Research paper

Uric acid in major depressive and anxiety disorders

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ABSTRACT

Background: Uric acid has neuroprotective effects, owing to its antioxidant properties. Lowered antioxidant capacity, causing increased oxidative stress, may be involved in affective disorders and might be altered by antidepressants. This study investigated the association of plasma uric acid, the greatest contributor to blood antioxidant capacity, with major depressive disorder (MDD) and anxiety disorders.

Methods: Data were from the Netherlands Study of Depression and Anxiety including patients with current (N = 1648), remitted (N = 609) MDD and/or anxiety disorders (of which N = 710 antidepressant users) and 618 controls. Diagnoses were established with the Composite International Diagnostic Interview. Symptom severity was assessed with the Inventory of Depressive Symptoms-Self Report, Beck Anxiety Inventory and Fear Questionnaire. Uric acid was measured in plasma. Analyses were adjusted for sociodemographic, health and lifestyle variables.

Results: Plasma uric acid adjusted mean levels were lower in current MDD and/or anxiety disorder(s) (289 μmol/l) compared to remitted disorders (298 μmol/l, p < .001) and controls (299 μmol/l, p < .001; Cohen’s d .10). This finding was independent of antidepressant use. Depressive (β-.05, p = .0012), anxiety (β-.04, p = .009) and phobic (β-.03, p = .036) symptom severity, and symptom duration (β-.04, p = .009) were negatively associated with uric acid.

Limitations: Limitations include the lack of data on dietary intake which could be a potential confounding factor. From these cross-sectional findings, the association between uric acid and psychopathology cannot be inferred to be causal.

Conclusion: This large scale study finds plasma uric acid levels are lower in current, but not remitted, MDD and/or anxiety disorders, according to a dose-response gradient. This suggests the involvement of decreased antioxidant status in affective disorders, and points to their potential as an avenue for treatment.

1. Introduction

Uric acid is the end product of purine metabolism, which breaks down the nucleosides adenosine and guanosine. It is best known for its central role in the pathophysiology of gout, but higher uric acid has also been reported in metabolic syndrome (Yuan et al., 2015) and cardiovascular disease, and is associated with mortality risk (Zhao et al., 2013). However, uric acid's role in health and disease is multifaceted, and there are indications it also has health promoting qualities.

Higher uric acid has been associated with a reduced risk of developing neurological disorders, such as Parkinson's disease (Weisskopf et al., 2007). In multiple sclerosis uric acid is decreased and decreases further as the disease progresses (Moccia et al., 2015). In cognitive impairment (Irizarry et al., 2008) higher uric acid has been associated with a slower rate of decline.

These findings suggest uric acid has neuroprotective effects, owing to its potent antioxidant capacity. Uric acid contributes to over half of plasma antioxidant capacity (Ames et al., 1981) as a free-radical scavenger. It may be a particularly important central nervous system (CNS) antioxidant, due to its stabilizing effect on a second antioxidant, ascorbic acid, which is abundant in neurons (Bowman et al., 2010). Uric acid therefore could be especially significant in depression and anxiety disorders, which have been associated with increased oxidative stress (Black et al., 2015). Major depressive disorder (MDD) and anxiety disorders are the most prevalent psychiatric disorders (Kessler et al., 2013), and very often co-occur, with a comorbidity rate of around 60% (Lamers et al., 2011). Together they account for extensive morbidity worldwide (Whiteford et al., 2013). Their pathophysiology is still only partially understood. Oxidative stress has been suggested as a mechanism, and increased oxidative damage and lower levels of

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Table 1
Sample characteristics of controls, subjects with remitted MDD and/or anxiety disorder(s) and subjects with current MDD and/or anxiety disorder(s).

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Control subjects</th>
<th>Subjects with remitted MDD and/or anxiety disorder(s)</th>
<th>Subjects with current MDD and/or anxiety disorder(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N 618 (Mean SD)</td>
<td>N 609 (Mean SD)</td>
<td>N 1648 (Mean SD)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% “yes”</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Antidepressants, symptom severity

<table>
<thead>
<tr>
<th>Antidepressant use</th>
<th>Control subjects</th>
<th>Subjects with remitted MDD and/or anxiety disorder(s)</th>
<th>Subjects with current MDD and/or anxiety disorder(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>N.A.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRIs</td>
<td>N.A.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCAs</td>
<td>N.A.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>other AD</td>
<td>N.A.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Physical activity (100 MET-min/wk)

<table>
<thead>
<tr>
<th>Sample characteristics</th>
<th>Median (IQR) (Mean SD)</th>
<th>p a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td>150.0 (121.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Subjects with remitted MDD and/or anxiety disorder(s)</td>
<td>160.0 (126.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Subjects with current MDD and/or anxiety disorder(s)</td>
<td>170.0 (130.5)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

### Plasma uric acid (mg/dl)

<table>
<thead>
<tr>
<th>Sample characteristics</th>
<th>Median (IQR) (Mean SD)</th>
<th>p a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td>4.0 (4.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Subjects with remitted MDD and/or anxiety disorder(s)</td>
<td>6.0 (6.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Subjects with current MDD and/or anxiety disorder(s)</td>
<td>2.0 (2.0)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

### Supplement use

<table>
<thead>
<tr>
<th>Supplement use</th>
<th>Control subjects</th>
<th>Subjects with remitted MDD and/or anxiety disorder(s)</th>
<th>Subjects with current MDD and/or anxiety disorder(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>N.A.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>N.A.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy</td>
<td>N.A.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Alcohol use

<table>
<thead>
<tr>
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<th>Median (IQR) (Mean SD)</th>
<th>p a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td>0.9 (0.9)</td>
<td>.001</td>
</tr>
<tr>
<td>Subjects with remitted MDD and/or anxiety disorder(s)</td>
<td>1.0 (1.0)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Subjects with current MDD and/or anxiety disorder(s)</td>
<td>2.0 (2.0)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

### Additional information

Antidepressants (Black et al., 2015; Hovatta et al., 2010; Jiménez-Fernández et al., 2015; Liu et al., 2015) have been demonstrated in depression and anxiety disorders.

For many markers of oxidative stress measured peripherally it is unknown whether they are reflective of CNS levels. Plasma levels of uric acid however correlate highly with cerebrospinal fluid levels (r = .669, p = .001) (Bowman et al., 2010), making uric acid of particular interest in affective disorders.

Previous literature on uric acid in depression is limited in scope, findings are conflicting and only one previous study addresses uric acid in anxiety disorders (Lyngdoh et al., 2013). Two small meta-analyses (Jiménez-Fernández et al., 2015; Liu et al., 2015) (N = 306 and N = 762 cases) found lower uric acid in depression, but also reported very high heterogeneity (I^2 ± 90%), meaning the findings are highly inconsistent. Neither included a large study (N = 3716) that found no association between uric acid and affective disorders, with the exception of social phobia (Lyngdoh et al., 2013).

This study used a large sample with well-defined diagnoses to examine the relationship between plasma uric acid and MDD and/or anxiety. We hypothesized that uric acid would be lower in subjects with a disorder. To our knowledge this sample comprises a larger number of cases than all previous studies on this association combined and includes most major confounding factors. In addition, it addresses whether the association is independent of antidepressants, which may also affect uric acid (Jiménez-Fernández et al., 2015). To gain insight into whether uric acid levels are a trait characteristic, or are associated are with the severity and duration of the state of a current episode, both current and remitted patients as well as severity and duration indicators were included.

### 2. Materials and methods

#### 2.1. Population

Data were derived from the baseline measurement of the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study conducted among 2981 adults aged 18–65 years. Between 2004 and 2007 participants were recruited from the general population, primary care and mental health care organizations in the Netherlands. The NESDA sample includes participants with current or remitted major depressive disorder, dysthymia, and/or anxiety disorders (social phobia, generalized anxiety disorder, panic disorder, agoraphobia) as well as healthy control subjects. Persons with another primary psychiatric diagnosis of e.g. bipolar disorder, severe substance use disorder or a psychotic disorder were excluded. Diagnoses were ascertained using the lifetime version of the Composite International Diagnostic Interview (CIDI, version 2.1). At baseline, participants underwent a 4-h assessment, including blood sampling, written questionnaires, an interview and physical examination. A full description of the NESDA design has been published previously (Penninx et al., 2008). NESDA was approved by the Medical Ethics Committees of the participating institutes. All participants provided

#### 2.2. Sample characteristics

The NESDA included a large sample of participants with current and remitted major depressive disorder, dysthymia, and/or anxiety disorders (social phobia, generalized anxiety disorder, panic disorder, agoraphobia) as well as healthy control subjects. Persons with another primary psychiatric diagnosis of e.g. bipolar disorder, severe substance use disorder or a psychotic disorder were excluded. Diagnoses were ascertained using the lifetime version of the Composite International Diagnostic Interview (CIDI, version 2.1). At baseline, participants underwent a 4-h assessment, including blood sampling, written questionnaires, an interview and physical examination. A full description of the NESDA design has been published previously (Penninx et al., 2008). NESDA was approved by the Medical Ethics Committees of the participating institutes. All participants provided
The duration of symptoms was established with the Life Chart interview (Lyketsos et al., 1994), which uses a calendar method, assessing the number of months in which depressive and/or anxiety symptoms were present during the past 4 years, expressed as percentage of time with symptoms.

2.2. Clinical characteristics

The severity of depressive symptoms, anxiety symptoms and phobic symptoms in the past week were assessed with the 30-item Inventory of Depressive Symptoms—Self Report (IDS-SR; range 0–84) (Rush et al., 1996), Beck Anxiety Inventory (BAI; range 0–63) (Beck et al., 1988) and Fear Questionnaire (FQ) score (range 0–120) (Van Zuuren, 1988). The IDS, BAI and FQ all have well-established validity and reliability (Beck et al., 1988; Rush et al., 1996; Van Zuuren, 1988).

The duration of symptoms was established with the Life Chart interview (Lyketsos et al., 1994), which uses a calendar method, assessing the number of months in which depressive and/or anxiety symptoms were present during the past 4 years, expressed as percentage of time with symptoms.

2.3. Plasma uric acid

Blood was collected after an overnight fast using a vacutainer tube and transported to local laboratory sites for processing within 1 h of withdrawal. Plasma samples were stored at −80 °C and transported to the Laboratory of the University Medical Center of Groningen. Plasma uric acid levels were determined with a commercially available kit (Roche/Hitachi) by a method modified from the colorimetric method. Detection limit for plasma uric acid was 11.9 μmol/l. Intra- and inter-assay coefficients of variance were < 1% and < 2% respectively.

2.4. Covariates

Socio-demographic factors included sex, age and education. Cotinine (a major metabolite of nicotine), as measure of cigarette smoke exposure, was assessed in plasma by solid-phase competitive ELISA (Cotinine Direct ELISA kit, Cat. No. COO96D, Calbiotech, Calif., USA). The detection limit was 1 ng/ml. Intra- and inter-assay coefficients of variation for values > 2 ng/ml were < 20 and < 15%, respectively. Participants with cotinine values below the detection limit of 1 ng/ml had their level set at the value .9 ng/ml. Participants scoring > 21 units p/wk for men and women), moderate users (≤ 21 units p/wk for men, ≤ 14 units p/wk for women) and heavy users (> 21 units p/wk for men, > 14 units p/wk for women).

Body mass index was calculated as kg/m².

Physical activity was assessed using the 7-item International Physical Activity Questionnaire (IPAQ) and expressed as total Metabolic Equivalent of Task – minutes per week (www.ipaq.sk.se).

Medication use was assessed by examination of pill containers and classified following the World Health Organization’s (WHO) Anatomical

<table>
<thead>
<tr>
<th>MDD, anxiety disorders &amp; antidepressants</th>
<th>Unadjusted</th>
<th>Model 1 sociodemographics</th>
<th>Model 2 sociodemographics &amp; lifestyle</th>
<th>Model 3 sociodemographics, lifestyle, health &amp; medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>mean (SD)</td>
<td>p</td>
<td>adjusted mean (SD)</td>
<td>adjusted mean (SD)</td>
</tr>
<tr>
<td></td>
<td>overall</td>
<td>p</td>
<td>overall</td>
<td>overall</td>
</tr>
<tr>
<td>1 Controls</td>
<td>618</td>
<td>271 (71)</td>
<td>ref</td>
<td>280 (60)</td>
</tr>
<tr>
<td>Remitted MDD and/or anxiety disorder(s)</td>
<td>609</td>
<td>267 (71)</td>
<td>.366</td>
<td>280 (61)</td>
</tr>
<tr>
<td>Current MDD and anxiety disorder(s)</td>
<td>1648</td>
<td>257 (71)</td>
<td>&lt; .0001</td>
<td>270 (62)</td>
</tr>
<tr>
<td>Current MDD only</td>
<td>618</td>
<td>271 (71)</td>
<td>ref</td>
<td>280 (60)</td>
</tr>
<tr>
<td>Remitted MDD and/or anxiety disorder(s)</td>
<td>609</td>
<td>267 (71)</td>
<td>.366</td>
<td>280 (61)</td>
</tr>
<tr>
<td>Current MDD only</td>
<td>609</td>
<td>267 (71)</td>
<td>.366</td>
<td>280 (61)</td>
</tr>
<tr>
<td>Current anxiety disorder(s) only</td>
<td>373</td>
<td>256 (71)</td>
<td>.002</td>
<td>268 (60)</td>
</tr>
<tr>
<td>Current anxiety disorder(s)</td>
<td>562</td>
<td>260 (71)</td>
<td>.007</td>
<td>271 (60)</td>
</tr>
<tr>
<td>Controls</td>
<td>713</td>
<td>256 (71)</td>
<td>&lt; .001</td>
<td>270 (61)</td>
</tr>
</tbody>
</table>

ANCova with uric acid as dependent variable; reported values are adjusted geometric means and standard deviations. Linear regression analyses with uric acid as dependent variable; reported values are standardized regression coefficients.

Model 1 includes sociodemographic variables: age, sex, education. Model 2 additionally includes lifestyle variables: plasma cotinine, alcohol, supplement use, physical activity. Model 3 additionally includes metabolic syndrome (yes/no), number of somatic disease, estimated glomerular filtration rate, of cardiac medication and salicylates.

*p value for pairwise comparisons, with controls as reference group.
Fig. 1. Mean plasma uric acid levels (μmol/l) by a) Inventory of Depressive Symptoms (IDS) categories; b) Beck’s Anxiety Inventory (BAI) categories; c) Fear Questionnaire (FQ), quartiles d) Percentage of time with symptoms (depression, anxiety or avoidance) in the last 4 years based on the Life Chart. “IDS category “severe” here includes both “severe” (39–48) and “very severe” (49–84). Reported levels are adjusted geometric means. Error bars indicate 95% confidence intervals. The ANCOVA included the socio-demographics (age, sex, education), lifestyle factors (plasma cotinine, alcohol use, BMI, physical activity, supplement use) and health indicators & medication (estimated glomerular filtration rate, number of chronic diseases, metabolic syndrome, use of cardiac medication and salicylates).

Fig. 2. Mean levels of plasma uric acid (μmol/l) in controls, subjects with remitted or current MDD and/or anxiety disorder(s) with and without antidepressants. Reported levels are adjusted geometric means. Error bars indicate 95% confidence intervals. The ANCOVA included the socio-demographics (age, sex, education), lifestyle factors (plasma cotinine, alcohol use, BMI, physical activity, supplement use) and health indicators & medication (estimated glomerular filtration rate, number of chronic diseases, metabolic syndrome, use of cardiac medication and salicylates).

Cohen’s d 0.10, p < 0.001

2.5. Statistical analyses

Analyses were performed using SPSS version 20.0. Characteristics of controls and subjects with remitted or current disorders were compared with ANOVA or Kruskal-Wallis tests (normally and non-parametrically distributed variables respectively) and Chi-square tests for categorical variables.

Effect modification by sex was examined by testing for a significant interaction by including a sex*MDD/anxiety diagnosis interaction term in a linear regression model with uric acid as dependent variable and MDD/anxiety diagnosis and sex as main predictors. As no interaction was present (p = .741), all further analyses were conducted in the full sample.

ANCOVAs were used to calculate the covariate-adjusted mean levels of uric acid for (1) controls, subjects with remitted and current MDD and/or anxiety disorders; and (2) controls, subjects with remitted disorders, current MDD (only), current anxiety (only), both current MDD and current anxiety (only), both current MDD and current anxiety (only), both current MDD and current anxiety (only).

The number of self-reported chronic somatic diseases was counted including: lung disease, cardiovascular disease, diabetes mellitus, osteoarthritis, cancer, hypertension, gastrointestinal disorders, liver disease, epilepsy, chronic fatigue syndrome, allergies, thyroid disease.

Glomerular filtration rate (GFR [ml/min/1.73 m²]) was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation (Levey et al., 2009).

Medications known to affect uric acid included use of cardiac medications (antihypertensive drugs, diuretics, peripheral vasodilators, beta-blocking agents, calcium channel blockers, agents acting on the renin-angiotensin system [ATC codes C02, C03, C04, C07, C08 and C09]) and salicylates (ATC code N02BA).
and anxiety disorder(s). Reported levels are adjusted geometric means and standard deviations (SD).

Linear regression analyses with uric acid as the dependent variable and symptom severity scores and duration of symptoms as continuous predictor variables were used to investigate dose-response associations. Reported values are standardized regression coefficients.

To examine the association with antidepressants ANCOVAs were used to calculate the mean levels of uric acid for (1) controls subjects, (2) subjects with remitted disorders without antidepressants, (3) subjects with remitted disorders with antidepressants, (4) subjects with current disorders without antidepressants, (4) subjects with current disorders with antidepressants. Reported levels are adjusted geometric means and standard deviations (SD).

Analyses were adjusted for socio-demographics including age, sex, education (model 1); additionally for lifestyle factors cotinine, alcohol, BMI, physical activity, supplement use (model 2); and chronic diseases, metabolic syndrome, GFR, cardiac medication, salicylates (model 3).

Effect's sizes Cohen's d were calculated based on the means, standard deviations and number of subjects. For all analyses, a p-value < .05 was defined as significant.

3. Results

3.1. Sample description

The sample comprised 2875 subjects, 66.1% female, with a mean (SD) age of 41.9 (13.1) years and 12.1 (3.3) years of education. Of these, 618 were control subjects, 609 were subjects with remitted MDD and/or anxiety disorder(s) and 1648 were subjects with current MDD and/or anxiety disorders. Subjects with remitted or current disorders were older, more likely to be female, smokers, and more likely to have less education, drink less alcohol, be less physically active, have higher BMI and more chronic diseases than controls (Table 1). Antidepressant use was reported by 13.5% of subjects with remitted and 38.1% of subjects with current disorders.

3.2. Plasma uric acid in MDD and/or anxiety disorder(s)

Plasma uric acid levels in subjects with current MDD and/or anxiety disorder(s) were lower than in controls (289 vs. 299 μmol/l, Cohen's d .10, p < .001). Subjects with remitted disorders did not differ from controls (p = .726; Table 2, model 3). Division of subjects into current MDD only, current anxiety disorder(s) only, and current comorbidity revealed that uric acid was lower than controls in each of these groups (all p < .01; Table 2). Effect sizes Cohen's for the comparison with controls for current MDD only, current anxiety disorder(s) only, current MDD and anxiety disorder(s), were .16, .10 and .11 respectively

Uric acid levels were inversely associated with all symptom severity and duration measures (all p values < .05; Table 2 model 3). To illustrate the trend graphically, adjusted means were calculated across IDS categories (p for linear trend = .012; Fig. 1a), BAI categories (p for linear trend = .032; Fig. 1b), FQ quartiles (p for linear trend = .034; Fig. 1c), and percentage of time with symptoms (past 4-5 years; p for linear trend = .005; Fig. 1d), which all indicated a linear trend.

Antidepressants did not affect the association between uric acid and current MDD and/or anxiety disorder: subjects with current disorders, with or without antidepressants, had lower levels than controls (Cohen's d .14, p < .001 and Cohen's d .09, p = .002 respectively), whereas those with remitted disorders, with or without antidepressants, did not differ from controls (p = .882 and p = .656; Fig. 2).

4. Discussion

This study finds that plasma uric acid is lower in subjects with current MDD and/or anxiety disorders, in comparison to controls. This finding was independent of antidepressant use. Uric acid levels of subjects with remitted MDD and/or anxiety disorders did not differ from controls suggesting lower uric acid is a state marker, not a trait characteristic of subjects with these disorders. Higher symptom severity and longer symptom duration were associated with lower uric acid, suggesting a dose-response relationship.

These findings are in agreement with the overall conclusion of two meta-analyses, both finding lower uric acid in depression (Jiménez-Fernández et al., 2015; Liu et al., 2015), and the growing body of evidence for involvement of increased oxidative stress and lowered antioxidants in depression in general (Black et al., 2015). A previous study of 40 MDD patients reported a negative association between serum uric acid and depression severity (Chaudhari et al., 2010).

A large study by Lyngdoh et al. (2013) however found no association of uric acid with MDD or anxiety disorders, with the exception of social phobia. It is likely that the subjects in the current study who were recruited from primary and secondary mental health care (and the general population) had more severe symptoms than the general population sample of Lyngdoh, which authors themselves suggested as an explanation for their findings. Their findings might also be explained by the a gap of one year between measurement of psychiatric diagnoses and uric acid in that study, considering this study's finding that uric acid was lower in current, but not remitted disorders. Kesebir et al. (2014) did report lower uric acid in 30 MDD patients in remission. This might be attributable to the difference in duration of remission; subjects in this study were categorized as remitted if no diagnosis was present in the past six months, whereas in Kesebir's study remission period was 8 weeks.

Health and lifestyle factors, including alcohol use, BMI, (lack of) physical activity and smoking may partially explain the association between affective disorders and uric acid because they are associated with both psychopathology and oxidative stress. Increased oxidative stress could lead to depletion of antioxidants, including uric acid. In this study however we included these factors with little effect on the association. The association was also demonstrated to be independent of metabolic syndrome, which itself is associated depression (Pan et al., 2012) and is characterized by higher uric acid levels (Yuan et al., 2015). A study on uric acid in bipolar disorder also demonstrated the association was only marginally attributable to comorbid metabolic syndrome (Bartoli et al., 2016a).

Lower uric acid in current MDD and/or anxiety disorders, if not caused by health and lifestyle factors, may be related to increased exposure to reactive oxygen species (ROS) through mitochondrial dysfunction (Gardner and Boles, 2011), which could deplete uric acid. Mitochondria are the primary sources of ROS and there is evidence to suggest mitochondrial dysfunction plays a role in affective disorders. In a post-mortem study profiles of expression of 16 mitochondrial genes in the dorsolateral prefrontal cortex differed between MDD patients and controls (Wang and Dwivedi, 2016). Lower mitochondrial DNA content has been demonstrated in MDD (Chang et al., 2015) and in elderly patients with depressive symptoms (Kim et al., 2011), and is suggestive of mitochondrial dysfunction.

Individuals with lower uric acid, implying lower antioxidant defenses, may be more susceptible to oxidative damage to the brain, which is particularly vulnerable due to its large oxygen consumption. This damage may make individuals susceptible to developing affective disorders and has been suggested as a mechanism in the relapsing course of affective disorders (Moylan et al., 2013). Based on the cross-sectional findings of this study no conclusions can be drawn on the direction of the association between uric acid and affective disorders. Consequently, the question whether affective disorders lead to lower uric acid levels or vice versa, remains to be explored.

Beside uric acid's role as an antioxidant, it is also a marker of purine metabolism, of which it is the final product. The purinergic system has been implicated in the pathophysiology of mood disorders (Ortiz et al., 2015) and is thought to influence mood, sleep, appetite, cognition and drive through the neurotransmitter adenosine triphosphate (ATP) and...
the neuromodulator adenosine, both of which are upstream metabolites of uric acid. Ali-Sisto et al. (2016) demonstrated altered levels of purine metabolites in 99 MDD patients and have argued that the purine cycle may be hyperactive in depression in an attempt to provide sufficient uric acid to counteract increased oxidative stress. Lower uric acid in MDD could therefore also be interpreted as reflecting possible dysfunction of the purine cycle (Ortiz et al., 2015). This suggestion is underlined by findings that uric is associated with externalized traits of temperament, such as disinhibition (Lorenzi et al., 2010), as well as impulsiveness and excitement seeking (Sutin et al., 2014). Studies on bipolar disorder provide further evidence for a role of uric acid in psychopathology. Uric acid has been demonstrated to be increased in bipolar disorder across all phases of the disorder (Albert et al., 2015), and in particular during the manic phases (Jahangard et al., 2014). A recent meta-analysis demonstrated uric acid was higher in bipolar disorder compared to both controls and subjects with MDD (Bartoli et al., 2016b). Allopurinol, an inhibitor of XO, that lowers uric acid and is used in the treatment of gout, has been successfully employed as (an add-on) treatment for manic episodes reducing both levels of manic symptoms and uric acid levels (Jahangard et al., 2014). Allopurinol add-on was demonstrated to be superior to placebo in a meta-analysis of 5 RCT’s in reducing mania symptoms and increasing remission rates (Bartoli et al., 2017).

Whether uric acid should be also be considered an avenue for intervention in unipolar depression will require further investigation. When considering the possible clinical impact of these findings it should be considered the effect sizes are small; statistical significance does not necessarily translate to clinical relevance. Nevertheless, the effect sizes are comparable to effect sizes found for other markers of oxidative stress and antioxidants (Black et al., 2015), inflammation (Howren et al., 2009) and cortisol (Vreeburg et al., 2009) in depression.

Overall, antioxidant treatments, both preventative and curative, so far have been disappointing (Murphy, 2014), and even harmful. There is increasing understanding that ROS are not only harmful but fulfill important roles in cellular signaling and the balance between enzymatic and non-enzymatic antioxidants makes the outcome of antioxidant therapies unpredictable. Uric acid itself acts as an antioxidant, in the extracellular environment, but can also act as a pro-oxidant, mainly in the intracellular environment (Sautin and Johnson, 2008), which potentially further complicates its use in treatment. Intervention studies have however demonstrated antidepressants can increase uric acid (Jiménez-Fernández et al., 2015; Liu et al., 2015). Lower uric acid on admission predicted the development of depression in stroke patients (Gu et al., 2015), which is an indication that investigation into clinical uses of uric acid in affective disorders is worthy of further pursuit.

4.1. Strengths and limitations

The main strengths of this study are the sample size, the well-established psychiatric diagnoses and adjustment for many health and lifestyle confounders. Limitations include the absence of diet measurements, and the fact that no causal relations can be inferred from these cross-sectional results. When interpreting this study, and many studies with similar methodology, it should be kept in mind that oxidative stress and the functioning of antioxidant defenses are an ongoing dynamic processes, the complexities of which cannot be captured in the measurement of levels of individual peripheral markers at a single time point. The levels of a single marker, in this case uric acid, may not be representative of the functioning of the whole system of redox-homeostasis, but nevertheless provide a clue that system is involved in psychopathology.

In summary, this study found lower plasma uric acid in subjects with current MDD and/or anxiety disorders, with evidence for a dose-response association, suggesting involvement of oxidative stress in these disorders. Future longitudinal and experimental studies should further explore these associations, and uric acid's potential as diagnostic tool or new avenue for treatment.

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