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Lipid profile and suicide attempt in bipolar disorder: A meta-analysis of published and unpublished data

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ABSTRACT

Evidence suggests an association between low lipid levels and suicidality in subjects with severe mental disorders. This is the first systematic review and meta-analysis aimed at exploring differences in lipid profile between suicide attempters and non-attempters with bipolar disorder. We included observational studies providing comparative cross-sectional data on total cholesterol, LDL-cholesterol and triglycerides levels. We searched main Electronic Databases, identifying 11 studies that met our inclusion criteria, including also unpublished data. Meta-analyses based on random-effects models were carried out, generating pooled standardized mean differences (SMDs). Heterogeneity among studies was estimated using the I^2 index. The meta-analyses included data on lipid profile from 11 studies based on 288 subjects with and 754 without suicide attempt, respectively. No differences in total cholesterol (SMD: −0.10; 95%CI: −0.30 to 0.10; $p = 0.34$), LDL-cholesterol (SMD: −0.26; 95%CI: −0.65 to 0.13; $p = 0.19$), and triglycerides (SMD: −0.06; 95%CI: −0.31 to 0.19; $p = 0.63$) were detected. Heterogeneity across studies was low-moderate and no risk of publication bias was found. Subgroup analyses showed no differences on effect size across different study characteristics, including different timeframes of suicide attempt, except for small sample size. Therefore, the evidence for an association between serum lipid profile and suicidality in bipolar disorder cannot be claimed. More research is needed to better understand the mechanisms underlying suicidal behaviours in bipolar patients, exploring further peripheral biomarkers as this may help clinicians screen and prevent suicidality.

1. Introduction

World Health Organization data report that over 800,000 subjects die due to suicide every year, with many more attempting suicide (WHO, 2017). Suicide represents the 15th leading cause of mortality, accounting for about 1–2% of global deaths (WHO, 2017). Due to its epidemiological burden, an increasing body of research aimed at identifying peripheral biomarkers of suicide, even if little is known about related neurobiological mechanisms (Pandey, 2013). In particular, during the last 25 years, the role of lipid parameters has attracted growing interest (Engelberg, 1992), with several studies exploring the relationship between low total cholesterol levels and suicide attempts (e.g., Golier et al., 1995; Fiedorowicz and Coryell, 2007; Perez-Rodriguez et al., 2008; Bartoli et al., 2017a). The main neurochemical hypothesis suggests that low peripheral lipid levels may be correlated to a decrease of cholesterol in the lipid rafts of synaptic membranes leading to a reduced serotonergic activity (Cantarelli et al., 2014; De Berardis et al., 2012). The hypoactivity of serotonergic signalling may, in turn, increase impulsivity and the risk of suicidal behaviours (Cantarelli et al., 2014). In addition, the potential role of polyunsaturated fatty acids in the pathogenesis of bipolar disorder and unipolar depression should be considered (Pompili et al., 2017). Previous studies reported an association between fatty acid depletion and suicidal behaviours, involving changes in membrane viscosity and modulation of gene expression (Pompili et al., 2017). A recent systematic review and meta-analysis, based on 65 studies accounting for 510,392 participants, pointed out that subjects who attempted suicide had significantly lower levels of serum total cholesterol, LDL cholesterol, and triglycerides, as compared with their non-suicidal counterpart (Wu et al., 2016). Subgroups analyses showed an association between lipid profile and suicidal behaviours in both major depressive disorders and schizophrenia (Wu et al., 2016). However, despite the body of evidence accumulated in the last few years (e.g., D'Ambrosio et al., 2012; Ahmadpanah et al., 2015; Shakeri et al., 2015) and the considerable contribution of bipolar disorder to suicidal behaviours (Novick et al., 2010), there are no studies that systematically pooled data on the association between lipid profile and suicidality in subjects with bipolar disorder. In order to fill previous research gaps, we

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conducted a MOOSE guidelines-based systematic review and meta-analysis (Stroup et al., 2000) of both published and unpublished data, testing if among subjects with bipolar disorder suicide attempters would have levels of total cholesterol and other lipid parameters (LDL cholesterol and triglycerides) lower than those without suicide attempts.

2. Materials and methods

2.1. Search strategy and selection of studies

We searched, via Ovid, Medline, PsycINFO and Embase electronic databases for articles published up to March 2017. We combined the following index terms: '*bipolar*' and '*suicide*' and ('*cholesterol*' or '*triglycerides*'). We also checked the reference list of a recent review exploring a similar topic (Wu et al., 2016). Two authors (FB and CDB) independently completed the preliminary screening based on titles and abstracts, and evaluated full texts for final eligibility. Differences in suitability for inclusion were resolved by discussion and consensus, involving all authors.

2.2. Eligibility criteria

We included observational studies providing comparative cross-sectional data on lipid profile, i.e., total cholesterol, LDL-cholesterol and/or triglycerides serum levels, in adults suffering from bipolar disorder with and without suicide attempts, respectively. In order to increase consistency of this meta-analysis, we included only studies assessing suicide attempt, excluding those considering suicidal ideation and/or plan without any action taken. Suicide attempt was defined as the engagement in potentially self-injurious behaviours in which there is at least some intent to die (Nock et al., 2008). We excluded duplicated studies, conference abstracts, dissertations, and grey literature.

2.3. Data extraction

We built a data extraction template, including key items for all eligible studies, i.e., year of publication, country, setting, sample size, mean age, male gender rates, assessed suicide attempt time-frame (current/recent or lifetime), and lipid parameters. Two authors (FB and CDB) independently extracted data for blind check of accuracy. To reduce the risk of reporting bias and to include also unpublished findings, one investigator (FB) contacted corresponding authors of those studies not explicitly reporting lipid profile values in subjects with bipolar disorder. We used additional, unpublished data of a recent study conducted by our research group (Bartoli et al., 2017b).

2.4. Data analysis

Meta-analyses of lipid profile of subjects with bipolar disorder were carried out generating pooled standardized mean differences (SMDs), with related 95% confidence intervals (CIs), between suicide attempters and non-attempters. Findings were aggregated according to random-effects models. Statistical significance was set at $p < 0.05$. In order to assess publication bias, we designed a funnel plot graph estimating the Egger's bias test (Egger et al., 1997), for comparisons including at least 10 studies (Sterne et al., 2008). Consistency across studies was measured using the I^2 index, with values of 25%, 50%, and 75%, taken to indicate low, moderate, and high levels of heterogeneity, respectively (Higgins et al., 2003). We additionally tested heterogeneity by χ^2 test with related *p*-value. Furthermore, we carried out subgroup analyses (Deeks et al., 2008), exploring if the estimated effect between lipid profile and suicide attempt could vary according to a set of single study characteristics. In particular, we considered setting (inpatients or outpatients), sample size (above or below 60 subjects), suicide attempt time-frame (current/recent or lifetime). In addition, to evaluate standard items for quality of non-randomized studies (Stang, 2010), we analysed whether age and gender comparability between attempters and non-attempters was met and could influence the pooled effect size. Finally, we tested potential differences in effect size between published and unpublished data. Analyses were performed using Stata statistical software package (release 14; StataCorp, 2015, College Station, Texas). Conventional forest and funnel plots were created using RevMan software (Version 5.3; The Nordic Cochrane Centre, 2014, Copenhagen, Denmark).

3. Results

3.1. Study selection and characteristics

Our search generated 200 records and, after removing duplicates, we identified 141 research articles. The preliminary evaluation by title and abstract identified 15 potentially eligible studies for further full text screening. The final assessment included also additional, unpublished information obtained by corresponding authors (Ainiyet and Rybakowski, 2014; Bocchetta et al., 2001; Fiedorowicz and Coryell, 2007; Pompili et al., 2010; Shakeri et al., 2015) and data from a recent study we conducted (Bartoli et al., 2017b). It allowed to identify 11 articles that met our eligibility criteria and were thus suitable to be included in our meta-analyses (Ahmadpanah et al., 2015; Ainiyet and Rybakowski, 2014; Bartoli et al., 2017b; Bocchetta et al., 2001; D'Ambrosio et al., 2012; Fiedorowicz and Coryell, 2007; Kim et al., 2002; Modai et al., 1994; Pompili et al., 2010; Shakeri et al., 2015; Vuksan-Cusa et al., 2009). We excluded four studies since these did not provide data on lipid profile in the subgroup of patients with bipolar disorder. The summary of characteristics of the studies included is reported in Table 1.

3.2. Total cholesterol and suicide attempts

Eleven studies (Ahmadpanah et al., 2015; Ainiyet and Rybakowski, 2014; Bartoli et al., 2017b; Bocchetta et al., 2001; D'Ambrosio et al., 2012; Fiedorowicz and Coryell, 2007; Kim et al., 2002; Modai et al., 1994; Pompili et al., 2010; Shakeri et al., 2015; Vuksan-Cusa et al., 2009), accounting for 1042 unique subjects, provided data on total cholesterol in suicide attempters ($N = 288$) and non-attempters ($N = 754$) with bipolar disorder. No differences in total cholesterol (SMD: -0.10; 95%CI: -0.30 to 0.10; $p = 0.34$) were estimated (Fig. 1). Heterogeneity across studies was low-moderate ($I^2 = 37.9\%$; $p = 0.10$). A partial asymmetry of funnel plot (Fig. 2) was found, without statistically significant risk of publication bias (Egger's bias coeff = -1.34; $p = 0.15$). Subgroup analyses (Table 2) showed no differences on the effect size across different study characteristics, except for small sample size (SMD: -0.39; 95%CI: -0.66 to -0.12; $p = 0.004$).

3.3. LDL cholesterol and suicide attempts

The meta-analysis, based on 5 studies (Ahmadpanah et al., 2015; Ainiyet and Rybakowski, 2014; Bartoli et al., 2017b; Shakeri et al., 2015; Vuksan-Cusa et al., 2009) and 256 subjects with bipolar disorder, showed no difference (SMD: -0.26; 95%CI: -0.65 to 0.13; $p = 0.19$) in serum LDL cholesterol, comparing attempters ($N = 96$) and non-attempters ($N = 160$), with low-moderate heterogeneity across studies ($I^2 = 44.8\%$; $p = 0.12$) (Fig. 1). Neither subgroup analyses nor publication bias assessment could be undertaken due to the paucity of data and the small sample size.

3.4. Triglycerides and suicide attempts

Seven studies (Ahmadpanah et al., 2015; Ainiyet and Rybakowski, 2014; Bartoli et al., 2017b; D'Ambrosio et al., 2012; Pompili et al.,