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Lipid profile disturbances in antipsychotic-naive patients with first-episode non-affective psychosis: A systematic review and meta-analysis

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ABSTRACT

Background: Dyslipidaemia is one of the most prevalent metabolic disturbances observed in schizophrenia patients and has been largely attributed to the effects of poor lifestyle habits and adverse effects of antipsychotic treatment. However, less is known whether patients with first-episode non-affective psychosis (FENP) present subthreshold indices of dyslipidaemia. Therefore, we tested the hypothesis whether subclinical lipid profile alterations occur already in antipsychotic-naïve FENP patients.
Methods: In this systematic review and meta-analysis we adhered to the PRISMA guidelines and searched PubMed, CINAHL Complete, Academic Search Complete, ERIC and Health Source: Nursing/Academic Edition from database inception to Dec 12, 2016, for case-control studies measuring the levels of total cholesterol, low- and high-density lipoproteins (LDL and HDL) and triglycerides in patients with FENP and controls. W calculated effect size (ES) estimates as Hedges' g and pooled data using random- or fixed-effects models depending on heterogeneity. Our study was registered in the PROSPERO database (CRD42016051732).
Results: Out of 2466 records identified, 19 studies representing 1803 participants were finally included in our systematic review and meta-analysis. Pooled analysis revealed that FENP patients had significantly lower levels of total cholesterol [ES = −0.16 (95% CI: −0.27, −0.06), p = 0.003], LDL [ES = −0.13 (95% CI: −0.24, −0.01), p = 0.034] and HDL [ES = −0.27 (95% CI: −0.49, −0.05), p = 0.018] as well as significantly higher levels of triglycerides [ES = 0.22 (95% CI: 0.11, 0.32), p < 0.001] compared to controls. After removing single studies in sensitivity analysis, ES estimate for LDL levels was insignificant.
Conclusions: Antipsychotic-naïve patients with FENP present subclinical dyslipidaemia. Future studies should disentangle whether our findings reflect disease-specific mechanisms.

1. Introduction

Cardiovascular morbidity is increasingly being recognized as a major contributor of mortality and reduced life expectancy in patients with schizophrenia (Laursen et al., 2014). Indeed, this group of patients presents with higher prevalence of metabolic syndrome together with its single components, and related abnormalities, including hyperglycaemia, obesity, lipid profile disturbances, elevated homocysteine levels and cigarette smoking (de Leon and Diaz, 2005; Mitchell et al., 2013; Muntjewerff et al., 2006; Vancampfort et al., 2015). Interestingly, a meta-analysis by Mitchell et al. (2013) revealed that about 40% of patients with schizophrenia and related disorders have lipid profile alterations, which might be the most prevalent cardiovascular risk factor in this population. High cardiovascular risk is largely attributable to environmental factors related to unhealthy lifestyle characteristics and the effects of antipsychotic treatment. In addition, patients with schizophrenia do not receive adequate monitoring of cardiovascular health and tackle with inequalities in the availability of healthcare provision (Baller et al., 2015; Lawrence and Kisely, 2010).

Accumulating evidence indicates that subthreshold metabolic dysregulation might be present already in the premorbid phase of the illness and in antipsychotic-naïve patients with first-episode psychosis. Indeed, there are studies showing that subjects at risk of psychosis have higher rates of metabolic syndrome and reduced high density lipoproteins (HDL) levels as well as higher levels of fasting blood glucose and blood pressure (Cordes et al., 2016). These abnormalities might be attributed to low levels of physical activity and high rates of cigarette smoking or alcohol abuse (Carney et al., 2016). In turn, studies

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performed on antipsychotic-naïve first-episode psychosis (FENP) patients indicate abnormal glycaemic control (Greenhalgh et al., 2016; Perry et al., 2016) as well as elevated levels of C-reactive protein and pro-inflammatory cytokines (Fernandes et al., 2016; Upthegrove et al., 2014).

Early metabolic dysregulation observed in antipsychotic-naïve patients with FENP suggests that schizophrenia-spectrum disorders might share overlapping genetic background with cardio-metabolic phenotypes. A recent analysis of combined data from genome-wide association studies (GWASs) identified ten loci associated with both schizophrenia and cardiovascular risk factors, mainly the levels of low- and high-density lipoproteins (LDL and HDL), but also waist-to-hip ratio, systolic blood pressure, and body-mass index (BMI) (Andreassen et al., 2013). Accumulating evidence also indicates that schizophrenia might be associated with alterations in biosynthesis of cholesterol, fatty acids, phospholipids and sphingolipids (Schneider et al., 2016; Steen et al., 2016). Indeed, there are studies showing alterations in the levels of polyunsaturated fatty acids, cholesteryl esters, phospholipids and triglycerides in prefrontal and frontal cortex of patients with schizophrenia (Horrobin et al., 1991; McNamara et al., 2007; Taha et al., 2013). Finally, it has been widely reported that patients with schizophrenia have various myelination abnormalities that might be attributed to genetic factors (Mighdoll et al., 2015). In turn, previous studies addressing peripheral blood lipid profile alterations in the early course of psychosis have provided mixed results. A recent meta-analysis by Perry et al. (2016) revealed decreased levels of total cholesterol and HDL. However, this meta-analysis primarily investigated parameters of glucose homeostasis and included patients with affective and non-affective psychosis. Therefore, in this study we performed a systematic review and meta-analysis of lipid profile alterations in antipsychotic-naïve patients with FENP.

2. Methods and materials

2.1. Search strategy

Independent online search was performed by two authors (BS and BM), using the following combination of single keywords from the following groups: 1) “antipsychotic-naïve”, “antipsychotic-free” “drug-naïve”, “drug-free”, “neuroleptic-naïve”, “neuroleptic-free”, “never-medicated” and “untreated”; 2) “first-episode psychosis”, “first-episode schizophrenia”, “FEP”, “FES”, “psychosis”, and “schizophrenia” and 3) “cholesterol”, “HDL”, “LDL”, “triglycerides”, “lipid”, “lipoprotein”, and “metabolic”. Relevant publications were identified in the following databases: PubMed, CINAHL Complete, Academic Search Complete, ERIC and Health Source: Nursing/Academic Edition. Additionally, our online search was supplemented by reference lists from relevant publications. We included studies that determined peripheral blood levels of total cholesterol, HDL, LDL and triglycerides in adult antipsychotic-naïve patients with FENP (DSM-IV and ICD-10 criteria) and healthy controls. Studies were included if necessary data was available in the article or upon request (contact with corresponding authors). Our exclusion criteria were: 1) non-English language publications, 2) non-original publications (commentaries, editorials, hypotheses, reviews and study protocols) and meta-analyses, 3) animal model studies and 4) studies that did not include a group of matched healthy controls. Discrepancies were resolved through discussion with the third author (DF). Search strategy followed PRISMA guidelines (Moher et al., 2009).

2.2. Data analysis

The following data of antipsychotic-naïve FENP patients and healthy controls were extracted from eligible publications by one author (BM): 1) age; 2) body-mass index (BMI); 2) the levels of total cholesterol, HDL, LDL and triglycerides; 3) the number of male and female participants and 4) the number of cigarette smokers. Continuous variables extracted from relevant publications were expressed as mean ± SD. In case of potential duplicate data, corresponding authors of relevant publications were asked to provide data from the whole sample of participants without duplicates. Quality of studies was assessed using the Newcastle-Ottawa Scale (NOS) for case-control studies (Wells et al., 2000). Publication bias was analysed using funnel plots of asymmetry, the Begg & Mazumbar's test and the Egger's test. Effect size (ES) estimates were calculated as Hedges' *g* with corresponding 95% confidence intervals (95% CI). Fixed-effects models were used unless significant heterogeneity was demonstrated. Otherwise, all analyses were performed under random-effects models. Heterogeneity between studies was evaluated using the Cochran's Q test and I^2 estimates. Sensitivity analysis was performed in two steps: 1) by removing one study at a time and repeating calculations to examine the impact on the ES estimates; 2) by removing studies with significant differences between patients and controls in at least one of potential confounding variables, such as age, gender distribution, BMI or cigarette smoking, together with outliers, and repeating calculations to examine the impact on the ES estimates. Following the second step of sensitivity, studies were dichotomized as those with perfect matching and those with at least one significant difference in potential confounding variables. This dichotomous variable and the NOS score were included in meta-regression. Results were considered as statistically significant if the p-value was <0.05. Statistical analysis was performed using the STATISTICA software, version 12.5. Our systematic review with meta-analysis was registered in the PROSPERO database on 28th November 2016 (registration number: CRD42016051732).

3. Results

Out of 2466 records identified, 57 full-text articles were assessed for eligibility and 19 studies met our inclusion and exclusion criteria (Fig. 1).

There were 15 case-control studies (McCreadie and the Scottish Schizophrenia Research Group, 2000; Chen et al., 2016; Dasgupta et al., 2010; Enez Darcin et al., 2015; Hepgul et al., 2012; Kavzoglu and Hariri, 2013; Kirkpatrick et al., 2010; Misiak et al., 2016a; Petrikis et al., 2015; Ryan et al., 2003; Sengupta et al., 2008; Spelman et al., 2007; Venkatasubramanian et al., 2007; Wu et al., 2013; Zhang et al., 2016) and 4 observational studies with baseline comparisons of FENP patients and healthy controls (Basoglu et al., 2010; Cai et al., 2012; Nyboe et al., 2015; Saddichha et al., 2008) (Table 1). In total, 1803 participants were recruited in studies included in this meta-analysis (866 FENP patients and 937 controls with mean age of 28.0 years and 28.7 years, respectively). Sample size of antipsychotic-naïve FENP patients varied from 3 (Hepgul et al., 2012) to 172 (Chen et al., 2016) cases, while the number of controls was between 11 (Cai et al., 2012) to 146 (Misiak et al., 2016a) participants. There was a relative predominance of males in the group of FENP patients (58.4%) and controls (55.2%).

Patients and controls were matched for age and sex in almost all studies with exception of two studies (Enez Darcin et al., 2015; Zhang et al., 2016). There were significantly more males in the group of patients compared to the group of controls in the study by Enez Darcin et al. (2015). In turn, in the study by Zhang et al. (2016), patients were significantly younger than controls. In the majority of studies, authors measured BMI (except for one study (Saddichha et al., 2008)) and recorded information about cigarette smoking status (McCreadie and the Scottish Schizophrenia Research Group, 2000; Basoglu et al., 2010; Cai et al., 2012; Chen et al., 2016; Dasgupta et al., 2010; Enez Darcin et al., 2015; Kavzoglu and Hariri, 2013; Misiak et al., 2016a; Nyboe et al., 2015; Petrikis et al., 2015; Ryan et al., 2003; Spelman et al., 2007; Zhang et al., 2016). In two studies, BMI was significantly lower (McCreadie and the Scottish Schizophrenia Research Group, 2000; Spelman et al., 2007), while in one study it was significantly higher (Nyboe et al., 2015) in the group of patients compared to controls. In one study (Spelman et al., 2007), the number of cigarette smokers

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