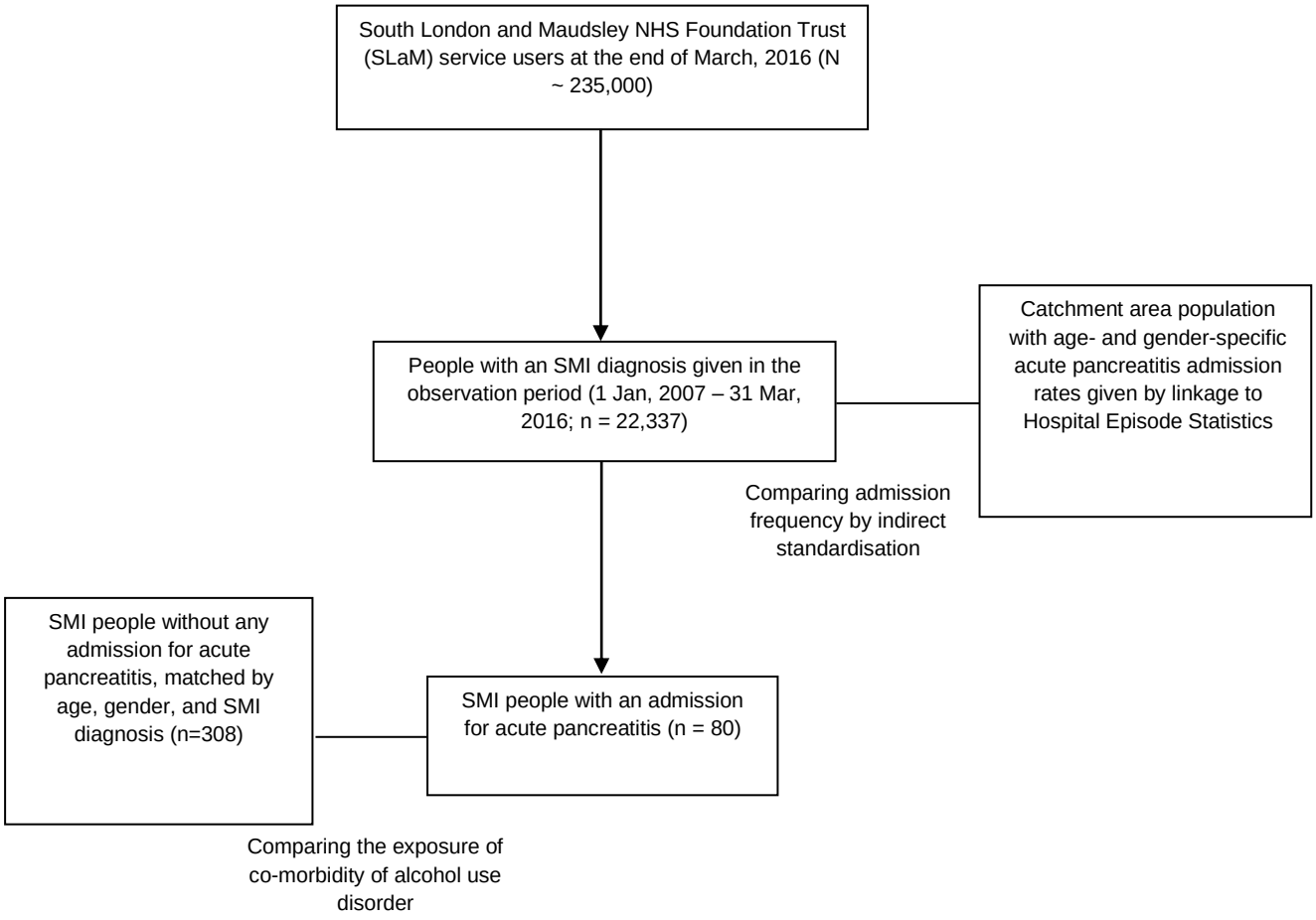
Figures

Figure 1 - Process for identifying study subjects and constructing comparison groups in statistical analyses



Tables

Table 1. Age- and gender-standardised admission ratios (SARs), stratified by gender, for people with serious mental illness in SLAM (N = 22,337)[a]

	Standardised admission ratios in 2007-16 (95% CI; number of admissions)		
	Total (N=22,337)	**Female (N=10,308)**	**Male (N=12,029)**
Acute Pancreatitis (including all re-admissions)	2·33 (1·97, 2·74; n = 148)	2·06 (1·54, 2·70; n=52)	2·52 (2·04, 3·07; n=96)
Acute Pancreatitis (excluding re-admissions)	1·75 (1·39, 2·17; n=80)	1·42 (0·94, 2·05; n=28)	2·00 (1·49, 2·62; n=52)

[a] Standard population: residents in SLAM service coverage area (London boroughs of Lambeth, Southwark, Lewisham, and Croydon) in 2011 UK Census

Table 2. Age- and gender-standardised admission ratios (SARs), stratified by gender, for people with serious mental illness without a diagnosis of co-morbid Alcohol use in SLAM (N = 21,030)[a]

	Standardised admission ratios in 2007-16 (95% CI; number of admissions)		
	Total (N=21,030)	**Female (N=9,890)**	**Male (N=11,140)**
Acute Pancreatitis (including all re-admissions)	1·55 (1·25, 1·90; n = 92)	1·52 (1·07, 2·10; n=37)	1·56 (1·18, 2·03; n=55)
Acute Pancreatitis (excluding re-admissions)	1·25 (0·94, 1·63; n=54)	1·10 (0·68, 1·69; n=21)	1·37 (0·94, 1·92; n=33)

[a] Standard population: residents in SLAM service coverage area (London boroughs of Lambeth, Southwark, Lewisham, and Croydon) in 2011 UK Census

Table 3. Population Attributable Fraction for co-morbid Alcohol Use Disorder in patients admitted with acute pancreatitis, for combined and separate diagnoses of severe mental illness, stratified by gender.

	Population Attributable Fraction for Co-Morbid Alcohol Use Disorder (%)		
	Total (N=22,337)	**Female (N=10,308)**	**Male (N=12,029)**
All SMI Diagnosis (Combined)	33·97	25·84	38·14
F20 - Schizophrenia	36·98	26·09	43·49
F25 - Schizoaffective Disorder	21·80	-*	26·07
F31 - Bipolar Affective Disorder	36·90	24·81	41·08

*There were no cases of acute pancreatitis in female patients with a diagnosis of F25 and Alcohol use Disorder

Table 4. Characteristics of cases and matched controls on demographics, psychiatric diagnosis, and co-morbidity of alcohol use disorder, and univariate and multivariate analyses outcomes by conditional logistic regressions for the risk of acute pancreatitis admission among people with severe mental illness (N=388)

	Number (%) / Mean ± SD		Odds Ratio (95% Confidence Interval)	
Variable	Case (n= 80)	Control (n=308)	Unadjusted	Adjusted
Sex				
Female	28 (35·00%)	110 (35·71%)	--	--
Male	52 (65·00%)	198 (64·29%)		
Age at pancreatitis admission for cases or on index date for controls (years old)	41·67 ± 12·42	41·94 ± 12·51	--	--
Diagnosis				
Schizophrenia (ICD10 code: F20)	51 (63·75%)	203 (65·91%)	--	--
Bipolar disorder (F31)	24 (30·00%)	90 (29·22%)		
Schizoaffective disorder (F25)	5 (6·25%)	15 (4·87%)		
Ethnicity				
White	50 (62·50%)	134 (43·51%)	Ref	Ref
Black	18 (22·50%)	120 (38·96%)	0·38 (0·21, 0·72)*	0·67 (0·34, 1·34)
Others / mixed / unknown	12 (15·00%)	54 (17·53%)	0·57 (0·28, 1·17)	0·92 (0·40, 2·15)
Marital Status				
Married/Cohabiting	8	40	Ref	Ref
Single	56	211	1·39 (0·60, 3·25)	0·95 (0·38, 2·42)
Separated/Divorced	8	35	1·07 (0·36, 3·16)	0·89 (0·28, 2·75)
Others	8	22	1·89 (0·60, 5·93)	1·39 (0·40, 4·83)
Co-morbid alcohol use disorder (F10)				
No	53 (66·25%)	297 (96·43%)	Ref	Ref
Yes	27 (33·75%)	11 (3·57%)	18·11(6·93, 47·34)*	16·10 (5·92, 43·79)*

-- Matched variables
* Statistical significance