Reviewer's report

**Title:** Physical and mental health comorbidity is common in people with multiple sclerosis: nationally representative cross-sectional population database analysis

**Version:** 1  
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**Reviewer:** Mauro Giovanni Carta

**Reviewer’s report:**

Major Compulsory revision

The study is interesting and has relevant results. Although some contradictory and unexpected results should be better analyzed before accepting it

Authors found in a primary care register on 1/3 of the Scotland population a prevalence rate of MS of 0.3%. In my knowledge the prevalence of MS in Scotland is around 255 x 100,000 thus 0.25% in the general practice setting (Mackenzie et al. Incidence and prevalence of multiple sclerosis in the UK 1990–2010: a descriptive study in the General Practice Research Database J Neurol Neurosurg Psychiatry. Jan 2014; 85(1): 76–84.). These differences must be discussed by authors

Specifically the findings about Bipolar Disorder are really limited for several issues:

Firstly the prevalence of Bipolar Disorders in the cases of MS and in controls is really lower than expected on the basis of the epidemiologic surveys in the community in the world. Authors found a cumulative prevalence rate (Bipolar Disorders + Schizophrenia) of 1% in both cases and controls. The World Health Organization World Mental Health Survey Initiative (MHSI) found, in a cross-sectional, face-to-face, household surveys of 61,392 community adults in 11 countries in the World, a prevalence of 1% only for severe Bipolar Disorders and of 2.4% for Bipolar Spectrum disorders (Merikangas et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry. 2011 Mar;68(3):241-51). A review about epidemiology of schizophrenia found prevalence rates around 0.4% in recent surveys (Mura et al. Schizophrenia: from epidemiology to rehabilitation. Clin Pract Epidemiol Ment Health. 2012;8:52-66). It is well known that bipolar disorders have high risk of co-morbidity with general medical conditions and with chronic diseases as cardiovascular disease (Crump et al. Comorbidities and mortality in bipolar disorder: a Swedish national cohort study. JAMA Psychiatry. 2013 Sep;70(9):931-9). Thus in a sample of attenders of primary care (as in the study sample) we could expect a rate of Bipolar disorders higher than in the community due to the risk of comorbidity can cause a selection bias. Another point is that community surveys as MHSI excluded people in institution or sheltered houses in which schizophrenia and severe Bipolar Disorders are overrepresented. For these reasons one can expected a higher rate of BP disorders and Schizophrenia in the study sample than in the community surveys.
On the contrary the study report lower rates!

In fact a large body of studies have recently underlined the problem of misdiagnosis of Bipolar Disorders in primary care leading to delay in the diagnosis of 10 years average and to consult at least 4 primary care physicians before the correct diagnosis (Smith et al. Unrecognized bipolar disorder in primary care patients with depression. Br J Psychiatry. 2011 Jul; 199(1):49-56). This issue is today considered a really public health problem encouraging the improve of the screening tools for Bipolar Disorders in primary care (Menzin et al, A model of the economic impact of a bipolar disorder screening program in primary care. J Clin Psychiatry. 2009 Sep;70(9):1230-6).

Considering these results it is clear that the methodology of recruitment of this sample can have underdiagnosed Bipolar Disorders and particularly Bipolar II Disorders. Because people with Bipolar II Disorder spend 50% of their life in depression and when hypomanic feels their condition of a really wellbeing and not recognize it as a pathological condition, thus is well known that their refers to primary care when depressed and don’t report hypomanic states inducing clinicians to misdiagnosis.

In fact the diagnosis of Bipolar Disorders in the study didn’t have made with the use of psychiatric diagnostic manuals (DSM or ICD) carried out by standardized interviews administered by trained clinicians as request by the normal standard of research on Bipolar Disorders. In these conditions the large body of previously cited research in primary care has shown that a large proportion of people diagnosed with Major Depressive Disorders in primary care (the condition of the study sample) have actually a Bipolar II Disorders. The study on association between Bipolar Disorders and MS cited by authors (Carta et al. 2013) was conducted adopting a standardized diagnosis methodology both in cases and controls, thus these results have a higher level of accuracy. Apparently the bias may be the same in cases and controls of the present survey but the study of Carta et coll has indicated a specific risk for Bipolar II Disorder in MS, and Bipolar II Disorder cause the most part of misdiagnosis with Major Depressive Disorders, thus the misdiagnosis of BD is probably higher in cases than in controls. The overrepresentation of MS in the sample (0.3% more than expected even in Scotland) may be amplified the bias.

Bipolar II Disorder is considered as the mood disorders with higher suicide risk. This point is really of relevance due the suicide risk found in MS and the possibility of misuse of antidepressants in MS with BP. Remarkably a biased conclusion can strongly impact the clinical practice.

Finally, summarize Bipolar Disorders with Schizophrenia is highly questionable. These two conditions are distinct both from an etiopathogenesis point of view and for the profile of public health issues of associated at risk behaviors.

I suggest these limits, specifically amplified for Bipolar Disorders, can correctly underlined and conclusion on association between BD and MS must be done with caution.
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests