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Disparities in the management of cardiovascular risk factors in patients with psychiatric disorders: a systematic review and meta-analysis

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Abstract

Background. The high cardiovascular (CV) morbidity and mortality reported for patients with psychiatric disorders may possibly be due to a poorer management of CV risk factors (CVRFs). However, these healthcare disparities remain poorly understood. In this paper, studies comparing the management of smoking, diabetes, hypertension and dyslipidaemia, in patients with and without depression, anxiety, schizophrenia, bipolar or personality disorder, were reviewed.

Methods. Prospective studies comparing rates of screening, diagnosis, treatment and control of CVRFs were searched in PubMed, Embase, PsychInfo, Scopus and Web of Science (inception to January 2017). The Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria were used. Studies were assessed for quality. Wherever possible, meta-analyses were conducted to summarize the findings.

Results. Twenty studies, out of the 18 333 references initially identified, were included. Most studies were heterogeneous in design. Two areas permitted meta-analyses: the pooled odds ratio for quitting smoking for those with depression was 0.64 (0.49–0.80) $p < 0.001$; the pooled difference of glycated haemoglobin for patients with type 2 diabetes and depression was 0.18 (0.06–0.31) $p = 0.005$. Individual studies showed associations between: schizophrenia and lower probability of having smoking habit recorded; schizoid personality disorder and higher probability of remaining non-smokers after quitting; anxiety and poorer control of type I diabetes; depression, anxiety or schizophrenia and lower probability of having a diagnosis of hypertension; schizophrenia or bipolar disorder and lower use of antihypertensive and lipid-lowering drugs.

Conclusions. A proactive clinical management, together with further studies, are needed to reduce the CV morbidity and mortality of patients with psychiatric disorders.

Introduction

The life expectancy of patients with mental health disorders is reduced between 1 and 32 years (Colton & Manderscheid, 2006; Viron & Stern, 2010; Walker *et al.* 2015). A number of meta-analyses have reported in those with psychiatric conditions an increased frequency of cardiovascular risk factors (CVRFs), which varies for different patients and can be 27% higher for hypertension among those with bipolar disorders, to six times higher for smoking in those with schizophrenia, compared with those without each mental disorder (de Leon & Diaz, 2005; Chaiton *et al.* 2009; Meng *et al.* 2012; Jiang *et al.* 2014; Pan *et al.* 2015; Vancampfort *et al.* 2015; Vancampfort *et al.* 2016; Ayerbe *et al.* 2018). Strong evidence also shows that those with psychiatric disorders have higher incidence of cardiovascular (CV) diseases, which can be 34–71% higher for those with depression or schizophrenia, respectively, compared with those without each disorder, and are the biggest contributor to the premature death of these patients (de Leon & Diaz, 2005; Colton & Manderscheid, 2006; Van der Kooy *et al.* 2007; Roest *et al.* 2010; Viron & Stern, 2010; Dong *et al.* 2012; Meng *et al.* 2012; Fan *et al.* 2013; Jiang *et al.* 2014; Prieto *et al.* 2014; Pan *et al.* 2015; Walker *et al.* 2015; Vancampfort *et al.* 2016; Wu & Kling, 2016; Perez-Pinar *et al.* 2017). A relevant and modifiable factor that could explain the high CV morbidity and mortality of those with psychiatric disorders is that they probably have poorer access to healthcare, including adequate management of CVRFs (Viron & Stern, 2010; Kaufman *et al.* 2012). How these disparities in healthcare

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may affect the management of different CVRFs for those with different mental health disorders is however poorly understood. It is also unclear at what stage of the care pathway, screening, diagnosis, treatment or control these disparities happen. Previous reviews addressing the potential disparities in preventive care among patients with psychiatric disorders have not used a comprehensive approach to CVRFs, focused on specific psychiatric disorders or presented only narrative summaries of the literature (Mitchell *et al.* 2009; De Hert *et al.* 2011; Baller *et al.* 2015; Mangurian *et al.* 2016). Therefore, it remains difficult for clinicians, researchers and policy makers to design evidence-based interventions that effectively prevent premature CV diseases for people with psychiatric disorders. Stronger evidence on the differences in healthcare of each CVRF affecting specific psychiatric patients would help to correct disparities. It would allow focusing clinical resources on the most vulnerable individuals, and the management of the CVRF could become better targeted, more timely, feasible and effective. A good understanding of the disparities of CV care could also inform future clinical trials of innovative interventions aiming to reduce the incidence of CV diseases among psychiatric patients with poorest access to healthcare. Finally, the management of CVRFs informed by stronger evidence in this area would become more cost-effective with potential savings in acute CV care. All of these should potentially result in an effective and sustainable reduction of CV morbidity and overall mortality for psychiatric patients.

This review will test the following hypothesis: patients with specific psychiatric disorders, compared with those without them, have poorer care of different CVRFs. In this paper, we review the studies that compare the management of smoking habit, diabetes, hypertension and dyslipidaemia, in patients with and without depression, anxiety, schizophrenia, bipolar or personality disorder.

Methods

The Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria were used to undertake this review (online Supplement 1) (Stroup *et al.* 2000). Electronic searches were conducted in PubMed, Embase, PsycINFO, Scopus and the Web of Science, from database inception to the 25 January 2017.

We aimed to identify studies in compliance with the following inclusion criteria:

(1) Observational prospective studies reporting original research data
(2) Studies presenting differences in rates of screening, diagnosis, follow-up, treatment or control of smoking habit, diabetes, hypertension or dyslipidaemia, for patients with and without each of the following mental disorders: depression, anxiety, schizophrenia, bipolar or personality disorder, identified with a validated scale or clinical assessment.

Studies were excluded if they were:

(1) Conducted in specific patient sub-populations (e.g. patients receiving specific medication);
(2) Interventional studies;
(3) Only presented results of univariate analyses;
(4) Using composite exposures (e.g. affective disorders) unless separate results for each of them were presented;
(5) Exposure analysed as continuous variable (e.g. score in a depression scale instead of a medical diagnosis, or a validated score above a cut-off point, which are the methods for categorization commonly used in clinical practice (National Institute for Health & Care Excellence, 2009, 2011);
(6) Exposure presented as syndromes or symptoms (e.g. psychosis or hallucinations) rather than distinct diagnoses, which are the categories from the commonly used by clinicians who manage CVRFs (World Health Organization, 1978, 2010; American psychiatric Association, 1994, 2013);
(7) Reporting a composite outcome (e.g. metabolic syndrome) unless separate results for each of its component had been provided. The reason not to include composite outcomes is because, according to the guidelines, clinicians have to care for each and every CVRF, therefore understanding the disparities affecting the management of each individual one is clinically relevant (National Institute for Health & Care Excellence, 2016*a*, *b*; National Institute for Health & Care Excellence, 2017*a*, *b*, *c*).

The search strategy is presented in online Supplement 2. Given the large number of CVRFs and psychiatric disorders reviewed in this paper, only standard terms for searching were used. The titles and abstracts of all the references identified in the initial search were checked by one doctor (LA) against inclusion criteria. The bibliography of all papers fitting the inclusion criteria and relevant reviews was checked for further articles. Papers citing all the included studies or relevant reviews were also searched in the Web of Science and considered for inclusion. There were no restrictions on the basis of language, sample size or duration of follow-up. Authors of the studies were contacted in some cases for further results or for clarifications in the ones presented. Two doctors extracted the data from the included studies (LA, IF, QFB, EG and/or JA). A standardized data-collection form was used to record author and publication year, country, number of participants, psychiatric disorder and measure, follow-up, proportion of male and female participants, age, outcome and measure of association. The risk of bias and overall methodological quality of the studies fitting the inclusion criteria was assessed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Institute of Health (USA) (online Supplement 3) (National Institute of Health 2016). In some cases, similarities between studies indicated the possibility of multiple publications from the same cohort. In the absence of explicit cross-referencing, we considered articles to be from the same cohort if there was an evidence of overlapping recruitment sites, study dates and grant funding numbers, or there were similar reported patient characteristics in the studies.

Statistical analysis

When three or more studies with similar design observed the same exposures and outcomes, meta-analyses were considered possible and the best way to summarize these associations (Dwyer *et al.* 2001; Higgins, 2008). When meta-analyses were conducted, pooled estimates of differences were obtained, using random-effects models (Der Simonian & Kacker, 2007). The heterogeneity between studies was measured using I^2 index, which represents the percentage of the total variation which is due to heterogeneity rather than chance (Higgins *et al.* 2003). With the exception of one study, that reported hazard ratio (HR) for the association between depression and smoking, all other studies reported odds ratios (OR) for the associations (Anda *et al.*

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1990). In that one HR was used in the meta-analysis as a proxy for OR (Steele, 2005). When studies on smoking cessation reported the final results as ratios of not quitting, these estimates were reversed to quitting. Confidence intervals were calculated using the formula described by Altman and Bland for one study that reported only p values (Altman & Bland, 2011; Musselman *et al.* 2014). When a study reported results from a multivariable model exploring the differences of management of CVRFs for patients with and without psychiatric disorders, and then further modelling had been conducted to explore potential explanatory factors for these differences, only the results from the first model were included in the meta-analysis. Alternatively, when a study reported results from a preliminary analysis and then further adjustment was conducted to reach a model considered final by the authors, only the results of the later analysis were included in the meta-analysis. If a study presented associations between minor and major depression, as an outcome, only the associations with major depression were included in the meta-analysis. Where a study reported gender-specific but not combined estimates, the results for each gender were included in the meta-analysis separately. We did not test for possible publication bias and small study effect formally, due to the small number of studies observing similar exposures and outcomes, which makes most formal tests inappropriate (Borenstein *et al.* 2009). All statistical analyses were conducted using the software STATA version 14. The studies that reported other CVRFs (not smoking cessation and type 2 diabetes) among patients with other psychiatric disorders (not depression) were either not enough in number or too heterogeneous in design to be included in a meta-analysis, therefore their results are summarized narratively.

Results

The electronic search retrieved 16 101 articles, 17 of which were reviews relevant to the topic (Lustman *et al.* 2000; de Groot *et al.* 2001; Hitsman *et al.* 2003; Leucht *et al.* 2007; Mitchell *et al.* 2009; Oud & Meyboom-de Jong, 2009; Lord *et al.* 2010; Heffner *et al.* 2011, De Hert *et al.* 2011, Egede & Dismuke, 2012; George *et al.* 2012; Mitchell *et al.* 2012; Baller *et al.* 2015; McGinty *et al.* 2015, Mitchell *et al.* 2015, Chen *et al.* 2016; Mangurian *et al.* 2016). The papers assessed at each stage of the search are presented in Fig. 1. No papers written in languages other than the ones understood by the authors were identified at any time. The full-text version of 165 papers was examined. Finally 20 studies were included in the review. They were all considered to be of good quality, with score ⩾8 in the 14-item quality checklist (National Institute of Health 2016). Most studies were heterogeneous in designs and observed different exposures in patients with different psychiatric disorders, therefore were summarized narratively. However, the similarities in design, exposures and outcomes made possible to undertake two meta-analyses of studies that reported associations between depression and smoking cessation, and between depression and management of type 2 diabetes.

Smoking

Eight studies including 9835 participants, conducted in Canada, the USA, Australia, the Czech Republic, France, Spain and the UK, used smoking habit as an outcome (online Supplement 4). Follow-up was between 1 and 9 years, and one study included only adolescent participants (Zhu *et al.* 1999). Six studies compared patients with and without depression, which was recorded from results of four scales or was self-reported by participants (Anda *et al.* 1990; Breslau *et al.* 1998; Zhu *et al.* 1999; Fond *et al.* 2013; Stepankova *et al.* 2013; Cooper *et al.* 2016). The outcome in all six was the proportion of patients who quit smoking, which was significantly lower for those with depression in four of the studies. The pooled OR for quitting smoking for those with depression, compared with those without, was 0.64 (0.49–0.80) $p < 0.001$, and there was an evidence of moderate heterogeneity across the six studies, I^2 56.8%, $p = 0.031$(Fig. 2). It was acknowledged that two studies used reports from patients as measures of depression. These are subjective measures and can introduce bias (Stepankova *et al.* 2013; Cooper *et al.* 2016). One of them caused the heterogeneity of the results as it reported a much stronger association with a smaller OR compared with the other studies (Cooper *et al.* 2016). Removing this study from the meta-analysis resulted in the remaining studies being homogeneous with I^2 equating to zero, while the association between depression and giving up smoking remained significant, with an overall OR of 0.74 (0.62–0.85) $p < 0.001$.

One study reported that patients with a medical diagnosis of schizophrenia were less likely to have their smoking habit in their medical records compared with those with no diagnosis (Roberts *et al.* 2007). Finally, one study used personality disorders as a mental condition of interest, which was assessed with a questionnaire, and reported that the schizoid personality disorder was associated with higher rates of maintenance of abstinence after quitting. Other specific personality disorders, or the whole category of personality disorders, showed no association with abstinence after quitting (Pineiro *et al.* 2013).

Diabetes mellitus

Two studies, conducted in the Netherlands and the USA, including 422 participants, comparing control of type 1 diabetes, using reduction in glycated haemoglobin (HbA1c) levels as an indicator of good management, were identified (online Supplement 5) (Hilliard *et al.* 2011; Bot *et al.* 2013). One of them included participants aged 13–18 (Hilliard *et al.* 2011), while the other one assessed participants equal or above 18 years of age (Bot *et al.* 2013). Follow-up was for 1 year in both of them and they reported the absence of an association between depression (measured with two scales) and diabetes control. However, one of them also reported that anxiety (measured with a scale) was associated with significantly poorer diabetes control at follow-up (Hilliard *et al.* 2011).

Five studies, conducted in Germany, the Netherlands and the USA, including a total of 20 661 participants, looking at the management of type 2 diabetes, were identified (online Supplement 6) (Richardson *et al.* 2008; Heckbert *et al.* 2010; Bot *et al.* 2013; Musselman *et al.* 2014; Kostev *et al.* 2016). Follow-up ranged between 3 months and 10 years. In one study, 97% of participants were men (Richardson *et al.* 2008). All of them compared patients with and without depression, which was recorded from the results of two scales and from medical notes. Four studies investigated the association between depression and levels of HbA1c at follow-up (Richardson *et al.* 2008; Heckbert *et al.* 2010; Bot *et al.* 2013; Musselman *et al.* 2014). Three of these studies expressed control of type 2 diabetes as percentage of HbA1c, and were included in a meta-analysis. The pooled difference of HbA1c% at follow-up between those with and without depression

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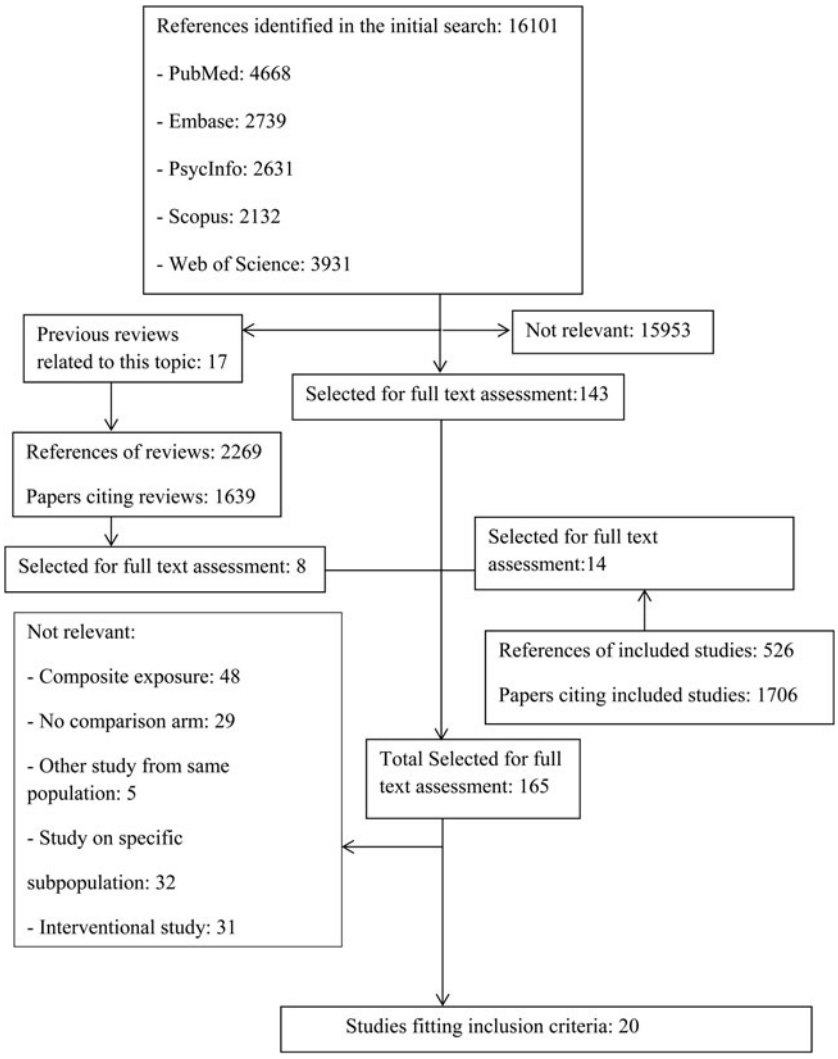

Fig. 1. Flow chart of study selection.

at baseline, across the three studies, was 0.18 (0.06–0.31) $p = 0.005$, with an I^2 of 41.1%, $p = 0.18$ (Fig. 3). Another study compared those with and without depression, the control of type 2 diabetes, as mmol per mol of HbA1c, and could not be included in the meta-analysis together with the other three (Bot *et al.* 2013). In the later study, no significant association between depression and control of type 2 diabetes was observed. Finally, one study reported that depression was associated with higher risk of insulin discontinuation (Kostev *et al.* 2016).

Hypertension

Seven studies conducted in the USA, Denmark, Finland and the UK, including a total of 1 296 899 participants, observed the management of hypertension (online Supplement 7). Follow-up ranged between 1 and 35 years. Four studies compared patients with or without depression, three used schizophrenia for comparison, one study used anxiety disorders, and another study compared those with and without bipolar disorder. One study showed that those with depression or anxiety were more likely to have a second blood pressure (BP) reading after having one showing high BP, but less likely to have a hypertension record after having two high BP readings, compared with those without depression or anxiety(Byrd *et al.* 2012). Another study reported that depression was associated with lower probability of receiving hypertension treatment (Wang *et al.* 2005), while a different study found no differences (Goldberg *et al.* 1980). Finally, depression was associated with lower rate of hypertension control only for women in one of the three sites where a multicentre study was conducted (Simonsick *et al.* 1995). One study showed that patients with schizophrenia were less likely to have their BP recorded (Roberts *et al.* 2007), and two studies showed lower use of antihypertensive drugs in these patients (Lahti *et al.* 2012; Laursen *et al.* 2014), although in one of them schizophrenia patients were more likely to have diuretics (Laursen *et al.* 2014). Finally, those with bipolar disorders were reported to be less likely to receive angiotensin converting enzyme inhibitors, angiotensin 2 receptor blockers, but more likely to have diuretics, calcium channel blockers and β-blockers (Laursen *et al.* 2014).

Dyslipidaemia

Three studies, conducted in Denmark, Finland and the UK, including a total of 1 073 032 participants, reported the management of dyslipidaemia (online Supplement 8). Follow-up ranged from 3 to 35 years. Patients with and without schizophrenia were compared in all three studies and one of these additionally compared those with and without bipolar disorder. Data on

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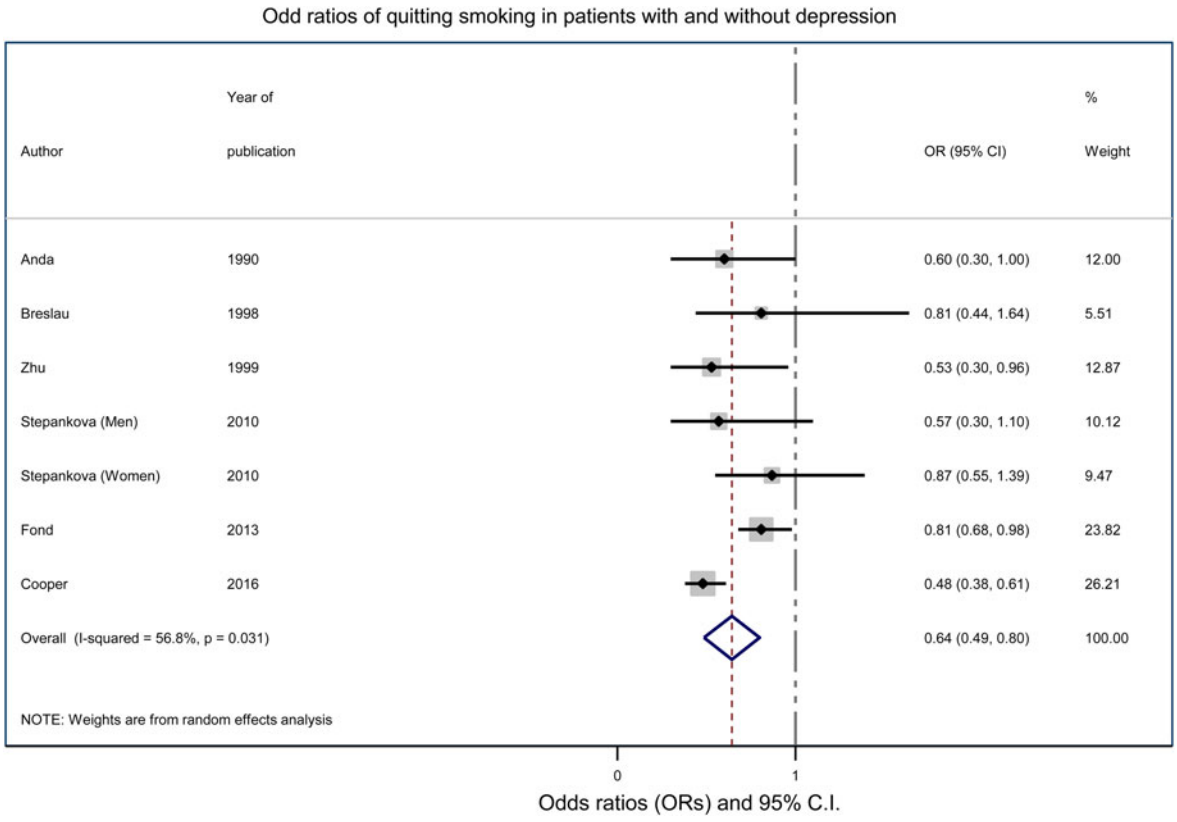

Fig. 2. Odd ratios of quitting smoking in patients with depression.

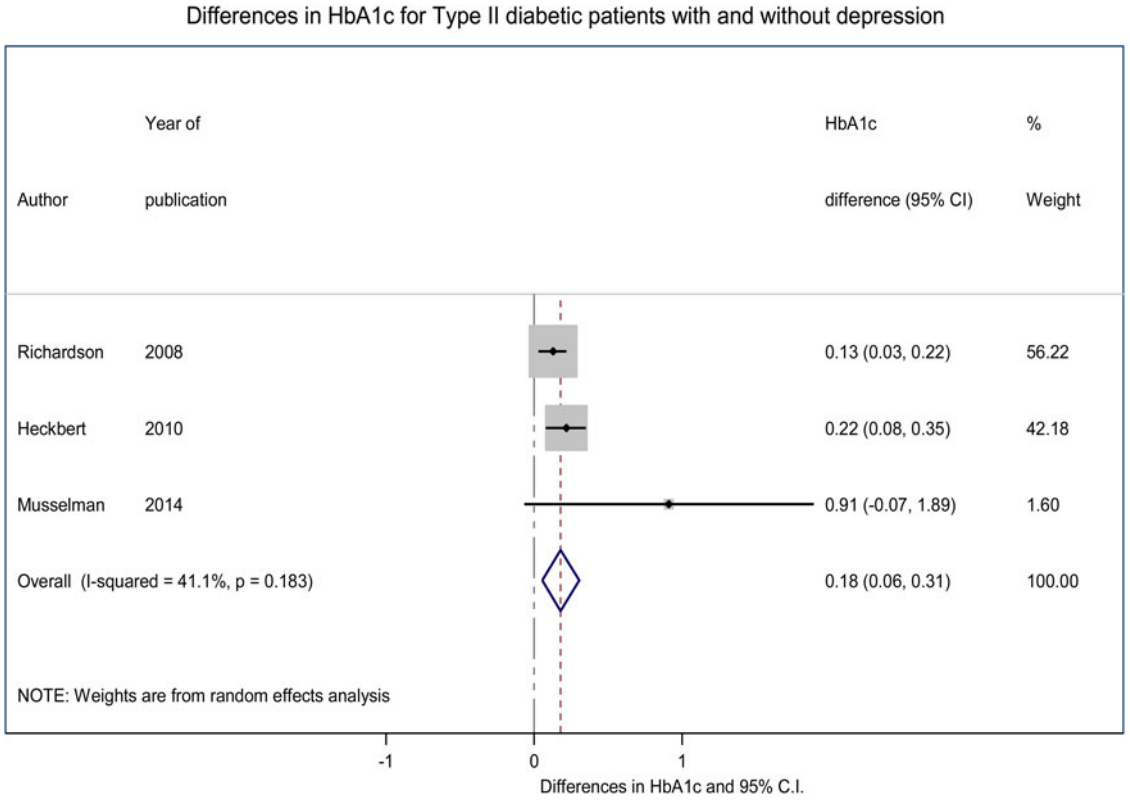

Fig. 3. Differences in HbA1c for type 2 diabetic patients with and without depression.

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schizophrenia or bipolar disorder were collected from medical records. Schizophrenia was associated with a lower probability of having cholesterol recorded in one study (Roberts *et al.* 2007), while two studies reported that these patients were less likely to use lipid-lowering drugs (Lahti *et al.* 2012; Laursen *et al.* 2014). Those with bipolar disorder were also observed to be less likely to use lipid-lowering drugs (Laursen *et al.* 2014).

Discussion

A limited number of studies of good quality have investigated the differences of the management of major CVRFs among patients with specific psychiatric disorders. Our meta-analyses show that patients with depression have lower probabilities of giving up smoking, and also poorer control of type 2 diabetes, compared with those without depression. Few studies have reported other disparities in the management of CVRFs: those with schizophrenia are less likely to have their smoking habit recorded; schizoid personality disorder is associated with patients remaining non-smokers after giving up; anxiety, but not depression, affects the control of type 1 diabetes; those with depression, anxiety or schizophrenia are less likely to have a diagnosis of hypertension; patients with schizophrenia or bipolar disorder use less antihypertensive and lipid-lowering drugs.

The disparities in care for CVRF among patients with mental health issues observed in this review are in line with the results of previous narrative reviews that have approached specific groups of psychiatric patients or wider areas of healthcare (Mitchell *et al.* 2009; De Hert *et al.* 2011; Baller *et al.* 2015; Mangurian *et al.* 2016).

A number of factors affect the CV care of patients with mental health disorders and may explain the disparities observed in this review. Psychiatric symptoms can disrupt the process of healthcare, e.g. lack of motivation leads to poor attendance of appointments, though disorder can complicate the process of taking a clinical history, and agitation or social phobia may make it difficult for the patient to report his problems clearly (Viron *et al.* 2012). Many people with psychiatric conditions also have a substance use disorder, which interferes with treatment adherence and efficacy (Viron & Stern, 2010). It has been reported that smoking may help regulate negative mood states, and that patients who give up experience negative emotions shortly after quitting. These factors affect the lower rate of giving up smoking observed in patients with depression (Besson & Forget, 2016; Mathew *et al.* 2017). The medication used to treat psychiatric disorders can also have negative effects on the control of CVRFs. Associations between antidepressants and higher risk of diabetes, hypertension and hyperlipidaemia, and between antipsychotics and dyslipidaemia, and diabetes have been reported (Correll *et al.* 2015; Perez-Pinar *et al.* 2016; Salvi *et al.* 2017). A strong association particularly between atypical antipsychotics, such as olanzapine, clozapine, quetiapine or risperidone, and diabetes has been observed (Correll *et al.* 2015). Furthermore, some clinicians feel uncomfortable with these patients because of limited experience or resources and this can also lead to a poor care of CVRFs. Stigmatization of psychiatric patients is common, not only among the general public but also among clinicians (Kaufman *et al.* 2012). In addition, some doctors may underestimate patients as capable partners in their own care (Viron & Stern, 2010). It has been reported that those with mental disorders feel that clinicians take their physical symptoms less seriously once the psychiatric diagnosis is revealed (Viron *et al.* 2012). The organization of the health service may represent another obstacle to healthcare that can explain the disparities in the management of CVRF for people with mental disorders. The fragmentation of the health service between primary care and psychiatry makes the coordination of care particularly challenging (Kaufman *et al.* 2012). Finally, in countries without universal access to healthcare, those with psychiatric problems are more likely to have financial barriers to access healthcare than those without mental health issues (Viron & Stern, 2010; Kaufman *et al.* 2012). All these factors can contribute to the poorer management of CV risk in those with psychiatric disorders, and explain the findings of this review.

This review has some limitations. Only one doctor screened the initial list of references (LA). Since only studies assessing psychiatric disorders categorically were included, large population-based studies using continuous measures for assessment, or overlapping constructs (e.g. psychosis), might have been missed, which limits the external validity of this review. The diversity of the methods across studies, including the different statistical management, may have an effect on the external validity of each individual one. Another limitations is that the heterogeneity of many studies made impossible to obtain mathematical summaries of healthcare disparities, which could have aided clinical and health policy decisions. While these pooled estimates were obtained on studies observing similar psychiatric disorders and CVRFs, the low number of these studies did not allow to analyse for possible publication bias (Borenstein *et al.* 2009). Finally, the exclusive use of standard terms for searching, which can lead to some relevant studies being missed, may represent a limitation of this review. However, the comprehensive search, which included electronic searches in five different databases, hand searches, backward and forward citation searching, and had no restrictions on the basis of language, sample size or duration of follow-up, substantially reduces the chances of missing relevant studies, and represents a strength of this paper. This paper has other strengths as well. The association between depression and both smoking and control of type 2 diabetes was obtained on a fairly large number of patients. The use of a random-effect model based on the assumption that studies were independently conducted and do not necessarily share a common effect size, allowing for more uncertainty of the final summary estimate, was a conservative choice.

Clinicians should be aware that those with depression are less likely to quit smoking and to have good control of type 2 diabetes. Since depression is a manageable condition, screening for it with a brief and reliable tool all patients who are going to receive treatment for smoking cessation or type 2 diabetes could be recommended (Mitchell *et al.* 2016). Doing this could lead to the management and improvement of low mood and to higher rates of smoking cessation and diabetes control. Clinicians should also be particularly proactive in the care of CVRFs in all psychiatric patients, as the available studies suggest that it is substandard. However, the evidence on the disparities on CV care for patients with psychiatric disorders is still very limited. For many psychiatric patients, it remains unknown when and where along the care pathway they lose access to clinical care of good quality. The evidence is particularly poor for those with anxiety, bipolar or personality disorders. More studies are needed to understand where the healthcare disparities happen, for those with a variety of psychiatric problems. Future investigations on healthcare disparities could consider comparing differences in outcomes defined by guidelines as the main steps of CV prevention (screening, diagnosis, treatment, follow-up and control of

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CVRF) (National Institute of Health & Care Excellence, 2016). Such studies could inform innovative interventions to improve the CV care, and ultimately reduce the CV morbidity and overall mortality of patients with psychiatric disorders.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291718000302

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Conflict of Interest. None.

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