

Attention-deficit hyperactivity disorder and anxiety disorders as precursors of bipolar disorder onset in adulthood

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Background

Attention-deficit hyperactivity disorder (ADHD) and anxiety disorders have been proposed as precursors of bipolar disorder, but their joint and relative roles in the development of bipolar disorder are unknown.

Aims

To test the prospective relationship of ADHD and anxiety with onset of bipolar disorder.

Method

We examined the relationship between ADHD, anxiety disorders and bipolar disorder in a birth cohort of 2 409 236 individuals born in Denmark between 1955 and 1991. Individuals were followed from their sixteenth birthday or from January 1995 to their first clinical contact for bipolar disorder or until December 2012. We calculated incidence rates per 10 000 person-years and tested the effects of prior diagnoses on the risk of bipolar disorder in survival models.

Results

Over 37 394 865 person-years follow-up, 9250 onsets of bipolar disorder occurred. The incidence rate of bipolar disorder was 2.17 (95% CI 2.12–2.19) in individuals with no prior diagnosis of

ADHD or anxiety, 23.86 (95% CI 19.98–27.75) in individuals with a prior diagnosis of ADHD only, 26.05 (95% CI 24.47–27.62) in individuals with a prior diagnosis of anxiety only and 66.16 (95% CI 44.83–87.47) in those with prior diagnoses of both ADHD and anxiety. The combination of ADHD and anxiety increased the risk of bipolar disorder 30-fold (95% CI 21.66–41.40) compared with those with no prior ADHD or anxiety.

Conclusions

Early manifestations of both internalising and externalising psychopathology indicate liability to bipolar disorder. The combination of ADHD and anxiety is associated with a very high risk of bipolar disorder.

Declaration of interest

None.

Keywords

Bipolar disorder; anxiety disorders; attention-deficit/hyperactivity disorder; developmental psychopathology; early identification of risk; internalizing disorders; externalising disorders.

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Rationale for predicting bipolar disorder

Prediction of bipolar disorder is important from clinical and public health perspectives, because bipolar disorder is associated with a high risk of suicide and other adverse outcomes, is often initially misdiagnosed as depression and requires specific treatment different from that for major depressive disorder.¹ In addition, understanding the developmental psychopathology leading to bipolar disorder and the early identification of individuals at risk are essential for the development of early pre-emptive interventions that may prevent the onset of bipolar disorder.^{2,3}

Internalising and externalising psychopathology as antecedent to bipolar disorder

One way of indexing early liability to bipolar disorder is as a combination of externalising and internalising domains of psychopathology. Bipolar disorder manifests with both internalising (depression, anxiety) and externalising (impulsivity, risk-taking) symptoms. It has been proposed that a 'dysregulation' profile characterised by increases in both externalising (for example inattention and hyperactivity) and internalising (for example anxiety) psychopathology may identify youth at high risk for developing bipolar disorder.⁴ The evidence for an association between the dysregulation profile and liability for bipolar disorder has been mixed. Although the dysregulation profile was found in children diagnosed with broadly defined paediatric bipolar disorder⁵ and in offspring of parents with bipolar disorder,⁶ longitudinal studies report inconsistent evidence for an association between a dysregulation profile early

in life and bipolar disorder onset in adulthood.^{7,8} At the level of diagnosed disorders, both internalising (for example anxiety disorders) and externalising (for example attention-deficit hyperactivity disorder (ADHD)) disorders with childhood onset have been proposed to index early manifestations of liability for bipolar disorder.

Anxiety disorders and ADHD as precursors of bipolar disorder

Childhood-onset anxiety disorders are associated with a family history of bipolar disorder^{2,9,10} and have been reported to precede and predict bipolar disorder in familial high-risks studies.¹⁰ The evidence for ADHD being associated with liability for bipolar disorder is less consistent: ADHD is more common among offspring of parents with bipolar disorder⁹ and bipolar disorder is more common in relatives of individuals with ADHD,¹¹ but ADHD did not consistently predict bipolar disorder in longitudinal familial high-risk studies.¹² At present, it is unknown whether the combination of ADHD and anxiety disorders increases the risk of bipolar disorder more than either disorder alone.

Research questions

Prior evidence on whether ADHD and anxiety alone or in combination predict bipolar disorder may be inconsistent because it is limited to familial high-risk samples of moderate size, where the number of prospectively ascertained onsets may not be sufficient to conduct tests with adequate statistical power and existing genetic diathesis may confound the apparent associations.

Additional inconsistencies may have been introduced by mixing of narrowly defined bipolar disorder that typically onsets in late adolescence or adulthood with broader definitions of paediatric bipolar disorder.^{5,8,12,13} Therefore, we aim to test the prospective relationship of prior ADHD and anxiety with onset of bipolar disorder in adulthood in a large representative population sample. Specifically, we tested the hypotheses that (a) prior ADHD predicts adult-onset bipolar disorder; (b) prior anxiety disorders predict adult-onset bipolar disorder; (c) the combination of prior ADHD and prior anxiety diagnoses predicts bipolar disorder more strongly than either disorder alone.

Method

Participants

We conducted a nationwide follow-up study using linked data from the Danish Psychiatric Central Research Register,¹⁴ The Danish National Patient Register¹⁵ and the Danish Civil Registration System.¹⁶ Data were collected on individuals born in Denmark between 1 May 1955 and 31 December 1991. The follow-up-time started on their sixteenth birthday or on 1 January 1995, whichever came later, to ensure follow-up to a minimum age of 21 years. Follow-up ended at date of emigration from Denmark, date of death or 31 December 2012, whichever came first. This provided a minimum follow-up period of 5 years between the ages of 16 to 57 years. The cohort was restricted to individuals with known parents resulting in a total of 2 409 236 individuals. A detailed description of the cohort is available in Supplementary Table 1 available at <https://doi.org/10.1192/bjp.2018.111>.

The present study was completed as part of the iPSYCH project.¹⁷ The procedures have been reviewed and approved by the Scientific Ethics Committee in the Central Denmark Region, which has concluded that the study does not involve risk to participants health or other risk and has approved the use of data for the above analyses without the need to collect informed consent from individual participants. The project has also been approved by the Danish Health Data Authority and the Danish Data Protection Agency.

Data sources

Data on cohort members were obtained by linking three Danish population-based registers. All live-born children and new residents in Denmark since 1968 are assigned a unique personal identification number, which is used across all registration systems enabling perfect linkage. The Danish Civil Registration System contains information on sex, date and place of birth, vital status (continuously updated) and parents' personal identifiers.¹⁶ The Danish National Hospital Registry has recorded all in-patient treatments in Danish hospitals since 1977. This registry has also recorded all out-patient and emergency room contacts from 1995 onward.¹⁵ The Danish Psychiatric Central Research Register covers all psychiatric in-patient facilities since 1969 in addition to out-patient contacts since 1995.¹⁴ For both registers, diagnostic information was based on ICD-8 from 1977 to 1993 and on ICD-10 from 1994 onward.^{18,19} The registered admissions are representative of the entire Danish population because every individual living in Denmark has equal and free access to both somatic and mental healthcare.

Predictors

The main predictor variables were defined as a clinical contact for ADHD or an anxiety disorder (generalised anxiety disorder, panic disorder, agoraphobia, social anxiety disorder, specific phobia,

obsessive-compulsive disorder, post-traumatic stress disorder) at any time from early childhood until the follow-up point. We selected ADHD as a representative externalising disorder because it is the childhood disorder that provides most information about the externalising psychopathology spectrum and because it is primarily defined by externalising symptoms.²⁰ This contrasts with disruptive disorders, such as oppositional-defiant disorder, which are defined by a combination of internalising and externalising symptoms and show developmental continuities with early temperament emotionality and later emotional disorders.^{21–23} We identified all patients diagnosed with ADHD or anxiety disorders using definitions consistent with previous studies, which have established the validity of registry diagnoses of ADHD^{24,25} and anxiety disorders.²⁶ During the follow-up period, the Danish Psychiatric Central Research Register and the Danish National Patient Register consistently used the ICD-10.¹⁹ However, prior to January 1994, these registries used the ICD-8.¹⁸ In order to maximise the capture of childhood-onset diagnoses across a large cohort, we used prior diagnoses of ADHD and anxiety disorders recorded with either ICD-10 or ICD-8 in the primary analyses. Specifically, we identified all patients diagnosed with ADHD (ICD-10: F90; ICD-8: 308.01) and anxiety disorders (ICD-10: F40.00–F41.19, F42.00–F43.10; ICD-8: 300.09, 300.29, 300.39), as described in prior studies.^{24–26} The date of onset was defined as the day of the first recorded clinical contact for the diagnosis in question. Since the diagnostic conceptualisation of ADHD and, to a lesser extent anxiety, changed from the ICD-8 to ICD-10, we also completed sensitivity analyses restricted to diagnoses of ADHD and anxiety disorders recorded with the ICD-10 between January 1994 and December 2012.

Outcome

The outcome variable was defined as the first recorded clinical contact with the diagnosis of a manic episode, hypomanic episode, mixed affective episode or bipolar disorder (ICD-10: F30–F31, F38.00).

Covariates

Information on age (16–20, 21–25, 26–30, 31–35, 36–40, 41–45, 46–50, >50 years), gender, calendar period (1955–1965, 1966–1975, 1976–1985, <1985), maternal and paternal age at time of birth (≤ 20 , 21–25, 26–30, 31–35, <35) were derived from the Danish Civil Registration System.

Censoring

We censored individuals with a diagnosis of autism spectrum disorders because it is not compatible with reliable diagnosis of bipolar disorder. Information on autism spectrum disorders (ICD-8: 299.00–299.03; ICD-10: F84.00–F84.12; F84.50–F84.99) was retrieved from the Danish Psychiatric Central Research Register and the Danish National Patient Register.

Data analysis

The data were examined by survival analysis. Cohort members were followed from their sixteenth birthday or 1 January 1995 until the onset of bipolar disorder, date of death, date of emigration from Denmark, or 31 December 2012, whichever occurred first. The survival time was initiated at age 16 (rather than at the onset of ADHD or anxiety) so that the risk for adult-onset bipolar disorder associated with early- and later-onset precursors is assessed in a comparable fashion.

In incidence analyses, we first determined the risks of bipolar disorder in patients with ADHD or anxiety disorders compared

with the general population, using a log-linear Poisson regression model as implemented in SAS, version 9.4 and adjusted for calendar year, age, gender, parental age at time of birth, and the interaction of age with gender. Age, calendar year and the occurrence of an ADHD or anxiety disorder diagnosis were treated as time dependent variables, whereas all other variables were considered time independent. Analyses with additional adjustment for family history of mental disorder in parents are provided in Supplementary Table 2.

To confirm that the results were not unduly influenced by changes in diagnostic classification, we repeated the main tests in sensitivity analyses with a sample restricted to individuals where all disorders were diagnosed according to ICD-10. All sensitivity analyses were adjusted for calendar year, age, gender, parental age at time of birth, and the interaction of age with gender. Next, following the recommendation that additive risk models are most informative for both population health implications and causal mechanisms,²⁷ we tested whether the risk of bipolar disorder in individuals with prior diagnoses of both ADHD and anxiety differs from the addition of risks conferred by each precursor in isolation, using additive hazards models with the Aalen function through the R package 'timereg'.²⁸ Additional analyses tested the specificity of predictors and outcomes (see Supplementary Tables 2, 3 and 4).

Results

Risk of bipolar disorder

From 1 January 1995 to 31 December 2012 a total of 2 409 236 individuals were included in the study cohort. In 115 571 (4.8%) cohort members, follow-up was ended before the end of the study, because 43 775 died, 67 586 emigrated from Denmark, 1232 were lost to follow-up and 2978 were censored because of an autism diagnosis. Over the remaining 37 394 865 person-years of follow-up, 9250 individuals with bipolar disorder were identified, with a mean age at onset of 33.49 years (s.d. = 9.84). The overall incidence rate of bipolar disorder among individuals aged 16–57 years was 2.47 per

10 000 person-years (95% CI 2.42–2.52). Among individuals with no prior diagnosis of ADHD or anxiety, the incidence rate of bipolar disorder was 2.17 (95% CI 2.12–2.19; Fig. 1).

Prior ADHD and risk of bipolar disorder

There were 13 628 individuals with a prior diagnosis of ADHD. During 66 353 person-years of follow-up of these individuals, 182 new onsets of bipolar disorder were recorded, resulting in an incidence rate of 27.43 per 10 000 person-years (95% CI 23.44–31.41). After excluding individuals with prior anxiety disorders, the incidence rate of bipolar disorder in those with prior ADHD only was 23.86 per 10 000 person-years (95% CI 19.98–27.75; Fig. 1). A prior diagnosis of ADHD increased the incidence of bipolar disorder 11.29-fold (95% CI 9.72–13.03; $P < 0.001$; Table 1) compared with individuals without ADHD. Adjustment for gender, age, interaction of gender and age, calendar year and parental age reduced the incidence rate ratio slightly to 10.00 (95% CI 8.58–11.57; $P < 0.001$). In sensitivity analysis restricted to individuals diagnosed according to ICD-10, 168 new cases of bipolar disorder were recorded among individuals with ICD-10 diagnosis of ADHD resulting in an incidence rate ratio of 11.72 (95% CI 9.99–13.66; $P < 0.001$).

Prior anxiety disorders and risk of bipolar disorder

There were 56 349 individuals diagnosed with one or more anxiety disorders. During 408 358 person-years of follow-up of these individuals, 1086 new cases of bipolar disorder were recorded, resulting in an incidence rate of 26.59 per 10 000 person-years (95% CI 25.01–28.18; Fig. 1). After excluding individuals with prior ADHD, the incidence rate of bipolar disorder in those with prior anxiety only was 26.05 per 10 000 person-years (95% CI 24.47–27.62; Fig. 1). Overall, prior diagnosis of anxiety disorder increased the incidence of bipolar disorder 12.05-fold (95% CI 11.30–12.83; $P < 0.001$; Table 1) compared with individuals without a prior diagnosis of an anxiety disorder. Adjustment for gender, age, interaction of gender and age, calendar year and parental age reduced the incidence rate ratio slightly to 9.61 (95% CI 9.01–10.24; $P < 0.001$). In

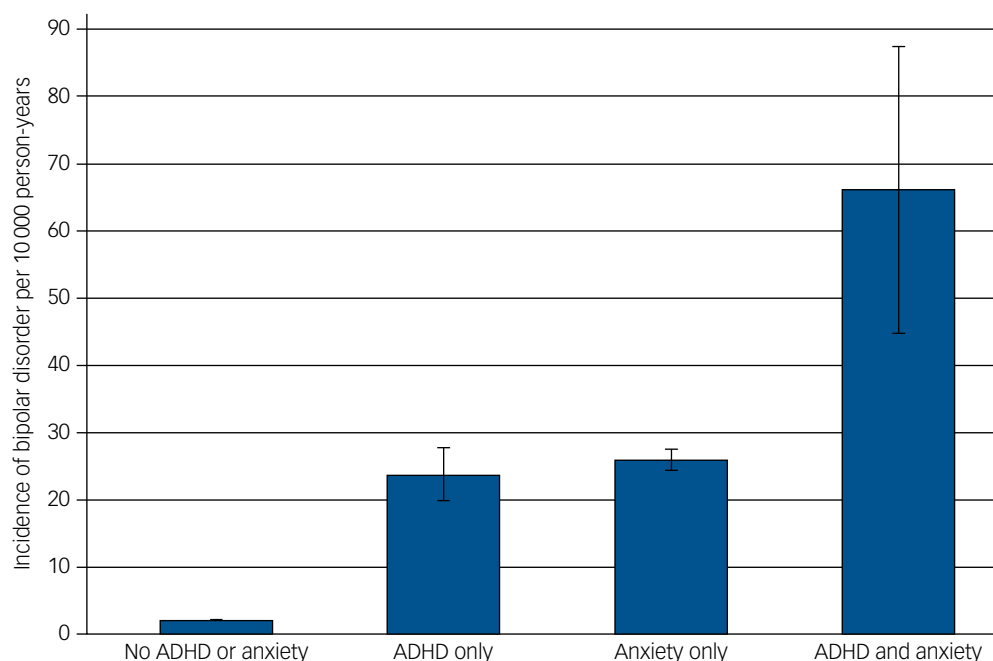


Fig. 1 Incidence rates of bipolar disorder in adults with and without prior diagnoses of attention-deficit hyperactivity disorder (ADHD) and/or anxiety disorders. Error bars indicate 95% CIs.

Table 1 Risk of bipolar disorder associated with prior attention-deficit hyperactivity disorder (ADHD) and anxiety diagnoses (1995–2012)

	Onset of bipolar disorder, <i>n</i>	Incidence rate ratio (IRR)			
		Crude		Adjusted ^a	
		IRR	95% CI	IRR	95% CI
Single diagnosis effects					
ADHD	182	11.29	9.72–13.03	10.00	8.58–11.57
Anxiety disorders	1086	12.05	11.30–12.83	9.61	9.01–10.24
Joint effects					
No ADHD or anxiety disorder	8019	1.00	Reference	1.00	Reference
ADHD only	145	10.99	9.28–12.90	10.13	8.54–11.92
Anxiety disorders only	1049	11.99	11.24–12.78	9.61	9.00–10.25
ADHD and anxiety disorders	37	30.46	21.66–41.40	21.15	15.02–28.78

a. Adjusted IRR are corrected for gender, age, interaction of gender and age, calendar year and parental age. Single diagnosis effects consider one prior diagnosis at a time (i.e. effect of prior diagnosis of ADHD, regardless of whether a diagnosis of anxiety disorder is present or not). Joint effects take into account the presence or absence of both disorders (i.e. ADHD only compares individuals with ADHD and no anxiety disorder to those with neither ADHD nor anxiety disorder).

sensitivity analysis restricted to individuals where both anxiety and bipolar disorders were diagnosed according to ICD-10, there were 1014 new cases of bipolar disorder among individuals with a prior ICD-10 diagnosis of anxiety disorder, resulting in an incidence rate ratio of 9.70 (95% CI 9.07–10.36; $P < 0.001$).

ADHD, anxiety disorders and risk of bipolar disorder

There were 2105 individuals with prior diagnoses of both ADHD and anxiety disorders. During 5593 person-years of follow-up of these individuals, 37 new onsets of bipolar disorder occurred, resulting in an incidence rate of 66.16 per 10 000 person-years (95% CI 44.84–87.47; Fig. 1). The combination of prior diagnoses of ADHD and anxiety disorders increased the risk of bipolar disorder 30.46-fold (95% CI 21.66–41.40; $P < 0.001$; Table 1) compared with those with no prior diagnosis of anxiety or ADHD. After adjustment for gender, age, interaction of gender and age, calendar year and paternal age, the incidence rate ratio was 21.15 (95% CI 15.02–28.78; $P < 0.001$). The risk conferred by a combination of ADHD and anxiety was substantially higher than the risk conferred by either ADHD or anxiety alone. The test of interaction between ADHD and anxiety did not show statistically significant departure from additive risk ($P = 0.103$), suggesting that the risk in those with both prior disorders approximately corresponds to the addition of risks associated with prior ADHD and prior anxiety. In sensitivity analysis restricted to individuals where ADHD, anxiety and bipolar disorders were diagnosed according to ICD-10, the combination of prior ICD-10 diagnoses of ADHD and anxiety disorder resulted in a 22-fold increased risk of bipolar disorder (incidence rate ratio 22.35, 95% CI 15.79–30.54; $P < 0.001$). Additional analyses probed the specificity of associations to ADHD, anxiety disorder and bipolar disorder (Supplementary Tables 2, 3 and 4).

Discussion

Main findings

In a representative national register, we found that prior diagnoses of ADHD and anxiety disorders were associated with similarly increased risk of bipolar disorder. The risk of bipolar disorder increased further in those who received prior diagnoses of both ADHD and anxiety. The results of sensitivity analyses suggested that the findings are robust and were not influenced by changes in mental disorder definitions from ICD-8 to ICD-10. These findings suggest that manifestations of both internalising and externalising psychopathology indicate increased risk of bipolar disorder.

The effect sizes of the associations were substantial: ADHD or anxiety increased the risk of adult-onset bipolar disorder 10-fold and the combination of ADHD and anxiety increased the risk of

adult-onset bipolar disorder 30-fold, compared with those with no prior diagnosis of either ADHD or anxiety. Therefore, the present findings have implications for further research on the aetiology of bipolar disorder and for public health.

We selected ADHD and anxiety as prototypes of externalising and internalising disorders that do not share diagnostic symptoms with bipolar disorder. Unlike oppositional-defiant disorder that has both internalising and externalising components,^{21–23} ADHD is a relatively pure externalising disorder that is tightly linked with the externalising psychopathology spectrum.²⁰ Anxiety disorders frequently co-occur with bipolar disorder,²⁹ but have distinct defining symptoms and clinical course³⁰ and are the prototype of internalising psychopathology.^{31,32} The strong prospective heterotypic associations between both ADHD and anxiety and bipolar disorder suggest that the diathesis for bipolar disorder overlaps with both externalising and internalising psychopathology spectra. This is consistent with the previously proposed dysregulation profile,⁸ the extensive overlaps between genetic risk variants associated with a range of childhood- and adult-onset disorders^{33,34} and with the disproportionately frequent comorbidity of bipolar disorder with anxiety^{29,30} and with ADHD.³⁵ Prospective studies aiming to examine the developmental precursors of bipolar disorder should assess and consider both internalising and externalising psychopathology as potential antecedents. Aetiological research may benefit from a transdiagnostic perspective where bipolar disorder is examined as one of the endpoints of a broad vulnerability to psychopathology.

Implications for clinical practice

Quantification of risk for bipolar disorder in each subgroup is essential to inform public health and clinical decisions. The present registry-based data suggest that a substantial proportion of bipolar disorder onsets are concentrated in a small section of the population. The 10-fold increase in risk of bipolar disorder among individuals with a history of ADHD or anxiety may indicate increased caution, especially after exposure to additional factors that are associated with onset of bipolar disorder. The 30-fold increase in risk of bipolar disorder among those with a history of both ADHD and anxiety may indicate the need for targeted early pre-emptive interventions. The finding of our supplementary analyses (that individuals with a history of both ADHD and anxiety are also at markedly increased risk for schizophrenia in addition to bipolar disorder underline the importance of this group as a potential target for prevention (Supplementary Table 4).

Strengths and limitations

The present study benefits from a large representative nationwide sample, which enables highly generalisable results that are free of

biases associated with research that enrolls individual participants. The results were robust and not unduly influenced by changes in the diagnostic classification system. Yet, our results should be interpreted with two limitations in mind. First, we identified diagnoses of bipolar disorder, ADHD and anxiety from a register that covers in-patient and specialist out-patient care, but not care received through general practitioners. The absence of records of diagnoses from general practitioners may have resulted in an underestimation of the prevalence of mental disorders, in particular ADHD and anxiety disorders. Additionally, separation anxiety disorder is not adequately covered in the registry and could not be included.²⁶ It is also likely that the recorded diagnoses reflect individuals with the more severe cases that tend to be seen in specialist services. Thus, our results may not generalise to milder forms of ADHD and anxiety disorders. However, the sample represents individuals who access services and, therefore, provide opportunities for interventions. It is also possible that individuals with multiple comorbid disorders may be more likely to access secondary care than those with a single disorder. Such differences in help-seeking may have affected the relative proportions of individuals with single disorders *v.* comorbid ADHD and anxiety in our analyses. However, since the vast majority of individuals with bipolar disorder in Denmark receive treatment through secondary care,³⁶ help-seeking behaviour should not have a major impact on the reported relationships with bipolar disorder.

A second limitation is that treatment contact is delayed in most affected individuals. Individuals not yet diagnosed with bipolar disorder might have had early manifestations of a mood disorder that were misclassified as a different diagnosis. We have sought to minimise the risk of misclassification bias by selecting antecedent diagnoses that do not have direct symptom overlap with bipolar disorder and by focusing on onsets of bipolar disorder occurring in late adolescence and adulthood. Therefore, the enhanced risk is unlikely to be because of coexisting untreated bipolar disorder alone.

In conclusion, we have observed that prior diagnoses of ADHD and anxiety disorders are associated with an increased risk of bipolar disorder. The very high risk of bipolar disorder among individuals with a history of both ADHD and anxiety supports the hypothesis that the propensity to bipolar disorder overlaps with both internalising and externalising psychopathology. Individuals with both ADHD and anxiety disorders may be candidates for pre-emptive interventions to reduce the risk of bipolar disorder.

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Supplementary material

Supplementary material is available online at <https://doi.org/10.1192/bjp.2018.111>.

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