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Higher Prevalence of Metabolic Syndrome in Child-adolescent Patients with Bipolar Disorder

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Objective: Previous studies have indicated a convergent and bidirectional relationship between metabolic syndrome (MetS) and bipolar disorder (BD). As most of these studies focused mainly on adults diagnosed with BD, our study aims to investigate and characterize metabolic disturbances in child-adolescents diagnosed with BD.
Methods: We retrospectively examined the medical records of psychiatric hospitalizations with admitting diagnosis of BD in child-adolescents (age < 18 years). Body mass index (BMI), lipid profile, fasting blood glucose, and blood pressure were primary variables. National Cholesterol Education Program criteria were used to define MetS. Reference group data was obtained from the National Health and Nutrition Examination Survey study. Statistical analyses included *t* tests, chi-square tests, and Fisher's exact tests.
Results: We identified 140 child-adolescent patients with BD (mean age = 15.12 ± 1.70 years, 53% male). MetS was significantly more common in BD compared to the reference group: 14% (95% confidence interval [95% CI] 8−20) vs. 6.7% (95% CI 4.1−9.2), $p = 0.001$ with no significant difference by sex. MetS components were higher in the BD group, particularly BMI ≥ 95% (25% vs. 11.8%, $p < 0.001$) and high blood pressure (17% vs. 8%, $p = 0.05$). Moreover, female patients had lower odds of high blood pressure (odds ratio = 0.24 [95% CI 0.08−0.69], $p = 0.005$).
Conclusion: Compared with the general child-adolescent population, the prevalence of MetS was significantly higher in patients with BD of same age. This reiterates the notion of an increased risk of MetS in patients diagnosed with BD; and thus, further exploration is warranted.

KEY WORDS: Bipolar disorder; Metabolic syndrome; Child-adolescents; Body mass index; Lipids; Blood glucose.

INTRODUCTION

Bipolar disorder (BD) is a chronic and debilitating disorder associated with recurring episodes of (hypo-) mania and/or depression and is diagnosed based on the severity of symptoms [1]. The international prevalence rate was noted to be 1.8% (95% confidence interval [95% CI], 1.1%−3.0%) [2]. Per the National Comorbidity Survey Adolescent Supplement data, American adolescents (age 13−18 years) have a 2.9% lifetime prevalence of bipolar disorder, with 2.6% experiencing severe impairment [3]. However, under-reporting and misdiagnosis of BD has been noted in adolescents BD [4]. BD can drastically impair functioning in adolescents due to cognitive impairment in their formative years [5-7].

An estimated 4% of adolescents in the United States (US) meet criteria for metabolic syndrome (MetS); based on an age modified definition of the Adult Treatment Panel (ATP) III criteria established for adults [8]. MetS was reported highly prevalent (16.7%−67%) among patients with BD worldwide [9-11]. Metabolic abnormalities are a major clinical concern due to their relationship with psychiatric outcomes [12]. Specifically, obesity and MetS have routinely been linked to BD [12]. Reviews by Taylor and MacQueen [13], Fagiolini *et al.* [14] addressed the common pathophysiological link between BD and MetS through several mechanisms, namely-dysregulations in

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glucose, insulin, hemostasis, sympathetic nervous system, and disturbances in the hypothalamic-pituitary-adrenal and the hypothalamic-pituitary-thyroid axes. Genetic studies have further contributed to the understanding of this association between BD and MetS through interconnected genes [15,16]. In the light of such recent evidences, the link between BD and metabolic abnormalities has been postulated to be bidirectional [17].

Moreover, studies have demonstrated a higher prevalence of manic and depressive symptoms in the setting of metabolic disturbances as well as poor medication compliance and lower functional outcome [18]. A cohort study on a population of adolescents diagnosed with BD reported an increased prevalence of obesity, type 2 diabetes mellitus, endocrine abnormalities and cardiovascular disorders [19]. This study also reported a significant association between adolescent-onset BD and pre-existing obesity, hypertension and endocrine disorders, postulating that MetS precedes early-onset BD [19]. Additionally, studies have found differences in MetS prevalence by sex in the patients with BD; including increased waist circumference in women and increased triglycerides (TG) in men [20-22]. To the best of our knowledge, there is a lack of literature examining any individual and combined metabolic disturbances in youth diagnosed with BD, or any sex differences within this age group.

Our study aims to review the prevalence of metabolic syndrome and its individual components (i.e., body mass index [BMI], lipid profile, fasting blood glucose, and blood pressure) in a sample of children and adolescent patients ($<$ 18 years) with BD; and to compare our findings with reference group data from the National Health and Nutrition Examination Survey (NHANES) study for under age 18 individuals without BD.

METHODS

This study employed a cross-sectional design. After acquiring Institutional Review Board (IRB) approval (IRB No. HSC-MS-16-0746) and de-identified data consent waiver, data was retrospectively obtained from records of patients (age $<$ 18 years) admitted to the University of Texas Health Harris County Psychiatric Center between January 2010 and December 2015. Records were de-identified and then uploaded to a secure, confidential server prior to data analysis. Inclusion criteria included: (i) age $<$ 18 years, (ii) discharge diagnosis of bipolar I disorder, bipolar II disorder and bipolar disorder not otherwise specified (NOS) based on Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria, determined by the assessing psychiatrist, and (iii) inpatient hospitalization between January 2010 and December 2015. Patients who were not fasting at least 10 hours before blood drawn were excluded.

In addition to demographic information, age of onset, prior hospitalization history, previous psychotropic medication history, and discharge psychotropic medications regimen were identified. Family psychiatric history was gathered from patient interviews and obtained collateral information. Blood samples were drawn within 24 hours of admission in a fasting state, before starting any medications. Systolic and diastolic blood pressures, tobacco smoking status, height, weight, fasting serum glucose and lipid panel including total cholesterol, high-density lipoprotein (HDL), and TG were retrieved for metabolic disturbance assessment.

Blood pressures were manually measured and recorded by trained medical staff using age-appropriate cuff sizes with auscultation at time of admission. BMI was calculated by the electronic medical record after trained staff members entered manually measured heights and weights at the time of admission. National Cholesterol Education Program (NCEP) ATP III-modified criteria was used for MetS diagnosis [23], and at least 3 out of the 5 following components were required for diagnosis of MetS: (i) TG $\geq$ 150 mg/dl, (ii) HDL $\leq$ 40 mg/dl in men and $\leq$ 50 mg/dl in women, (iii) blood pressure $\geq$ 130/85 mmHg, (iv) fasting blood glucose $\geq$ 110 mg/dl, and (v) BMI $\geq$ 28.8 kg/m^2 [23]. We used equivalent BMI parameters instead of the waist circumference ($>$ 102 cm in men and $>$ 88 cm in women) [23,24]. Reference group data was obtained from the findings of the NHANES 1999−2000 dataset [25-27]. Data was analyzed using SPSS 20 for Windows (IBM Co., Armonk, NY, USA) [28]. A univariate statistical analysis was performed with calculation of means and standard deviations (SD). Normality assumptions were verified using the Kolmogorov−Smirnov test, with application of 95% CI. Bivariate statistical analyses were conducted on all study variables, with presence or absence of MetS as the dependent variable. Quantitative variable comparisons were performed using the student's t test. Qualitative variable comparisons were performed using the chi-square test and Fisher's exact tests (for n $<$ 5).

RESULTS

Sociodemographic and Clinical Characteristics of the Study Population

One hundred forty patients diagnosed with BD were identified ([age 15.12 ± 1.7 years, average ± SD]; 53% males; 52% African-American, 39% Caucasian). The predominant diagnosis was Bipolar NOS (95.71%) In comparison, the reference group was comprised of younger age (9.22 ± 5.93 years) and predominant Hispanic population (46.8%) as seen in Table 1. The groups were not statistically significant from each other for sexes; but were significantly different by age and race/ethnicity.

Individual Components of MetS in Study Population

Patients diagnosed with BD had mean BMI: 26.12 ± 6.73 kg/m^2, mean systolic blood pressure: 120.12 ± 12.50 mmHg, mean diastolic pressure: 73.99 ± 8.86 mmHg, mean serum glucose: 89.22 ± 14.35 mg/dl, mean serum triglycerides: 104.66 ± 87.15 mg/dl, and mean HDL: 48.82 ± 12.78 mg/dl (Table 2).

Patients with ≥ 1 MetS components had a positive psychiatric family history (67%), were diagnosed with the following: comorbid conduct disorder (42%) and cannabis use disorder (42%), and history of following psychotropic medication use: antipsychotics (83%), valproic acid (67%), and antidepressants (42%).

Prevalence of Individual Risk Factors of MetS in Study Population and Comparison with Normal Healthy Controls

When assessed for MetS individual criteria, 25% of patients with BD had BMI ≥ 95th percentile, 13% had TG ≥ 150 mg/dl, 24% had HDL ≤ 40 mg/dl in males or ≤ 50 mg/dl in females, 17% had systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg. Nine percent of patients diagnosed with BD had fasting blood glucose ≥ 110 mg/dl (Table 3).

Table 1. Sociodemographic and clinical characteristics of study and reference groups

Parameter	Patients with BD (n = 140)	Controls (n = 4,804)	*p* value
Age (yr)	15.12 ± 1.7	9.22 ± 5.93	0.000
Sex, male (%)	53	51.5	0.909
Race/Ethnicity			0.000
White	54 (39)	1,092 (22.7)	
African-American	73 (52)	1,260 (26.2)	
Hispanic	11 (8)	2,246 (46.8)	
Other/unknown	2 (1)	206 (4.3)	
Diagnosis (DSM-IV)			
Bipolar I	2 (1.43)	-	
Bipolar II	4 (2.86)	-	
Bipolar NOS	134 (95.71)	-	

Values are presented as or mean ± standard deviation or number (%).
BD, bipolar disorder; DSM-IV, the Diagnostic and Statistical Manual of Mental Disorders 4th edition; NOS, not otherwise specified.

Table 2. Individual components of MetS in study population

Parameter	BD cases (n = 140)
Body mass index 95th percentile	26.12 ± 6.73
Systolic blood pressure (mmHg)	120.12 ± 12.50
Diastolic blood pressure (mmHg)	73.99 ± 8.86
Serum glucose (mg/dl)	89.22 ± 14.35
Triglycerides (mg/dl)	104.66 ± 87.15
HDL-C (mg/dl)	48.82 ± 12.78

Values are presented as mean ± standard deviation.
MetS, metabolic syndrome; BD, bipolar disorder; HDL-C, high-density lipoprotein-C.

Table 3. Prevalence of individual risk factors of metabolic syndrome among patients with BD vs. reference group

Variables of MetS	Bipolar disorder (n = 140)			Reference group (n = 991)			OR (95% CI)	*p* value
	Female	Male	Total	Female	Male	Total		
BMI 95th percentile	25	25	35 (25)	11.6	12.1	117 (11.8)	2.49 (1.62−3.82)	< 0.001*
SBP and/or DBP (mmHg)	7	26	18 (17)	5.1	10.8	79 (8)	1.82 (1.05−3.13)	0.05*
Serum glucose (mg/dl)	12	7	13 (9)	5.3	10	75 (7.6)	1.25 (0.67−2.32)	0.48
Triglycerides (mg/dl)	12	14	18 (13)	20.9	25.5	230 (23.2)	0.49 (0.29−0. 81)	0.005*
HDL-C (mg/dl)	25	23	34 (24)	19.3	27.3	230 (23.4)	1.06 (0.7−1.6)	0.77
Metabolic syndrome	12	16	20 (14)	3.8	9.6	66 (6.7)	2.33 (1.37−4.0)	0.001*

Values are presented as percent only or number (%).
BD, bipolar disorder; OR, odds ratio; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein-C.
An asterisk indicates the significant difference ($p \leq 0.05$).

BMI

When comparing BMI of the study and reference groups, the study sample had a significantly higher percentage with BMI ≥ 95th percentile (25% vs. 11.8%, respectively) (odds ratio [OR] = 2.49 [95% CI 1.62−3.82], $p < 0.001$). This correlation remained consistent between sexes in the study sample: males (25% vs. 12.1%) and females (25% vs. 11.6%).

Systolic and/or diastolic blood pressure

Twenty six percent of males (vs. 10.8% in the reference group) and 7% of females (vs. 5.1% in the reference group) in the study group met MetS criteria by blood pressure alone. Patients with BD had higher systolic and/or DBP than controls (17% vs. 8%) (OR = 1.82 [95% CI 1.05−3.13], $p < 0.05$).

Serum glucose

No significant statistical difference in percentage fasting serum glucose ≥ 110 mg/dl was found between the study and reference groups (OR = 1.25 [95% CI 0.67−2.32], $p = 0.48$).

Lipids

Surprisingly, a lower percentage of patients with BD had increased triglycerides compared to controls (13% vs. 23.2%) (OR = 0.49 [95% CI 0.29−0.81], $p = 0.005$). The difference in percentages between the study and reference groups was even greater when comparing sexes: males (14% vs. 25.5%) and females (12% vs. 20.9%). No significant statistical difference of HDL was observed between the study and reference groups (OR = 1.06 [95% CI 0.7−1.6], $p = 0.77$).

Combined MetS criteria

Considering all individual components, patients diagnosed with BD had a higher prevalence of MetS than healthy controls (14% vs. 6.7%) even when accounting for differences in sex: males (16% vs. 9.6%) and females (12% vs. 3.8%). The study group had significantly higher odds of having MetS compared to the reference group (OR = 2.33 [95% CI 1.37−4.0], $p = 0.001$).

Prevalence of MetS, Individual MetS Components, and Sex Differences in BD Patients

In the study group, 14% of patients with BD met diagnostic criteria for MetS. The mean age of patients with MetS was 14.73 ± 1.55 years and MetS prevalence was highest in Whites (n = 10, 19% of all White patients with BD). In the group with BD also diagnosed with MetS, females were less likely to have high blood pressure (OR = 0.24 [95% CI 0.08−0.69], $p = 0.005$). The remaining individual MetS components and the combination of MetS components were not significant different between sexes ($p > 0.05$) (Table 4).

Table 4. Prevalence of metabolic syndrome and its individual components by sex within patients with BD

Variables of MetS	Female	Male	OR (95% CI)	*p* value
BMI 95th percentile	17 (25)	18 (25)	1.09 (0.51−2.35)	0.82
Hypertriglyceridemia	8 (12)	10 (14)	0.89 (0.33−2.41)	0.82
Low HDL	17 (25)	17 (23)	1.18 (0.54−2.55)	0.67
High blood pressure	5 (7)	19 (26)	0.24 (0.08−0.69)	0.005*
High fasting glucose	8 (12)	5 (7)	1.92 (0.6−6.2)	0.27
MetS (three or more criteria)	8 (12)	12 (16)	1.38 (0.53−3.6)	0.63

Values are presented as number (%).
BD, bipolar disorder; BMI, body mass index; HDL, high-density lipoprotein; MetS, metabolic syndrome; OR, odds ratio.
An asterisk indicates the significant difference ($p \leq 0.05$).

DISCUSSION

Our study demonstrated that patients with BD met MetS criteria more often than healthy controls through BMI and SBP and/or DBP; as well combined MetS components. A strong correlation exists between MetS with in adults with BD [11,29,30], however there is a paucity of studies on MetS in children and adolescents diagnosed with BD. To the best of our knowledge, our study is a distinctive one to directly examine the prevalence of MetS and its individual subcomponents in this patient population.

A previous study addressed BMI in BD patients of age 7−17 years [31], and reported that 16.5% patients had BMI ≥ 95th percentile, while 25% patients in our study met such BMI criteria. In contrast to their predominantly non-Caucasian BD patients with high BMI [31], our study sample meeting MetS diagnostic criteria were predominantly White. Our findings align with another study that reported 64.7% adolescents with BD had ≥ 1 MetS component, mainly elevated TG and DBP [32]. Naiberg's study sample had higher TG levels than their controls, but in contrast we found significantly lower TG levels in our patients

with BD in comparison to our controls. This variability could be attributed to patients' diets, as TG levels are known to be affected by fasting status [33]. It also raises the possibility of the involvement of another unknown mechanism, as both the study and NHANES reference groups were assessed with an overnight fasting [26]. Previously MetS components were thought to precede BD [19]. If true, MetS demands more attention in the context BD management for better prognosis.

Genetics may play a crucial role as a positive family history of MetS, especially high blood pressure and serum glucose, is associated with a 1.5 relative risk of developing MetS in patients with BD [34,35]. Our study found 67% of patients with BD and MetS had a positive family psychiatric history, but family history for MetS or its components was unavailable. The risk for developing MetS or its components in young patients with BD may differ by sex as a study reported females (mean age 12.6 ± 3.6 years) had larger waist circumference and higher BMI, TG, LDL and total cholesterol, but had lower systolic blood pressure and fasting blood glucose than males (mean age 12.5 ± 3.5 years). After 6.6 years of follow-up in this study, females (mean age 16.6 ± 5.4 years) continued to have larger waist circumference, higher BMI and higher TG. Additionally, females had higher SBP and DBP and fasting blood glucose than males (mean age 16.0 ± 5.6 years) [36]. Our study did not find a significant difference in all MetS components between sexes in patients with BD, except female patients with BD showed a significantly lower frequency of high blood pressure.

Different theories seek to explain the relationship between metabolic abnormalities and BD. Patients diagnosed with BD show increased levels of inflammatory markers and altered steroid hormone concentrations and inflammation is associated with BMI and mood symptom severity [37,38]. Obesity is further exacerbated by poor dietary habits and an altered lifestyle [39,40]. Binge eating and emotionally driven eating behavior are highly prevalent in adolescent populations with BD [12,41].

Many psychotropic medications used in the treatment of BD have been linked with metabolic abnormalities [42]. Certain atypical antipsychotics (e.g., Olanzapine, Risperidone) prescribed as monotherapy or in combination with other psychotropics such as mood stabilizers, have been found to cause weight gain, metabolic abnormalities, and increased cardiovascular risk in adolescents [43-48]. In contrast, another study reported a high prevalence of obesity and metabolic syndrome in medication-naïve patients [49]. The patients in our study were on psychotropic medications: antipsychotics (83%), valproic acid (67%), and antidepressants (42%) treatment. These medications exhibit a propensity to increase specifically BMI in adolescents with BD [50]. Although these psychotropics significantly impact MetS profile, this can be ameliorated through cautious medication selection based on careful therapeutic risk-benefit analysis. Several studies have scrutinized the safety data for antipsychotics in younger aged populations and have postulated a few recommendations [51-54]. Quetiapine, Ziprasidone, Aripiprazole, and Paliperidone were comparatively found to have a less-severe impact on the MetS profile [43,55,56]. Our study also found the presence of MetS in patients with BD who were not on medications (13%). These divergent findings suggest metabolic abnormalities could be an inherent part of the BD disease process [57].

Our study is noteworthy because the adolescent population diagnosed with BD has not been well explored. Additional study strengths include comparison with a national reference group, MetS assessment via based on the NCEP individual and combined component criteria. Although this study was effective in assessing the differences between adolescent BD with patients and controls in setting of MetS and its associated components, it had certain limitations. Chart review yielded some significant variables especially comorbid conduct disorder and cannabis use disorder, family psychiatric history, and psychotropic medication history, but the overall analysis lacked some vital clinic information including history of self-harm and suicidality, duration and severity of the illness, and average length of hospitalization. The cross-sectional study design is limiting because the predictability and the temporal relationship between BD and MetS in younger aged patients cannot be assessed. Although demographic variables like mean age in the groups was significantly different, use of an inpatient sample for study purposes may not accurately reflect the prevalence of BD and MetS in adolescent patients in the community. Most patients were prescribed and taking psychotropic medication prior to admission which may confound the association between BD and MetS. Considering the role of psychotropics in treatment of BD and effect upon MetS, detailed retrospective data was warranted, but was not available for this

study. Another overlapping and limiting aspects were the high percentage of comorbid conduct disorder and cannabis use disorder in patient population. As literature suggests the strong interlink of BD with conduct disorder [58-60] and cannabis use disorder [61,62], thorough studies are needed in such BD population by excluding the comorbidities. A recent study reported the fluctuations in the discharge medications dosing and length of stay in adult BD population using cannabis and synthetic cannabis [63]. With a dearth of such studies in young BD population and increased prevalence of synthetic cannabis use in the community [64-66], it is crucial to integrate this factor in adolescent BD patients for further insight.

The reference group data used for this study is from the NHANES 1999−2000 report and a 2004 descriptive study [67]. To address the timeline difference between the data collected from the study and reference groups, we compared the prevalence of MetS in same age group from 2003 to 2011, which was reported to be 2.9% and 5.6% for younger and older age children and adolescent groups, respectively [68]. In contrast, mean weight, waist circumference, and BMI in adults has noticed to be increased over time [69]. It is safe to assume that prevalence of MetS in the young population did not drastically increase over time, otherwise it would have convoluted the impact of BD on MetS. All significant covariates from the NHANES were unable to be obtained which significantly restricts our ability to understand the clinical depth in BD and MetS. Our study sample was distorted by a higher frequency of BD-NOS, compared to BD-I or BD-II. The younger age population has high incidence of BD-NOS [70], with a conversion rate of 30−50% from BD-NOS to BD-I or BD-II later on in life [71,72]. The inpatient setting from which the study sample was derived is focused on acute stabilization and length of stays are relatively short. This may lead to difficulties in clinically differentiating BD-I and BD-II. In such a limited setting, with lack of in-depth historical information and a short window of clinical monitoring, the assessing psychiatrist might have preferred a discharge diagnosis of BD-NOS in light of insufficient data for BD-I or BD-II diagnoses. Adequate follow-up of this cohort and subsequent comparison to baseline data could better elucidate this slant in discharge diagnosis.

The selection of the appropriate MetS-defining criteria for this study was another substantial challenge as various criteria are recognized. The World Health Organization (WHO) criteria (1998) has insulin resistance as an absolute requirement [73], the European Group for the Study of Insulin Resistance (EGIR) deems hyperinsulinemia compulsory [74], and the International Diabetes Foundation (IDF) mandates obesity as a requirement for MetS diagnosis [75]. In contrast to these differing defining criteria, NCEP ATP-III does not necessitate any specific criteria as an absolute requirement for MetS diagnosis. For simplicity, NCEP criteria were selected and BMI was used as a proxy to waist circumference which limits our scope of obesity as a MetS component.

Compared to the general adolescent population, the prevalence of metabolic abnormalities in child and adolescents with BD found to be significantly higher. These findings support the notion of amplified risk of metabolic disturbances at an early age in patients diagnosed with BD. Keeping in mind the pubertal hormonal changes and its influence on several physiological changes [76]; such as body fat changes [77], increased leptin resistance [78], adiponectin and resistin fluctuations etc. [79], it is pertinent to incorporate the notion of age while assessing BD and MetS spectrum in young population. Majority of studies in the past were focused primarily on adults; as opposed to adolescent populations with BD. It is noteworthy that metabolic disturbances within the child and adolescent population presents with an array of additional issues; that are distinct from the adult population, raises unique concerns especially future quality of life. Furthermore, heterogeneity in MetS is observed in sex-based comparison in adult population [80,81]. Such data is conflicting in children and adolescent population, with some reporting higher prevalence in males and in Hispanic ethnicity [76,82,83], thus demanding a better grasp of the pathophysiology of MetS and its influence on BD.

This study recognizes metabolic disturbances in young patients diagnosed with BD to be a significant problem. It is essential to understand the effects of abnormal metabolic factors in early-onset BD; to allow the development of an improved patient-centered approach; to embrace preventive treatment, and thus to diminish morbidity and mortality associated with BD and metabolic abnormalities.

■ CDC Disclaimer

The findings and conclusions in this paper are those of the author(s) and do not necessarily represent the views of

the Research Data Center, the National Center for Health Statistics, or the Centers for Disease Control and Prevention.

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■ **Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

■ **Author Contributions**

Hanjing Wu, Teresa A. Pigott, and Jair C. Soares helped in conceptualization, Hanjing Wu and Teresa A. Pigott helped in data acquisition, formal analysis was performed by Hanjing Wu, original draft's writing was done by Satyajit Mohite, review and edits were provided by Shiva Sharma, Hanjing Wu, Luca Lavagnino, Christian P. Zeni, Terrence T. Currie, Jair C. Soares, Teresa A. Pigott.

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