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Francisco Diego Rabelo da Ponte

Aspectos neurodesenvolvimentais do Transtorno Bipolar em uma coorte populacional de nascimento.

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Orientador: Prof. Dr. Maurício Kunz
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SUMÁRIO

ABREVIATURAS E SIGLAS

BIOS	Pittsburgh Bipolar Offspring Study
COBY	Course and Outcome of Bipolar Youth
ADHD	Attention deficit hyperactivity disorder
AOR	Adjusted Odds Ratio
AUC	Area under ROC curve
BD-NOS	BD not otherwise specified
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders version IV
GAD	Generalized Anxiety Disorder
IA	Inteligência Artificial
IQ	Intelligence quotient
LASSO	Least Absolute Shrinkage and Selector Operator
MINI	Mini-International Neuropsychiatric Interview
ML	Machine Learning
OR	Odds Ratio
PNV	Predictive negative value
PPV	Predictive positive value
QI	Quociente de Inteligência
ROSE	Random over sampling examples
SDQ	Strengths and Difficulties Questionnaire
SHS	Subjective Happiness Scale

SRQ-20	Self-Reporting Questionnaire
TB	Transtorno Bipolar
TB-I	Transtorno Bipolar tipo I
TB-II	Transtorno Bipolar tipo II
TDAH	Transtorno de Déficit de Atenção e Hiperatividade
TDM	Transtorno Depressivo Maior
WAIS-III	Wechsler's Adult Intelligence Scale
WHOQOL	World Health Organization Quality of Life scale

RESUMO

Mundialmente, o Transtorno Bipolar (TB) é sexta causa de incapacidade. Entre os primeiros sintomas de humor e o diagnóstico formal, as pessoas com TB demoram cerca de seis anos para receber o tratamento adequado. Assim, objetivou-se desenvolver um modelo preditivo de indivíduos que desenvolverão TB aos 22 anos de idade usando algoritmos de inteligência artificial (*machine learning*). Foram acompanhadas 3.748 pessoas ao nascer e aos 11, 15, 18 e 22 anos de idade em uma coorte de nascimentos da cidade de Pelotas, RS, Brasil. Utilizou-se o algoritmo *elastic net* com *10-fold cross-validation* para predizer quais indivíduos desenvolverão TB aos 22 anos de idade,usando as variáveis coletadas do nascimento até aos 18 anos de idade. Posteriormente, foi desenvolvido um modelo de estratificação de risco de pessoas com TB. Um total de 107 (2,8%) indivíduos foi diagnosticado com TB tipo I (TB-I), 26 (0.6%) participantes com o tipo II (TB-II) e 87 (2,3%) pessoas com o tipo não-especificado. O modelo comas variáveis coletadas aos 18 anos de idade foi o que alcançou melhores medidas de desempenho: área sob a curva ROC (AUC) de 0,82 (95% IC, 0,75– 0,88), acurácia balanceada de 0,75, sensibilidade de 0,72 e especificidade de 0,77. As variáveis mais importantes foram risco de suicídio, transtorno de ansiedade generalizada e abuso físico parental. Além disso, o subgrupo com alto risco para TB apresentou uma alta freqüência para consumo de drogas e sintomas depressivos. A detecção precoce de TB usando variáveis clínicas e sociodemográficas pode ser clinicamente relevante para intervir precocemente e prevenir o curso pernicioso do transtorno.

O quociente de inteligência (QI) e o número de reprovações escolares podem ser importantes marcadores clínicos de neurodesenvolvimento para identificação do TB e essa associação permanece controversa na literatura. Objetivou-se identificar o QI e o número de reprovações escolares como fatores de risco para TB antes do diagnóstico formal em um estudo de coorte de nascimentos. Foi incluído 3580 participantes do estudo de coorte de nascimentos de base populacional de Pelotas na coleta de dados aos 22 anos e, na coleta anterior, nenhum sujeito deveria ter diagnóstico prévio de transtorno de humor. Foi realizado modelos de regressão controlando potenciais confundidores para avaliar o impacto do QI e do número de reprovações escolares obtido aos 18 anos em um diagnóstico subsequente de TB e Transtorno Depressivo Maior (TDM) aos 22 anos, comparando indivíduos sem transtornos de humor como comparadores. Encontrou-se que ter um QI baixo e limítrofe (abaixo de 70) aos 18 anos foi um marcador de risco para participantes com TB (Razão de Chance Ajustado [AOR] 1,75, IC 95%: 1,00–3,09, p<0,05) e QI superior (acima de 120) para indivíduos com TDM (AOR 2,16, IC 95%: 1,24–3,75, p<0,001). O número de reprovações escolares aumentou o risco de TB (AOR 1,23, IC 95%: 1,11–1,41, p<0,001), mas não paraindivíduos com TDM. O número de reprovações escolares foi um significativo marcador para TB-I (AOR 1,36, IC 95%: 1,17–1,58, p<0,001), porém não em indivíduos com TB-II ou sem transtorno de humor. Os resultados sugerem o TB tem um desempenho intelectual pré-mórbido característico. Estes achados podem contribuir paraa compreensão da fisiopatologia do TB e seu curso neurodesenvolvimental, auxiliando no desenvolvimento de ferramentas para sua detecção precoce.

Palavras-chave: transtorno bipolar, machine learning, inteligência artificial, coorte, estudo longitudinal, cognição, neurodesenvolvimento.

ABSTRACT

Bipolar Disorder (BD) is the sixth leading cause of disability worldwide. It takes about six years for people with BD to receive adequate treatment. Thus, the objective was to develop a predictive model of individuals who will develop BD at 22 years of age using data from a birth cohort through machine learning algorithms. A total of 3,748 participants were followed at birth and 11, 15, 18, and 22 years of age. The elastic net algorithm with 10-fold cross-validation was used to predict which individuals willdevelop BD at 22 years of age, using variables collected from birth to age of 18 years. Subsequently, a risk stratification model for subjects with BD was developed. A total of 107 (2.8%) individuals were diagnosed with BD type I (BD-I), 26 (0.6%) participants with type II (BD-II), and 87 (2.3%) people with type not otherwise specified. The model with the variables collected at 18 years of age was the one that achieved the best performance measures: area under the ROC curve (AUC) of 0.82 (95% CI, 0.75–0.88), balanced accuracy of 0.75, sensitivity of 0.72, and specificity of 0.77. The most important variables were suicide risk, generalized anxiety disorder, and parental physical abuse. In addition, the subgroup at high risk for TB had a high frequency of drug use and depressive symptoms. Early detection of TB utilizing clinical and sociodemographic variables may be clinically relevant to intervene early and preventthe pernicious course of the disorder.

The intelligence quotient (IQ) and the number of school failures may be important clinical neurodevelopmental markers for identifying BD. This association remains controversial in the literature. The objective was to identify IQ and the number of school failures as risk factors for BD before formal diagnosis in a birth cohort study. A total of 3580 participants from the Pelotas population-based birth cohort study were included in the data collection at the age of 22 years, and no subject should have had a previous diagnosis of mood disorder in a previous follow-up visit. Regression models controlling for potential confounders were performed to assess the impact of IQ and the number of school failures obtained at age 18 on a diagnosis of BD and Major Depressive Disorder (MDD) at age 22, comparing individuals without mood disorders. Having a low and borderline IQ (below 70) at age 18 was a risk marker for participants with BD (Adjusted Odds Ratio [AOR] 1.75, 95% CI: 1.00–3.09, $p<0.05$) and higher IQ (above 120) for individuals with MDD (AOR 2.16, 95% CI: 1.24–3.75, $p<0.001$). The number of school failures increased the risk for BD (AOR 1.23, 95% CI: 1.11–1.41, $p<0.001$), but not for individuals with MDD. The number of school failures was a significant marker for BD-I (AOR 1.36, 95% CI: 1.17–1.58, $p<0.001$), but not inindividuals with BD-II or without a mood disorder. The results suggest that BD has a characteristic premorbid intellectual performance. These findings may contribute to understanding the pathophysiology of BD and its neurodevelopmental course, aiding in developing tools for early detection.
Keywords: bipolar disorder, machine learning, artificial intelligence, cohort, longitudinal study, neurodevelopment, cognition.

1. APRESENTAÇÃO

Essa tese de doutorado intitulada "**Aspectos neurodesenvolvimentais no Transtorno Bipolar em uma coorte populacional de nascimento**", sendo apresentada ao Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento da Universidade Federal do Rio Grande do Sul na data de 20 de maio de 2022. Os estudos executados nesta tese fazem parte da coorte de nascimentos de 1993 realizados na cidade de Pelotas pelo Centro de Epidemiologia e pelo Programa de Pós-Graduação em Epidemiologia da Universidade Federal de Pelotas. Todas as pessoas nascidas desde o primeiro dia até último dia de 1993, moradoras da zona urbana de Pelotas, foram convidadas a participar do estudo epidemiológico chamado de Coorte de 1993. Essa é a segunda coorte realizada pelo Centro de Epidemiologia, sendo a primeira iniciada em 1982. O objetivo na realização da coorte de 1993 era compará-la com a Coorte de 1982. A Coorte de 1993 identificou 5.249 recém-nascidos vivos e são acompanhados em cinco diferentes ondas: nascimento, 11 anos, 15 anos, 18 anos e 22 anos de idade. Há outras ondas que coletaram informações de grupos específicos. Porém, nessa tese, focou-se nas ondas em que se avaliaram toda a população.

A motivação inicial para o desenvolvimento desta tese surgiu a partir do interesse em detectar o Transtorno Bipolar precocemente, isto é, antes do diagnóstico formal, já que há uma dificuldade no diagnóstico acurado de pessoas com TB, levando anos do primeiro episódio de humor até receber o tratamento adequado. Além disso, decidiu-se avaliar o funcionamento intelectual das pessoas com Transtorno Bipolar antes do seu primeiro episódio de humor. Os estudos até então são inconclusivos em relação ao funcionamento intelectual pré-mórbido do Transtorno Bipolar. É clinicamente relevante compreender esse aspecto, uma vez que ao entender o curso cognitivo longitudinal do transtorno, propor intervenções de reabilitação neuropsicológica ou o desenvolvimento de fármacos que tenham eficácia na cognição após o primeiro episódio de humor.

Desse modo, o primeiro estudo intitulado "**Early identification of bipolar disorder among young adults – a 22 year community birth cohort**" publicado na *Acta Psychiatrica Scandinavica* consistiu no construção de um modelo de *machine learning* para identificar precocemente pessoas que desenvolverão Transtorno Bipolar. Para isso, utilizamos um algortimo chamado *elastic net* para predizer quem desenvolverá Transtorno Bipolar aos 22 anos de idade, usando informações clínicas e sociodemográficas do nascimento até aos 18 anos de idade. Além disso, excluímos os sujeitos que tiveram esse diagnóstico em etapas anteriores. Posteriormente, estratificamos os sujeitos em alto e baixo risco de terem

Transtorno Bipolar e analisamos suas diferenças clínicas.

O segundo estudo é chamado **“Premorbid intelligence quotient and school failure as risk markers for bipolar disorder and major depressive disorder”** submetido na *Psychological Medicine.* Esse artigo tem como objetivo avaliar o funcionamento intelectual - Quoeficiente de Inteligência (QI) - e o número de repetência escolar em pessoas com Transtorno Bipolar antes do diagnóstico formal aos 22 anos de idade, comparando-os com indivíduos com Transtorno Depressivo Maior e pessoas sem transtornos de humor.

Esta tese está organizada em onze partes. A primeira parte possui uma breve descrição epidemiológica do Transtorno Bipolar. Em seguida, há uma descrição dos aspectos longitudinais do Transtorno Bipolar antes do primeiro episódio de humor, tratando sobre os diferentes modelos desenvolvimentais deste transtorno em estudos longitudinais de *ultra high risk samples*, bem como abordando a fenomenologia do Transtorno Bipolar após o primeiro episódio de humor, incluindo os modelos de neuroprogressão. A terceira parte versa sobre como é o funcionamento intelectual de pessoas com Transtorno Bipolar antes do primeiro episódio usando as evidências dediversos estudos longitudinais. A quarta seção refere-se sobre o que é inteligência artificial, *machine learning*, modelos supervisionados e não-supervisionados e como essa tecnologia vem sendo aplicada na pesquisa sobre Transtorno Bipolar. A quinta, sexta e sétima seção da tese conta com a Justificativa, Objetivos e Considerações Éticas desta tese respectivamente. Na sétima seção, há os artigos científicos na íntegra derivados da tese: Artigo 1 (Rabelo-da-Ponte et al., 2020, publicado no *Acta Psychiatrica Scandinavica*) e o Artigo 2 submetido no *Psychological Medicine*. Na oitava seção chamada “Prêmios e editais”, consta os prêmios recebidos durante o doutorado bem como o nome do órgão financiador da União Européia do estágio de doutorado no exterior. Na unidade seguinte, ésobre as atividade de divulgação científica envolvendo as pesquisas relacionadas a essatese e outras atividades de pesquisa desenvolvidas durante o período de doutorado. Por fim, na décima primeia seção, consta as considerações finais desse trabalho de doutorado.

2. INTRODUÇÃO

O Transtorno Bipolar (TB) é um transtorno de humor, crônico, grave e incapacitante, sendoa sexta causa de incapacidade no mundo entre os jovens adultos(Vieta *et al.*, 2018). O TB afeta mais que 1% da população global, cuja prevalência ao longo da vida é de 0,6% para TB tipo I (TB-I), 0,4% para TB tipo II, 1,4% a 2,4% para outras manifestações sub-limiares do TB (Vieta *et al.*, 2018). O surgimento do TB não dependede etnia, classe socioeconômica ou nacionalidade (Vieta *et al.*, 2018). Ao contrário, o histórico familiar de TB é um robusto fator de risco para o desenvolvimento do transtorno,pois possui uma taxa de herdabilidade que varia de ~23% a ~70%, dependendo do delineamento do estudo(Craddock e Jones, 2019; Zhang *et al.*, 2021). A prevalência de TBao longo da vida entre familiares em primeiro grau com TB é de 5 a 10% entre familiares de primeiro grau e de 40 a 70% entre gêmeos monozigóticos (Zhang *et al.*, 2021). Esses achados se mantém estáveis quando se compara a prevalência entre irmão monozigóticos eheterozigóticos, cujos primeiros apresentam maior concordância diagnóstica com TB em relação ao segundo(Zhang *et al.*, 2021). Em uma coorte de famílias, encontrou-se que há uma diferença na chance no desenvolvimento do TB tipo I e tipo II (TB-II), sugerindo que podem ter etiologias distintas (Song *et al.*, 2018). Nesse estudo, a chance de desenvolver TB-I foi de 17% se a pessoa tem um familiar de primeiro grau com TB-I, já a chance de TB-II foi maior que 13% se a pessoa tem um familiar de primeiro grau com TB-II (Song*et al.*, 2018).

O TB é caracterizado por episódios depressivos, maníacos ou mistos que impactam a capacidade da pessoa em realizar suas atividades cotidianas(WHO, World Health Organization e WHO Staff, 1992). As pessoas com TB podem apresentar períodos de completa remissão sintomatológica quando recebem tratamento adequado, mas há casos de pacientes resistentes ao tratamento com sintomas residuais e persistentes que dificultam a sua completa recuperação funcional(Vieta *et al.*, 2018). Entretanto, a prevalência de TB resistente ao tratamento permanece imprecisa, uma vez que carece um consenso sobre sua terminologia(Fornaro *et al.*, 2020). Sabe-se que cerca de 40% das pessoas com depressão bipolar não respondem à quetiapina após oito semanas do início do tratamento. O TB resistente ao tratamento está associado a altas taxas de morbidade, tentativas de suicídio e número de hospitalizações(Fornaro *et al.*, 2016, 2020). Uma recente meta-análise sugere algumas intervenções para TB resistente ao tratamento como pramipexol, eletroconvulsoterapia e clozapina, mas aponta para a necessidade de ensaios clínicos baseados nesse subgrupo bem como um consenso da comunidade científica na definição e critérios para TB resistente ao tratamento(Fornaro *et al.*, 2020).

3. CURSO DESENVOLVIMENTAL DO TRANSTORNO BIPOLAR

Além dos sintomas de humor descritos na seção anterior, muitos sujeitos com TB apresentam prejuízos cognitivos significativos mesmo em períodos eutímicos (sem sintomas agudos de humor). O prejuízo cognitivo e os recorrentes episódios de humor podem afetar significativamente a funcionalidade e qualidade de vida dos indivíduos com TB, sobrecarregando também a família e seus cuidadores(Oldis *et al.*, 2016). Uma recente coorte com 1 902 792 participantes apontou que pessoas com transtornos de humor,especialmente TB, apresentavam maiores riscos de incapacidade precoce quando comparados com participantes sem transtornos mentais(Frey *et al.*, 2020). Além disso, as pessoas acometidas pelo TB apresentam até 20 vezes mais chance de suicídio em relação à população geral(Gonda *et al.*, 2012). E, infelizmente, cerca de 20% de todas as tentativasde suicídio são letais entre pessoas com TB(Gonda *et al.*, 2012). Uma recente meta-análise com 50.004 sujeitos com TB mostrou que sexo feminino, polaridade depressiva atual ou recente, comorbidade com Transtorno de Personalidade Borderline, comorbidade comtranstornos ansiosos e uso de substâncias ilícitas foram os mais importantes fatores de riscopara tentativa de suicídio nessa população(Schaffer *et al.*, 2015). Enquanto, sexo masculino e histórico familiar de primeiro grau de tentativa de suicídio foi associado à morte por suicídio (Schaffer *et al.*, 2015).

Os prejuízos cognitivos possuem um importante papel na baixa qualidade de vida das pessoas com TB, já que prejuízos persistentes na memória e funções executivas estão associados à desfavoráveis desfechos ocupacionais, menor qualidade de vida e elevado níveis de estresse(Jensen *et al.*, 2016). Os sintomas residuais também exercem um relevante impacto na qualidade de vida de pessoas com TB, especialmente os sintomas depressivos residuais mais que os sintomas maníacos e/ou hipomaníacos (Michalak *et al.*, 2008). Como sugerido por uma meta-análise com uma amostra de mais de 6000 participantes, encontrou que os prejuízos cognitivos possuem um maior tamanho de efeito em desfechos de funcionalidade que os sintomas psiquiátricos e fatores sociodemográficos,sugerindo que seria clinicamente relevante o desenvolvimento de intervenções de reabilitação neuropsicológicas como uma das estratégias para melhorar a funcionalidade depessoas com TB(Tse *et al.*, 2014).

Para compreender melhor o curso longitudinal do transtorno, é importante que o clínico tenha em mente que o TB inicia em torno dos 20 anos de idade e, geralmente, começa com sintomas depressivos(Vieta *et al.*, 2018). A início precoce do transtorno e o tratamento tardio estão ligado à presença de maior número de comorbidades clínicas, maior refratariedade ao tratamento e maiores chances de tentativa de suicídio(Schaffer *et al.*, 2015). Sujeitos com TB demoram cerca de seis anos entre os primeiros sintomas e o diagnóstico formal bem como somente 20% dos indivíduos com TB em episódio depressivo são diagnosticados corretamente durante o primeiro ano de tratamento (Dagani *et al.*, 2017). Esse atraso no diagnóstico pode impactar severamente o curso da doença, já que pode aumentar as chances de novos episódios de humor, diminuir a funcionalidade e diminuir o intervalo inter-episódio(Passos *et al.*, 2016).

O diagnóstico adequado é uma tarefa bastante árdua para os clínicos, uma vez que esse transtorno apresenta uma trajetória heterotípica e complexa. Duffy *et al.*(2017) propôs um modelo longitudinal sobre o curso desenvolvimental do TB(Duffy *et al.*, 2017). No estágio um, a pessoa apresenta sintomas de ansiedade, problemas de sono, dificuldadesde aprendizado e Transtorno de Déficit de Atenção e Hiperatividade (TDAH). No estágio dois, são comuns sintomas depressivos inespecíficos (ex. apatia, anedonia), distimia, ciclotimia. Já o estágio três é caracterizado pela presença de Transtorno Depressivo Maior (TDM) com episódio único ou recorrente, alterações cognitivas, sintomas psicóticos e início do declínio funcional. Por fim, no estágio quatro, há a presença dos primeiros episódios maníacos, hipomaníacos e/ou psicóticos. Recentes achados de coortes de filhos de pessoas com TB dão robustez à idéia de que estes estágios apresentam uma transição progressiva de sintomas psicopatológicos inespecíficos (estágio um e dois) aos episódios do TDM (estágio três) e, por sua vez, aos episódios maníacos ou psicóticos (episódio quatro)(Duffy *et al.*, 2014). Ademais, o uso de substâncias psicoativas durante a adolescência poderia levar a piores desfechos clínicos(Duffy *et al.*, 2014). Outro importante achado desses estudos de coorte é que os filhos de pessoas com TB não- respondendores ao lítio possuem um quadro clínico severo com mais sintomas psicóticos emaior gravidade dos sintomas de humor, ao contrário do que ocorre com filhos de pessoas com TB respondendores ao lítio(Duffy *et al.*, 2014). Além disso, os transtornos neurodesenvolvimentais são mais comuns desde o estágio um dos filhos de pessoas com TB não-respondendores ao lítio que nos filhos dos respondedores(Duffy *et al.*, 2017).

Dados de outras coortes de filhos de sujeitos com TB como a *Pittsburgh Bipolar Offspring Study* (BIOS) e *Course and Outcome of Bipolar Youth* (COBY) apontam também para uma trajetória heterotípica do TB, apresentando sintomas psiquiátricos prévios desde a infância e adolescência antes do surgimento do transtorno(Axelson *et al.*, 2015; Goldstein *et al.*, 2010). Antes do diagnóstico formal, esses sujeitos em alto risco (filhos de pais com TB) apresentaram elevada prevalência de transtornos de ansiedade, transtornos disruptivos do comportamento, TDAH e transtorno por uso de substâncias quando comparado à amostra comunitária(Axelson *et al.*, 2015; Goldstein *et al.*, 2010; Hafeman *et al.*, 2016). Ademais, houve também maior incidência de episódios maníacos ou hipomania entre os sujeitos em alto risco (Axelson *et al.*, 2015).

Outro importante achado que corrobora com a perspectiva de um curso neurodesenvolvimental no TB é que, de acordo com uma meta-análise, filhos de pessoas com TB e seus irmãos possuem uma maior prevalência de TDAH (16.4%) que em controles (5.1%)(Lau *et al.*, 2018). Filhos em alto risco para TB têm mais de duas vezes o risco de desenvolvimento de TDAH comparado ao grupo controle(Lau *et al.*, 2018). Seguindo a mesma ideia, outra meta-análise aponta que filhos de pessoas com TB possuem alto risco para o desenvolvimento do Transtorno do Espectro Autista(Ayano, Maravilla e Alati, 2019). Em um estudo longitudinal, mostrou-se que o risco de esquizofrenia foi mais de duas vezes maior entre irmãos de pacientes com TB- I, mas não entre irmãos com TB-II(Song *et al.*, 2018). O TDAH, Transtorno do Espectro Autista e Esquizofrenia são transtornos com relevantes aspectos neurodesenvolvimentais e suasassociações com TB levam à hipótese que este compartilha de janelas de vulnerabilidade no desenvolvimento e similares bases fisiopatológicas com os transtornos citados(Kloiber *et al.*, 2020).

Assim, as atuais evidências científicas apontam que os fatores neurodesenvolvimentais no TB são mais robustos em sujeitos com sintomas psicóticos e entre aqueles com início precoce dos sintomas de humor(Kloiber *et al.*, 2020). Uma revisão sistemática indicou que fatores neurodesenvolvimentais como exposição à influenza são específicos para TB-I com sintomas psicóticos, compartilhando os mesmos fatores já conhecidos na esquizofrenia(Marangoni, Hernandez e Faedda, 2016). Isso corrobora com a ideia de que a ativação imune materna devido às infecções durante o período pré-natal pode aumentar o risco de TB em até quatro vezes como mostrou em um estudo de caso-controle aninhado de uma coorte de nascimento(Parboosing *et al.*, 2013).

Além disso, pessoas com TB de início precoce possuem menor desempenho cognitivo, reduzida substância cinzenta frontal no seu primeiro episódio quando comparado com pessoas sem transtornos mentais(Arango, Fraguas e Parellada, 2014). Uma revisão sistemática identificou três diferentes grupos em relação aos fatores de risco ambientais para o TB: 1) desenvolvimental como indicadores de desenvolvimento fetal e/ou gripe durante a gestação; 2) presença de estresse físico e/ou psicológico como morte dos pais, abuso infantil, lesões cerebrais; 3) uso de substâncias incluindo cannabis, cocainae outros tipos de drogas (Marangoni, Hernandez e Faedda, 2016).

O uso de substância é comumente precedido ao início dos episódios de humor no TB(Marangoni, Hernandez e Faedda, 2016). O uso de cannabis é relatado como um fator de risco em mais de 55% dos estudos incluídos em uma revisão sistemática(Lalli *et al.*, 2021). Em um estudo longitudinal, o uso de cocaína ao longo da vida aumentou o risco de desenvolvimento de TB em mais de três vezes(Azevedo Cardoso, de *et al.*, 2020). O uso de substâncias também está associado com uma aceleração do curso do TB após os seus primeiros episódios de humor, uma vez que o uso de álcool e cannabis têm sido associados com piores desfechos clínicos como menor taxa de remissão, maior severidade dos episódios de humor e prejuízos funcionais(Bahorik, Newhill e Eack, 2013; Kim *et al.*, 2015).

A partir dessas evidências, foi proposto modelos de estadiamento do TB após o seu diagnóstico com o objetivo de identificar marcadores que possam indicar piores desfechos clínicos, funcionais e cognitivos. Dentre eles, o mais reconhecido é o modelo de neuroprogressão de Kapczinski *et al.*(2009). O modelo de neuroprogressão teve influência do conceito de carga alostática (*allostatic load*) que foi aplicado ao TB(Salagre *et al.*, 2018). Carga alostática consiste na incapacidade de um organismo manter suas funções fisiológicas estáveis devido aos diversos insultos sofridos, alterando toda a fisiologia do organismo(DuBow, Melun e Juster, 2021). Dessa forma, cada estágio do TB seria caracterizado por alterações fisiológicas, clínicas, funcionais e cognitivas, sendo a exposição ao trauma, número de episódios e uso de drogas responsáveis por diminuir o intervalo entre os episódios, aumenta a duração dos episódios e leva à refratariedade ao tratamento(Costa, da *et al.*, 2016). O modelo de neuroprogressão consiste em quatro fases. A primeira é chamada de fase latente, cujas principais características são histórico familiarde TB e sintomas inespecíficos de ansiedade e depressão. No estágio I, o paciente apresenta episódios de humor bem definidos. No estágio II, há sintomas residuais entre os episódios e a presença de outras comorbidades. No estágio III, os indivíduos com TB já apresentam graves prejuízos cognitivos e funcionais, maior número de episódios com menor intervalo entre eles (Salagre *et al.*, 2018). No estágio IV, os sujeitos apresentam um grave prejuízo funcional e cognitivo que os incapacita de viverautonomamente(Kapczinski *et al.*, 2009).

O número de episódios de humor, especialmente, os de mania, é considerado um relevante fator associado à progressão no TB, pois está relacionado à pior prejuízo cognitivo em diversas funções neuropsicológicas como atenção, memória verbal, velocidade de processamento(Cardoso *et al.*, 2015). Têm-se demonstrado que a duração dadoença e o número de hospitalizações estão relacionados com desfavoráveis desfechos cognitivos e funcionais(Bearden *et al.*, 2006; Cardoso *et al.*, 2015; Y.w. *et al.*, 2013). Da mesma forma, idade de início também está relacionado negativamente com desempenho em testes de atenção sustentada, memória verbal e velocidade psicomotora(Ancín *et al.*, 2010; Bora *et al.*, 2007). Uma revisão sistemática avaliando a evolução das disfunções neuropsicológicas em sujeitos com TB sugere que as alterações cognitivas no TB podem ser consideradas elementos centrais na fisiopatologia e sintomatologia do transtorno, propondo que, a cada episódio de humor, as alterações neurocognitivas se intensificam e podem ser permanentes ao contrário das anteriores evidências a respeito das disfunções neuropsicológicas no TB serem consideradas humor-dependentes (Lewandowski, Cohen e Ongur, 2011).

Entretanto, o prejuízo cognitivo no TB após o primeiro episódio de humor e/ou psicótico parece não ser homogêneo. Estudos transversais utilizando algoritmos de clusterização para identificar subgrupos cognitivos encontrou que há, em geral, três *clusters* cognitivos com distintas funções neuropsicológicas alteradas(Burdick *et al.*, 2014;Lima *et al.*, 2019; Rabelo-da-Ponte *et al.*, 2020; Van Rheenen *et al.*, 2017). O primeiro subgrupo consta de sujeitos sem nenhuma alteração cognitiva com desempenho neuropsicológico similares às pessoas sem transtornos mentais(Burdick *et al.*, 2014; Lima *et al.*, 2019; Rabelo-da-Ponte *et al.*, 2020; Van Rheenen *et al.*, 2017). O segundo engloba os sujeitos com prejuízos cognitivos moderados em alguns domínios cognitivos e emoutras funções cognitivas não apresentam nenhuma alteração(Burdick *et al.*, 2014; Lima *etal.*, 2019; Rabelo-da-Ponte *et al.*, 2020; Van Rheenen *et al.*, 2017). Os domínios podem estar moderadamente alterados a depender do estudo, porém o grupo moderadamente prejudicado tende a ser qualitativamente similar entre os estudos(Burdick *et al.*, 2014; Lima *et al.*, 2019; Rabelo-da-Ponte *et al.*, 2020; Van Rheenen *et al.*, 2017). Por fim, há o grupo com danos cognitivos severos, isto é, com pobre desempenho cognitivo em todos os domínios neuropsicológicos(Burdick *et al.*, 2014; Lima *et al.*, 2019; Rabelo-da-Ponte *etal.*, 2020; Van Rheenen *et al.*, 2017). Os sujeitos do grupo severamente prejudicado apresenta desempenho cognitivo similar às pessoas com esquizofrenia como demonstrado em um estudo transversal comparando diferentes subgrupos cognitivos de TB e pessoas com esquizofrenia(Burdick *et al.*, 2014). O cluster globalmente prejudicado possuia um maior prejuízo funcional comparado àqueles do grupo intacto (Burdick *et al.*, 2014). Outroestudo transversal usando dados neuropsicológicos de pessoas com TB e esquizofrenia também apontou para a existência de heterogêneos grupos cognitivos no TB e que há pessoas com TB que compartilham elementos cognitivos entre indivíduos com esquizofrenia(Lee *et al.*, 2017).

Tais achados sugerem que os número de episódios, trauma infantil, episódios psicóticos e idade de início podem aumentam a vulnerabilidade da pessoa aos estressores psicológicos, impactando no funcionamento cerebral e, consequentemente, levando a piores desfechos cognitivos, disfuncionalidade psicossocial, reduzido intervalo inter- episódios, refratariedade ao tratamento, pior qualidade de vida e maiores taxas de hospitalização(Cardoso *et al.*, 2015; Passos *et al.*, 2016). Estas evidências corroboram com a hipótese de neuroprogressão no TB, todavia, nem todos os pacientes apresentarão esses desfechos desfavoráveis, enquanto outros já possuem piores desfechos desde o primeiro episódio de humor (Passos *et al.*, 2016). Alguns autores sugerem que apenas um subgrupo de sujeitos com TB desenvolverão um curso neuroprogressivo como descrito anteriormente(Passos *et al.*, 2016). Dessa maneira, a identificação daqueles que desenvolverão um curso neuroprogressivo seria clinicamente relevante ou a identificação precoce antes do primeiro episódio de humor, haja vista que seria possível desenvolver intervenções clínicas que possam retardar ou reverter determinados desfechos clínicos desfavoráveis.

4. FUNCIONAMENTO INTELECTUAL PRÉ-MÓRBIDO DO TRANSTORNO BIPOLAR

Popularmente, há uma concepção de que pessoas com TB tendem a serem gênios e que os sintomas de mania poderiam auxiliar os processos cognitivos relacionados à criatividade, facilitando suas habilidades como pintura, literatura e música(Duke e Hochman, 1992). Ademais, há uma glamourização acerca do TB e suas altas capacidades artísticas e intelectuais, uma vez que há celebridades com esse transtorno de humor(Johnson *et al.*, 2012). Porém, essas informações são anedóticas, baseando-se em avaliações retrospectivas, amostras pequenas e usando fontes secundárias o queenfraquece a validade científica de tais evidências por causa do viés de seleção(Poole, 2003).

Para investigar a associação entre inteligência e TB, a melhor forma seria utilizando testes cognitivos validados como os testes de Quociente de Inteligência(QI). A partir de uma bateria de testes cognitivos, é possivel obter um valor que expressa a habilidade cognitiva de um sujeito comum a sua faixa etária(Anastasi e Urbina, 1998). Outra forma para avaliar inteligência é através do desempenho escolar como relatado em um estudo longitudinal com 900.000 homens na Suécia que avaliou desempenho escolar aos 16 anos de idade como risco para o desenvolvimento de TB na vida adulta(MacCabe *et al.*, 2010). Os autores concluíram que uma baixa *performance* escolar é um fator de risco para desenvolver esquizofrenia na vida adulta(MacCabe *et al.*, 2010). Entretanto, entre osindividuos com TB, a distribuição das notas escolares e o risco de desenvolvimento de TB possui um padrão de forma em U, ou seja, tanto altas quanto baixas notas escolares aumentaram o risco para TB(MacCabe *et al.*, 2010). Esses achados possuem certas limitações, uma vez que, apenas homens foram recrutados para o estudo, não houve nenhuma medida de QI bem como avaliaram apenas aqueles que foram hospitalizados por episódio maníaco ou psicótico (MacCabe *et al.*, 2010). Assim, não incluíram pessoas com episódios hipomaníacos ou os que tiveram episódios maníacos sem hospitalização e, o mais importante epidemiologicamente, não houve mulheres no estudo. É uma importante limitação, pois a prevalência de TB-II é maior em mulheres que em homens e a prevalência de TB-I é igual entre os gêneros apesar de alguns dados controversos(Diflorio e Jones, 2010; Miller *et al.*, 2015). Também, clinicamente, mulheres têm mais episódios depressivos e mistos que podem contribuir com o atraso no diagnóstico(Diflorio e Jones, 2010; Miller *et al.*, 2015).

Corroborando com esses achados dessa coorte sueca, um estudo longitudinal com 1.049.607 homens evidenciou uma associação entre menor IQ e o risco de hospitalização por mania como também homens com altos escores nos testes de QI (Gale *et al.*, 2013). Essa associação em formato de U é mais evidente nos testes de habilidades verbais (Gale *et al.*, 2013). Um alto desempenho em testes de habilidades verbais aumentou significativamente em 41% o risco de hospitalização por mania e um pior desempenho aumentou o seu risco em 34%(Gale *et al.*, 2013). Os resultados de uma outa coorte sueca de registros hospitalares mostrou uma associação entre desempenho escolar e TB-I, porémessa associação foi maior entre pessoas com esquizofrenia(Kendler *et al.*, 2016). Nesse mesmo estudo, verificou-se que há uma diferença entre sexo entre desempenho escolar e TB-I, uma vez que essa associação foi mais evidente entre as mulheres que entre os homens(Kendler *et al.*, 2016). Entre os homens, a distribuição desses dados foi muito mais plana, enquanto que, entre as mulheres, os baixos e altos desempenhos escolares apresentaram-se como risco para TB-I(Kendler *et al.*, 2016).

Ao contrário dessas evidênciass, uma coorte de nascimento com 1037 pessoas apontou que alto QI durante a infância aumentou as chances de episódios maníacos na vida adulta(Koenen *et al.*, 2009). Contudo, esse achado possui certas limitações, haja vista que apenas oito pessoas tiveram episódios de mania ao longo da vida e não houve participantes com episódios hipomaníacos, dificultando a generalização dos achados(Koenen *et al.*, 2009). Um estudo transversal com 494 pessoas com TB-I indicou que este grupo possui 1.88 maiores chances de completar altos níveis educacionais apesar de terem menor QI depois do início do transtorno quando comparado aos sujeitos sem transtornos mentais(Vreeker *et al.*, 2016). Ao contrário, sujeitos com esquizofrenia apresentaram menores níveis educacionais que pessoas com TB-I e indivíduos sem transtornos mentais (Vreeker *et al.*, 2016). Já uma meta-análise demonstrou que pessoas com TB apresentavam um pequeno déficit no funcionamento intelectual pré-mórbido comparado aos controles, analisando estudos retrospectivos, mas o mesmo resultado não foi encontrado em estudos de coorte prospectivos(Trotta, Murray e MacCabe, 2015).

A literatura científica sobre esse tema permanece controversa, posto que outra coorte com 27 anos de acompanhamento usando informações de admissão hospitalar com uma amostra de 50.087 homens não achou nenhuma associação entre QI pré-mórbido e risco para episódios maníacos(Zammit *et al.*, 2004). Entretanto, o baixo QI estava relacionado com o risco de desenvolver esquizofrenia, transtorno esquizoafetivo e transtorno depressivo maior em homens(Zammit *et al.*, 2004). Não obstante, encontrou-se um moderado prejuízo cognitivo após o início dos episódios de humor(Zammit *et al.*, 2004).

Tais achados, apesar de controversos, podem indicar a presença de alterações neurodesenvolvimentais na fisiopatologia do TB, sendo o QI um importante marcardor do neurodesenvolvimento(Kloiber *et al.*, 2020). Recentemente, foi proposto um modelo neurodesenvolvimental do TB, apontando que fatores genéticos e insultos ambientais durante o desenvolvimento intrauterino podem impactar no amadurecimento cerebral de pessoas com TB(Kloiber *et al.*, 2020). Adicionados a isso, fatores estressantes em períodos críticos do neurodesenvolvimento após o nascimento podem ter impactos negativos na maturação neurológica como estresse precoce, baixa vitamina D e uso de cannabis(Kloiber *et al.*, 2020).

Comparar esquizofrenia e TB pode lançar luz para a caracterização do curso cognitivo das pessoas com TB, pois ambos compartilham de certos elementos fenotípicos e genotípicos. Em uma meta-análise avaliando desempenho cognitivo de pessoas com TBe esquizofrenia antes e após o primeiro episódio de humor/psicótico, apontou-se para direção de que pessoas com esquizofrenia apresentam déficits cognitivos pré-mórbidos significativos e um severo comprometimento após o início do transtorno(Trotta, Murray e MacCabe, 2015). O prejuízo cognitivo pré-mórbido em pessoas com TB parece ser bem menor comparado às pessoas com esquizofrenia(Trotta, Murray e MacCabe, 2015). Após o primeiro episódio de humor, esse prejuízo possui um menor tamanho de efeito (Trotta, Murray e MacCabe, 2015). Todavia, ainda há uma escassez de estudos avaliando sujeitos com TB antes do seu início, ligando esses dados às alterações clínicas após o primeiro episódio de humor e acompanhá-los até o prosseguimento de um quadro crônico. Além disso, os déficits cognitivos podem ser intrínsecos ao TB, mas não se deve descartar a hipótese que eles podem estar associados a fatores de estilo de vida como uso de substâncias psicoativas, problemas de saúde física e/ou efeitos das medicações(Trotta, Murray e MacCabe, 2015; Zipursky, Reilly e Murray, 2013).

Em uma meta-análise comparando familiares de primeiro grau de sujeitos com esquizofrenia e TB, indicou que os familiares de primeiro grau de pessoas com esquizofrenia tiveram prejuízo em todos os domínios cognitivos e familiares de primeiro grau de participantes com TB possuíam alterações em velocidade de processamento,fluência verbal e funções executivas(Bora, 2017). Porém, não foi encontrada diferença de QI de familiares de primeiro grau de TB e voluntários sem transtornos, mas familiares de primeiro grau de esquizofrenia tiveram menor QI que familiares de TB(Bora, 2017). Outrameta-análise com 16 estudos incluindo 728 familiares de primeiro grau de indivíduos com TB e 865 participantes sem transtornos mentais sugere que os familiares apresentaram prejuízos em Teoria da Mente e reconhecimento emocional facial em relação ao grupo comparador (Bora e Özerdem, 2017).

Esses achados fornecem evidências para a hipótese de que as alterações neurocognitivas no TB podem ser um endofenótipo relacionado às mudanças no neurodesenvolvimento. Dessa forma, a identificação de alterações neurodesenvolvimentais no TB podem ser cruciais para a compreensão da fisiopatologia e o desenvolvimento de terapias que possam reverter ou retardar o curso do transtorno (Kloiber *et al.*, 2020).

5. INTELIGÊNCIA ARTIFICIAL E TRANSTORNO BIPOLAR

Inteligência Artificial (IA) é um grande campo interdisciplinar, originalmente oriundo das Ciências da Computação, que visa *usar, compreender e construir* inteligência demonstrada por máquinas em contraste à inteligência humana(Nilsson, 1996). A área foi oficialmente criada na década de 50 por Allan Turing quando publicou seu artigo intitulado *"Computing Machinery and Intelligence"(Turing, 1950).* Os primeiros anos da área foram seguidos de grande entusiasmo na Academia, fortes campanhas publicitárias e altas expectativas dos usuários, mas logo foi suprimido pela falta de financiamento e a incapacidade de processamento dos computadores. Esse período ficou conhecido como “o inverno da Inteligência Artificial”(Oliveira, 2017). Porém, apenas nos anos 90, a IA entrou na sua fase primaveril com sua aplicação em diversos meios como logística, tradução automática, *sites* de busca, sistemas bancários, robótica, reconhecimento de voz e de face e diagnóstico médico.

Com o avanço tecnológico, alguns autores apontam que entramos na era do *Big Data*, uma vez que, a todo o momento, estamos produzindo dados por meio de satélites, câmeras de segurança, equipamentos de previsão do tempo, sismógrafos e, principalmente,pelo uso de *smartphones* com seus aplicativos de transações bancárias, redes sociais, geolocalização (Lantz, 2013). Essa quantidade de dados tenderá a crescer nos próximos anos com a ascensão da *Internet of things*(IoT) que consiste na transmissão de informações sem a necessidade da relação humano-humano ou humano- computador(Xia *et al.*, 2012). Somente é preciso que objetos, máquinas, pessoas ou animais possuam identificadores exclusivos (*unique identifiers*– UID)(Haller, 2010). Dessa maneira, a quantidade de dados coletados poderá crescer exponencialmente.

Então, *Big Data* é qualquer dado que possua a presença dos três “Vs” – volume, velocidade, variedade(Bhatt, Dey e Ashour, 2017). A primeira característica se refere à grande quantidade de dados gerados e armazenados para ser considerada *Big Data*. O segundo item é sobre a velocidade em que o dado é gerado e processado que, normalmente, ocorre em tempo real. As informações em *Big Data* são produzidas continuamente em contraste ao *small data* que possui um comportamento mais estático. Já a variedade dos dados consiste na presença de diversos tipos de informações (estruturadas,semi-estruturadas ou não-estruturadas)(Kitchin e McArdle, 2016). Porém, há outros elementos que caracterizam *Big Data*, diferenciando-o significativamente dos dados epidemiológicos e estatísticos tradicionais, dentre eles a *exaustividade.* Esta pode ser compreendida pela a coleta de informações de todo um sistema (*n*=todos) ao invés de uma amostra populacional(Kitchin e McArdle, 2016).

Assim, *Machine Learning* (ML), uma área dentro da IA, surge como uma possibilidade de analisar essa enorme quantidade de dados. ML consiste em desenvolver algoritmos computacionais, transformando os dados em ações inteligentes (Lantz, 2013) Em outras palavras, ML busca fazer predições ou decisões sem uma programação explícita para a execução de uma tarefa, apenas com as informações aprendidas anteriormente ou pela detecção de padrões dos dados. ML possui dois tipos de aprendizado: supervisionado e não-supervisionado. O aprendizado supervisionado ocorre quando se separa um banco de dados em treinamento e teste. A máquina aprende as informações no treinamento e, posteriormente, verifica-se o desempenho da máquina no banco de teste. Em termos práticos, no banco de treinamento, há uma coluna indicando o desfecho de interesse (ser ou não um bom pagador) para que a máquina consiga aprender como se comporta “bom pagador” e um “mau pagador” além das outras variáveis independentes. Já no banco de teste, não é apresentado à máquina o desfecho, apenas as variáveis independentes. Então, espera-se que a máquina consiga predizer quem será um bom ou mau pagador apenas com as variáveis dependentes (Fig.1). O aprendizado supervisionado é aplicado em diversos problemas, por exemplo, em análise de créditos, detecção de fraudes e de doenças (Maes *et al.*, 2002; Yazici, 2020; Zhan *et al.*, 2018).

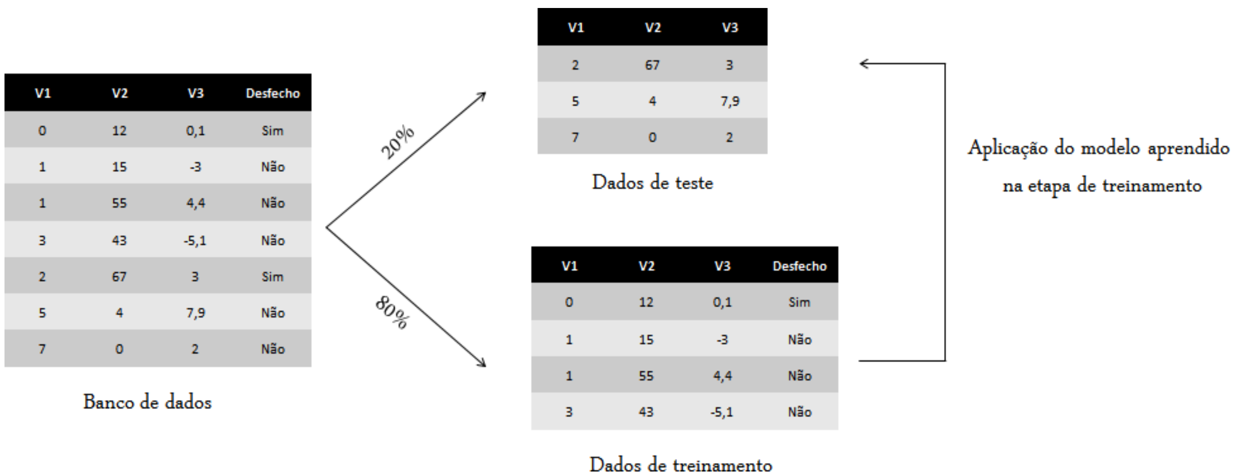

Figura 1 – Modelo explicativo de um protocolo padrão de *supervised machine learning*

Já o aprendizado não-supervisionado não possui um desfecho para ser aprendido ao contrário do aprendizado supervisionado, ou seja, identifica padrões desconhecidos de uma base de dados sem uma variável dependente pré-existente. A partir das informações já coletadas, o algoritmo é capaz de agrupar observações similares e separar observações distintas entre si (Fig. 2). Uma das aplicações desse método é no comportamento do consumidor ou no estudo de subtipos de transtornos psiquiátricos de caráter heterogêneo como o Transtorno Bipolar (TB) (Kachamas *et al.*, 2019; Rabelo-da-Ponte *et al.*, 2020).

V1	V2	V3
0	12	0,1
1	15	-3
1	55	4,4
3	43	-5,1
2	67	3
5	4	7,9
7	0	2

Banco de dados

Algoritmo para identificar padrões →

V1	V2	V3	Desfecho
0	12	0,1	Cluster A
1	15	-3	Cluster A
1	55	4,4	Cluster B
3	43	-5,1	Cluster C
2	67	3	Cluster A
5	4	7,9	Cluster B
7	0	2	Cluster B

Banco de dados

Figura 2 - Modelo explicativo de um protocolo padrão de *unsupervised machine learning*

O uso de técnicas de ML vem sendo utilizado nos últimos anos na pesquisa do TB. Uma recente revisão sistemática avaliando 51 artigos científicos sobre TB e ML encontrou que a maioria dos estudos avaliava neuroimagem estrutural ou funcional por meio de algoritmos de classificação (aprendizado supervisionado) para distinguir TB de esquizofrenia, depressão unipolar e pessoas sem transtornos mentais. Ademais, os autores encontraram também estudos genéticos, medidas de eletroencefalograma, biomarcadores e estudos neuropsicológicos aplicando algortimos supervisionados e não-supervisionados(Librenza-Garcia *et al.*, 2017). Eles sugerem que as técnicas de ML podem ser clinicamente relevantes para identificar os sujeitos em risco para o desenvolvimento de TB e, dessa forma, permitir a implementação de intervenções personalizadas(Librenza-Garcia *et al.*, 2017).

Outra aplicação clínica seria o uso desses algortimos para predizer resposta ao tratamento o que auxiliaria o clínico, por exemplo, na prescrição acurada de uma medicação e diminuir o risco envolvendo abordagens tentativa-e-erro, reduzindo o tempo até que o paciente responda adequadamente a uma medicação psiquiátrica(Cao *et al.*, 2020; Passos *et al.*, 2019). Para isso, os ensaios clínicos controlados e randomizados necessitariam mudar suas abordagens focadas em diferenças estatisticamente significativasentre grupos para uma perspectiva focada na probabilidade de um sujeito responder a uma medicação psiquiátrica ou uma intervenção psicosocial (Passos *et al.*, 2019). Além disso, torna-se crucial a coleta de dados com alta validade ecológica como *real-time data* usando *smartphones* e outro equipamentos eletrônicos e não apenas dados coletados em específicos períodos de tempo(Rutledge, Chekroud e Huys, 2019). Entretanto, não significa que os pesquisadores deverão abandonar a *theory-driven approach* para favorecer apenas a *data-driven approach* ou abordagem preditiva(Gabrieli, Ghosh e Whitfield-Gabrieli, 2015; Rutledge, Chekroud e Huys, 2019). Há uma falsa dicotomia entre elas, mas, na realidade, ambas são complementares e sua aplicação dependerá da pergunta do investigador(Rutledge, Chekroud e Huys, 2019).

Os algortimos usados em uma *data-driven approach* a possuem uma limitação, uma vez que são céticos em relação à natureza dos dados analisados e sobre o que já está ou não estebelecido na ciência, mas cabe ao cientista desenvolver um modelo de ML baseado no que já foi previamente conhecido na literatura científica(Huys, Maia e Frank, 2016; Rutledge, Chekroud e Huys, 2019). Ademais, os pesquisadores não devem confundir um modelo preditivo de ML com um modelo de associação, da mesma forma que correlações não indicam casualidade(Bzdok, Varoquaux e Steyerberg, 2021; Gabrieli, Ghosh e Whitfield-Gabrieli, 2015). São pesperctivas que não são mutuamente excludentes, porém não são intercambiáveis, uma vez que servem para objetivos epistemologicamente distintos (Breiman, 2001; Bzdok, Varoquaux e Steyerberg, 2021).

Os modelos inferenciais possuem alta transparência em relação à interpretabilidade dos achados e baixa capacidade preditiva, já os modelos preditivos possuem baixa interpretabilidade e elevado poder preditivo(Bzdok, Altman e Krzywinski, 2018; Bzdok, Varoquaux e Steyerberg, 2021). Um exemplo disso seriam os modelos baseados em regressões lineares simples amplamente usados em abordagens inferenciais, enquanto que os algortimos de *deep neural network* são aplicados para previsões. O primeiro modelo é altamente interpretável ao contrário do segundo, porém o primeiro é inadequado para previsões (Bzdok, Varoquaux e Steyerberg, 2021).

Dessa forma, já há esforços no desenvolvimento de modelos de ML para predição de resposta ao tratamento ou na predição de efeitos colatreais como demonstrado em uma coorte com 5700 sujeitos que estratificou o risco de desenvolver insuficiência renal devido ao uso de lítio(Castro *et al.*, 2016). Nesse estudo, o modelo teve boas medidas de desempenho com uma área sob a curva ROC superior a 81% e identificou-se que uso de antipsicóticos de primeira geração, uso de lítio mai de uma vez por dia e concentrações de lítio acima de 0.6mEq/L foram importantes para o risco de insuficiência renal (Castro *et* *al.*, 2016). No entanto, até a publicação da força-tarefa da *International Society for Bipolar Disorder*, não havia nenhum estudo usando técnicas de ML para prever o surgimento de TB em estudos longitudinais(Passos *et al.*, 2019). Até então, os artigos avaliando predição de risco de diagnóstico de TB utilizavam modelos de regressão logística e não algortimos de ML (Birmaher *et al.*, 2018; Hafeman *et al.*, 2016).

Outra aplicabilidade dos modelos de ML é a identificação de subgrupos de pessoas com TB ou identificação de determinadas similaridades entre TB e outros transtornos mentais como esquizofrenia(Lee *et al.*, 2017). Isso é clinicamente relevante haja vista a diversidade sintomatológica e cognitiva do TB, pois sua heterogeneidade fenotípica e genotípica são uma barreira para a compreensão dos seus mecanismos fisiopatológicos (Passos *et al.*, 2019). Muitos estudos estão focados em identificar diferentes *clusters*cognitivos do TB (Burdick *et al.*, 2014; Lima *et al.*, 2019; Rabelo-da-Ponte *et al.*, 2020; Van Rheenen *et al.*, 2017). Há também iniciativas para investigar heterogeneidade funcional em pessoas com TB na fase eutímia, pois, mesmo sem estarem em episódios de humor, cerca de 30 a 60% dos sujeitos não recuperam sua capacidade funcional após o episódio de humor (MacQueen, Trevor Young e Joffe, 2001; Solé *et al.*, 2018).

No cenário atual, esses estudos se encontram ainda em fase de prova de conceitocom pequeno tamanho amostral, carecendo de validade externa (Librenza-Garcia *et al.*, 2017). Os futuros estudos necessitarão validar seus modelos preditivos em amostras independentes, usar variáveis coletadas em tempo real associadas à multi-Omics e outras variáveis de diferentes clínico e biológico, permitindo a translação desses modelos para a prática clínica(Librenza-Garcia *et al.*, 2017). Mesmo assim, o uso dessas técnicas possibilitarão a transição de uma perspectiva homogênea sobre o TB para um estágio de medicina de precisão, englobando dados oriundos de distintos níveis explicativos, caracterizando-os com maior exatidão e, então, desenvolver tratamentos personalizados (Salagre *et al.*, 2018). Vale salientar que os usos dessas ferramentas não substituirão a importância do clínico na avaliação de saúde mental, mas será apenas mais um instrumento que o auxiliarão nas tomadas de decisão clínica como seleção de tratamento, estratégias de prevenção e prognóstico(Librenza-Garcia *et al.*, 2017).

6. JUSTIFICATIVA

Tendo em vista a complexidade em detectar precocemente o TB bem como identificar o papel do QI e do desempenho escolar como fatores de risco de TB comparando tipo I e tipo II, posto que poucos estudos os comparam, foi realizado esse trabalho usando dados clínicos e sócio-demográficos de uma coorte de nascimentos com22 anos de seguimento.

7. OBJETIVOS

7.1Objetivo geral

Desenvolver modelos preditivos baseados em ML para detectar preococementepessoas com TB e investigar o papel de duas medidas de inteligência (QI e número de reprovações escolares) como marcadores de risco pré-mórbidos de TB em uma coorte de nascimentos com 22 anos de seguimento.

7.2 Objetivos específicos

- Identificar precocemente pessoas que desenvolverão Transtorno Bipolar em umacoorte de nascimentos através de técnicas de ML.
- Estratificar o risco dos participantes em desenvolver Transtorno Bipolar aos 22anos de idade.
- Investigar o papel do QI antes do diagnóstico formal de TB tipo I e II.
- Analisar o número de reprovações escolares como um marcador para odesenvolvimento do TB tipo I e II.

8. CONSIDERAÇÕES ÉTICAS

A presente pesquisa foi realizada seguindo as resoluções do Conselho Nacional de Saúde, exigindo assinatura do termo de consentimento livre e esclarecido com explicaçõesclaras em relação aos riscos e benefícios da participação dos sujeitos na pesquisa. Ademais, a pesquisa foi aprovada no comitê de ética da Universidade Federal de Pelotas. A análise dos dados foi realizada usando a anonimização dos voluntários.

9. ARTIGOS DA TESE

9.1Artigo publicado

Title: Early identification of bipolar disorder among young adults - a 22-year community birthcohort.

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Objective: We set forth to build a prediction model of individuals who would develop bipolar disorder (BD) using machine learning techniques in a large birth cohort.

Methods: A total of 3,748 subjects were studied at birth, 11, 15, 18, at 22 years of age in acommunity birth cohort. We used the elastic net algorithm with 10-fold cross-validation to predict which individuals woulddevelop BD at endpoint (22-years) at each follow-up visit before diagnosis (from birth up to 18 years). Afterward, we used the best model to calculate the subgroups ofsubjects at higher and lower risk of developing BD and analyzed the clinical differences among them.

Results: A total of 107 (2.8%) individuals within the cohort presented with BD type I, 26 (0.6%) with BD type II, and 87 (2.3%) with BD not otherwise specified. Frequency of female individuals was 58.82% (n=150) in the BD sample and 53.02% (n=1,868) among the unaffected population. The model with variables assessed at the 18-years follow-up visit achieved the best performance: AUC 0.82 (CI 0.75–0.88), balanced accuracy 0.75, sensitivity 0.72, and specificity 0.77. The most important variables to detect BD at the 18-years follow-up visit were suicide risk, generalized anxiety disorder, parental physical abuse, and financial problems. Additionally, the high-risk subgroup of BD showed a high frequency of drug use and depressive symptoms.

Conclusions: We developed a risk calculator for BD incorporating both demographic and clinical variables from a 22-year birth cohort. Our findings support previous studies in high-risk samples showing the significance of suicide risk and generalized anxiety disorder prior to the onset of BD, and highlight the role of social factors and adverse life events.

Key-words: bipolar disorder, clinical aspects, epidemiology, population surveys.

Significant outcomes

- We identified early BD in the youth in a large population-based birth cohort.
- Suicide risk, generalized anxiety disorder, parental physical abuse, and financial problems were relevant factors prior to the onset of BD.
- The high-risk subgroup of BD showed a high frequency of depressive symptoms and drug use.

Limitations

- Our predictive models have low predictive positive value (PPV), which leads to a higher number of false positives.
- This birth cohort was not originally designed with a specific focus on BD.
- Predictor variables assessed at each visit were different in the present cohort.

Introduction

Bipolar disorder (BD) is the sixth cause of disability in the world[1], however, its proper identification still frequently represents a challenge, with an average delay of six years between firstsymptoms and formal diagnosis[2]. Additionally, only 20% of people with BD presenting a depressive episode are diagnosed with BD within the first year of seeking treatment[3].Diagnostic andtreatment delays have harmful consequences for the clinical course of illness[4,5].For instance, it is known that the incidence of death by suicide among people with BD is high, 20–30 times higher than in the general population, especially if untreated[6].It is also known that, following a chronic course, BD often results in enduring functional and cognitive impairment[7]. Therefore, early recognition and effective intervention are important clinical priorities; however, how to predict whowill develop a BD is still an elusive goal. Longitudinal studies of high-risk offspring of parents withBD have clearly demonstrated a developmental trajectory of psychopathology, with anxiety or sleep problems frequently evolving into a depressive disorder in adolescence, preceding an index hypomanic or manic episode[8]. However, the existing evidence from prospective cohorts is far too meager given the topic's importance, and thus unable to provide a clinically applicable prediction model for an early diagnosis of BD[9].

Two major groups of risk factors for the development of BD have been described in the literature: homotypic and heterotypic continuity. The former includes mood liability, subsyndromal depressionand hypomania, cyclothymia, and psychotic symptoms as relevant antecedents of BD, and most of these studies carried out inpatients or outpatients with major depressive disorder who later developed to BD[10–12]. In relation to the heterotypic continuity of BD, a recent systematic review identified internalizing disorders, for example, generalized anxiety disorder,post-traumatic stress disorder, separation anxiety, and externalizing disorders, for instance, substance abuse, oppositional defiant disorder, conduct disorder, attention deficit hyperactivity disorder as important precursors of

BD[10,11]. Moreover, there is a wide description of the literature concerning perinatal and juvenile exposure-related risk factors for BD. For example, maternal influenza, maternal smoking, gestational age and childhood stress, but all of these factors are nonspecific and common in other psychiatric disorders, that is, there are low specificity in predicting BD adequately[10,12].

The possibility to calculate an individual's risk for BD is the first step to a significant paradigmshift in preventive strategies[13].To achieve this goal, machine learning techniques have been widely used in health sciences and in the field of BD to build risk stratification tools[14].These algorithms have been used in mental health to identify different subgroups within a diagnosis and to predict response to a treatment or illnessdevelopment[15,16].This approach allows the machine to determinethe best set of features for prediction instead of relying on a human decision to include or not include a variable, therefore with a potential to change current paradigms in the prediction and stratification of clinical outcomes[17].

. Three studies have built risk calculators for illness development using other mathematical approaches in at-risk populations[18–20]. One of these assessed the probability that an offspring of a parent with BD will develop a new-onset bipolar spectrum disorder within the next 5 years. The authors found an AUC of 0.76 (95%CI 0.71–0.82) by using the Cox proportional hazards regressionmodel[18]. A similar study built a risk calculator to predict the individual risk of transition from subthreshold bipolar symptoms to bipolar I or II in youth and reported an AUC of 0.71(95%CI 0.67–0.74)[20]. Furthermore, a Chinese study showed a logistic regression model for diagnosing BD based on the clinical characteristics of depressive symptoms in a population of individuals with major depressive episodes (AUC 0.85; 95%CI 0.80–0.90)[19].

To date, no study has used machine learning techniques to detect BD early, i.e., there is a gap in the literature on the use of individual-level models as machine learning to detect and stratify subjects at risk for BD, contributing to personalized psychiatry[14]. However, the risk factor identification and the traditional regression model use do not objectively stratify the risks of subjects who will develop BD at the individual level, since it provides a likelihood of developing BD for each person[14–16]. Identifying BD early is a growing interest because many patients are mistreated and misdiagnosed as it claimed in a recent task force on precursors of BD[10]. We hypothesized that it is possible to develop a risk prediction model for BD using clinical and sociodemographic variables in a population-based birth cohort. If possible, our findings may add another level of evidence to the understanding of the developmental course of BD, which in turn it can contribute to the development of better prediction models.

Aims of study

To fill these gaps, we aimed to predict and stratify the risk of developing BD by the age of 22 years analyzing prospective data from a large population-based birth cohort with machine learning techniques.

METHODS

Samples

We included 3,781 individuals who belonged to a prospective population-based birth cohort called the 1993 Pelotas Birth Cohort. Participants in this cohort were born in Pelotas, a city in the south of Brazil. From 5,265 subjects who were born in 1993, a total of 5,249 newborns were enrolled in the study with the mother's agreement. We followed the participants at birth, 11, 15, 18, and 22 yearsof age[21]. The retention rate, including those who known to have died(n=196), was 76.3% with 3,810 subjects interviewed at the 22-year follow-up visit[21]. For our objective, we included participants who had answered the Mini-International Neuropsychiatric Interview (Brazilian Version 5.0 for DSM-IV) at the previous follow-up. Therefore, we assessed diagnosis of BD type I and II by using DSM-IV criteria. Furthermore, we chose to assess BD not otherwise specified (BD-NOS) by using the Course and Outcome of Bipolar Youth (COBY) cohort because DSM-IV criteria for BD-NOS are vague[22]. The 1993 Pelotas Birth Cohort study was approved by the local ethics committee. All participants provided written informed consent. Research data are not shared.

Procedures

Mental health assessments were applied by trained psychologists. A recommended method to select variables is the use of expert domain knowledge – largely from previously published literature(see Table S1 in the supporting information)[23].

- Perinatal follow-up visit: gender,parental socioeconomic status,psychiatric family history,parental health problems, smoking and drinking during pregnancy, hospitalization during pregnancy, mother's age, maternal years of education, birth weight, size at birth, head size at birth, familial income.

- 11-years follow-up visit: gender,parental socioeconomic status,psychiatric family history,parental health problems, Strengths and Difficulties Questionnaire (SDQ), tobacco smoking, alcohol use, illicit drug use, hours of sleep.

- 15-years follow-up visit: gender,parental socioeconomic status,psychiatric family history, SDQ, school performance, tobacco smoking, alcohol drinking.

- 18-years follow-up visit:socioeconomic status, gender,years of education, severe health problems, seeking mental health services (in the last year), death of someoneclose, financial problems,moving house against own will, breaking up, gang conflict where living, feeling of insecurity, physical aggression engagement, parental psychological abuse, victim of theft, psychiatric family history, drug use, tobacco smoking (Fagerstrom Test for Nicotine Dependence), alcohol use (Alcohol Use Disorders Identification Test [AUDIT]), quality of life (World Health Organization QualityofLife scale [WHOQOL]),Self-Reporting Questionnaire (SRQ-20), subjective well-being

(Subjective Happiness Scale [SHS]), psychiatric conditions according to the MINI (suicide risk, generalized anxiety disorder[GAD], social phobia, attention deficit hyperactivity disorder [ADHD]),intellectual functioning of the Wechsler Adult Intelligence Scale (WAIS-III).

Statistical analysis

We reported descriptive analyses as means (with standard deviations) or absolute and relative frequencies. The Shapiro-Wilk test was used to assess normality of data distribution. We used Chi- square tests to analyze categorical data and Mann-Whitney test to analyze non-parametric continuous variables between subjects with or without BD diagnosis. P-values< 0.05 were considered as significant. The descriptive statistical analysis was performed using R software(version R 3.6.1) and RStudio (version 3.5.3).*Machine learning analysis*

The machine learning analysis was performed using R software and RStudio as mentioned above with the R package "caret" (version 6.0-73), and "glmnet" (version 2.0-18)[24] (Figure 1a). We used each follow-up visit (perinatal, 11 years, 15 years, and 18 years) to predict BD at age 22years through the elastic net algorithm (Figure 1b). Elastic net is an improvement from the Least AbsoluteShrinkage and Selection Operator (LASSO) and Ridge Regression methods since they show severaldrawbacks compared to elastic net. This, in turn, displays some advantages: 1) it selects variables automatically, setting coefficients to zero (as in LASSO) and shrink coefficient (as in RidgeRegression) simultaneously; 2) it is able to handle a large set of variables; 3) it specifies groups of correlated variables; 4) it shows low risk of overfitting[25].

Please inserte here the figure 1

Missing data and imputation

We split our dataset into training (80% of the whole sample) and test dataset (20%) randomly. Afterwards, we imputed data on variables that have equal to or less than 6% of missing values by using the median for numeric variables and mode for categorical variables. We performed imputation using the training dataset (see Table S2 in the supporting information). In the next step, we used a standard machine learning protocol with repeated 10-fold cross-validation and class imbalance correction in the training dataset. This problem happens when one category has more subjects than another one.

Class imbalance problem

Class imbalance is a common problem in machine learning analysis where observations in one class(e.g. subjects who did not develop BD) exceed observations in the other class (e.g.

subjects who develop BD). A typical machine learning algorithm trained using an imbalanced dataset assignsnew observations to the majority class and leads to very different sensitivity and specificity scoresin the model. For this reason, we used Random Over-Sampling Examples (ROSE) for the class imbalance problem with the package “ROSE” (version 0.0.3)[26].

Model Performance

We tested the trained models in the testing “unseen” datasets. Individual-level predicted probabilities of conversion to BD were calculated based on balanced accuracy, sensitivity, specificity, the positive predictive value (PPV), the negative predictive value (PNV), and the AUC. We selected the predictive model with the best AUC to calculate concentration risk of BD in each quintile, i.e., five groups of equal frequency in which quintile represents the group of subjects witha higher risk for BD[27].The predictive model produces a probability of each individual being classified as BD in the test dataset based on pattern that it was learnt early (i.e. training dataset). Hence, the concentration risk is built with individual-level predicted probabilities, so we may identify the risk of participants in each stratum. After, we compared individuals within the highest risk quintile with subjects within other low-risk quintiles concerning sociodemographic and clinical variables using a chi-square test.

Permutation test and estimation error of cross-validation

Furthermore, we performed the permutation test shuffling the outcome 1,000 times with the best predictive model. The permutation test assesses whether the predictive model identified a random pattern, i.e., whether the original data contains or does not contain a real relationship between the variables and the outcome[28].Lastly, we calculated the estimation error of cross-validation with the best predictive model using different splits and cross-validation methods because these methods show failures with large error bars mainly in a small sample size[29].

RESULTS

We assessed 3,810 subjects at 22-years follow-up visit but we included 3,778 individuals for the present study (see Figure S1 in the supporting information).Of these, 255 (6.7%) participants received a diagnosis of BD according to the Mini-International Neuropsychiatric Interview at the last visit. The sociodemographic characteristics of the birth cohort can be seen in Table 1.

Please insert here Table 1.

Regarding sociodemographic variables, years of education and economic status were significantly different between both groups. Elastic net algorithm displayed a good performance to predict BD four years before the diagnosis. The model performance measures can be seen in Table 2(see FigureS2 in the supporting information). Only at the 18-years follow-up visit was the algorithm able to predict who will develop BD at 22years of age with an AUC of 0.82 (10-fold cross-validation; 95% CI 0.75–0.88)(Figure2).

Please insert here Table 2

Please insert here Figure 2

The most important variables at the 18-years follow-up in predicting BD were suicide risk, GAD, parental physical abuse, and financial problems (Figure 3). This result cannot be explained by collinearity because the variables showed weak correlations between them (see Figure S3 in the supporting information).

Please insert here Figure 3

Additionally, we compared the distribution of random rearrangement permutation) of the outcome with the original dataset, using 1,000 permutations. We verified a statistical difference between the original model and permutation models ($p < 0.001$) (see Figure S4 in the supporting information), which means that the predictive model using the 18-years follow-up visit to predict who will develop BD at 22years of age is not random. Our model exhibited low estimation error (mean [SD], 0.04[0.01]) (see Figure S5 in the supporting information).Figure S6 in the supporting information provides the concentration risk for having BD based on model output probability. The concentrationrisk is the proportion of observed BD in each quintile, that is, five groups of subjects of equal frequency ordered by individual-level predicted probabilities of conversion to BD. In other words, itis possible to identify the risk for BD conversion based on a probability produced by the predictive model. Lastly, Table 2showsclinical and sociodemographic features between the 5th quintile and all other quintiles, which were clustered, since the 5th quintile is the highest risk.

Please insert here Table 3.

DISCUSSION

As far as we are aware this is the first study to use a machine learning algorithms to identify an individual's risk of having BD in a population-based birth cohort. The AUC was 0.82 (95% CI0.75–0.88), balanced accuracy 0.75, sensitivity 0.72, specificity 0.77, PPV 0.18, NPV 0.97at the 18-years follow-up visit. Accurate early detection and prognosis remain uncertain in psychiatry, unlike othermedical fields. So, machine learning might be a powerful tool to improve the ability of prognosis and early detection, since a good machine learning model is able to predict whether or not a patient will have a more severe course of the disease or if he/she has previous signs of any disease[14,31]. Thistechnique is one of the most robust that allows the generability of the findings because we separate the data that is learned from the data that is tested, which is similar to the real world, where the models need to be applied to new individuals[25]. Furthermore, the identification of risk factors forBD is unspecified, because of this machine learning is crucial to change the paradigm of risk factorsto machine learning-based risk algorithms[32].

In a recent task force on prodrome and precursors of bipolar disorder, it was claimed that there is a growing interest to predict bipolar disorder or to identify it earlier because many patients with bipolar disorder suffer for many years without appropriate treatment[10]. Then, our work is clinically relevant because BD identified in the early stages may be less treatment refractory with a greater probability of response to monotherapy[5]. Therefore, the contribution of a predictive tool is important since it provides an unique window of opportunity to intervene therapeutically, thus preventing a more pernicious course of the illness[33].

Suicide risk was the most important variable in predicting BD, followed by GAD, and parental physical abuse. A community study with 3,021 adolescents and young adults showed that increased suicidality and depressive symptoms were highly associated with BD conversion[34]. Furthermore,the suicide attempt rate among subjects with BD is 25% to 50% and the suicidal death rate is 8% to 19%[35].A systematic review with 34 studies also reported BD individuals show a suicide risk 20–30 times greater than the general population, especially during the early years of diagnosis[6].Another study with seven years' follow-up evidenced that veterans with BD had the strongest association with suicide compared to other psychiatric conditions[36]. It is described in the literature that anxiety disorders in childhood and adolescence are relevant precursors of the development of full-blown BD[37]. Anxiety symptoms increased the risk of developing mood disorder 2.5- to 3-foldin a longitudinal and prospective study of subjects at risk for BD[38]. Other studies reported that around 40% of subjects who developed BD showed anxiety disorders, mainly GAD[39,40].Anothercohort study with BD offspring indicated that one of the most important variables in predicting BD conversion was anxiety symptoms[18].A recent meta-analysis with 10 studies totaling 2,120 participants showed that subjects with BD (even euthymic) are 4.6- fold more likely to have anxiety disorder compared to healthy controls[41].

The third most important variable in predicting BD was parental physical abuse. Trauma exposure is associated with earlier onset of BD, increased number of suicide attempts and manic episodes, comorbid substance use, and severity of mood symptoms[42]. Furthermore, early traumatic eventsmay lead to more sensitization to stressors in adulthood, accelerating the illness progression[43].In a population-based cohort, physical abuse increases 2.23-fold the risk for first-onset mania and 1.55- fold the risk for recurrent mania[44].

In relation to the risk stratification, subjects at the high-risk quintile showed more anhedonia symptoms and sought more psychotherapy in the last year compared to individuals in the other quintiles. Our finding is similar to prior publications that showed that high-risk offspring of BD parents showed increased substance use and depression symptoms compared with controls[45].Additionally, psychiatry may provide more appropriate treatments with risk stratification of subjects with mental disorders, since there is wide phenotypic heterogeneity in each mental disorder as well as machine learning captures complex interactions between variables as opposed to traditional statistical methods based on between-group differences[15,16].Our study has some limitations. First, our predictive models have low PPV, which leads to a higher number of false positives. This is a common scenario when assessing outcomes with rare events in the general population, such as conversion to BD, which has a prevalence of 6.7% in our sample[46]. However, a conversion to BD could still be ahead for people who were considered to be false positive since we followed up patients only until the age of 22 years. It is worth mentioning that we are already inviting participants for a new wave of data collection. Second, some of the variables identified by our model as the most relevant may not have a causal relationship with the conversion to BD. On the one hand, suicide risk, GAD, physical aggression engagement, social phobia, ADHD, and cannabis use may be part of the developmental trajectory of BD and represent heterotypic course of BD according to prior work[8,10,37].On the other hand, parental physical abuse and financial problems may have a causal relationship with the conversion to BD. Psychiatric family history was also an important variable and may represent the contribution of genetics in the risk for developing BD. Our cohort was not originally designed with a specific focus on BD because of this we do not have information about family history of BD. Third, predictor variables assessed at each visit were different in the present cohort. At the 18-years follow-up visit important variables to assess mental health symptoms, such as the Mini-International Neuropsychiatric Interview and AUDIT, were included in the data collection procedure. Therefore, models built using predictor variables from prior visits might have better performance if more mental health variables were included from the beginning.

Notwithstanding these limitations, it is the first time that machine learning methods are used to predict bipolar disorder in a general population birth cohort. Additionally, our research is the first one to develop risk stratification (concentration risk) in subjects with bipolar disorder, indicatingthat the subjects of the most severe stratum (fifth quintile) present more symptoms of anhedonia, greater use of drugs, and sought more psychotherapy in the last year after the bipolar disorder diagnosis. To the best our knowledge, there is no work using a cohort design that evaluates bipolar disorder in the low and the middle income countries.

This is important when considering these countries may have different social issues impacting development of psychiatric disorders such as violence and poorer access to health care. Hence, our results suggest that it is possible to utilize psychosocial and clinical measures to predict BD at the individual level. Future research should replicate our findings in other cohorts and incorporate other biological markers, such as genetics and metabolomics, and other time points to build more accurate risk algorithms such as long short-term memory neural networks[47].Furthermore, we need cohorts with even longer follow-up periods to address the issue related to PPV stated earlier.

Thus, we developed a multivariable risk model to predict BD in a general population cohort based on demographic and clinical factors. Our data corroborate previous findings from high-risk cohorts regarding the existence of prodromal psychopathology in the developmental trajectory of BD but highlight the interaction of social and clinical variables as risk predictors. Risk models may provide framework for testing the effectiveness of preventive interventions and for investigating the neurobiological features associated with the developmental trajectory of BD.

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Table 1. Sociodemographic characteristics of participants with bipolar disorder and the general population at 22-years follow-up visit.

	Bipolar disorder (n=255)	General population (n=3,523)	Statistics
Bipolar Disorder			
Type I	107 (2·8%)	..	..
Type II	26 (0·6%)	..	..
Not otherwise specified	87 (2·3%)	..	..
Female gender	150 (58·82%)	1,868 (53·02%)	$\chi2(1) = 2{\cdot}98$, $p > 0{\cdot}05$
Employed	152 (59·60%)	2,240 (63·58%)	$\chi2(1) = 1{\cdot}45$, $p > 0{\cdot}05$
Marital Status			
Single	209 (81·96%)	2,957 (83·93%)	$\chi2(3) = 44{\cdot}35$, $p <0{\cdot}001$
Married	45 (17·64%)	545 (15·46%)	..
Divorced	1 (0·39%)	20 (0·56%)	..
Economic Status			
Upper	53 (21·11%)	1,389 (39·69%)	$\chi2 (2) = 44{\cdot}05$, $p < 0{\cdot}001$
Middle	151 (60·15%)	1,773 (50·67%)	..
Lower	47 (18·72%)	337 (9.63%)	..
Years of education †	8 [6–11]	11 [8–12]	$U = 5.83 \cdot 10^5$, $p < 0.001$

†Median [1st–3rd quartiles], Mann–Whitney U test.

Table 2. Performance measures to identify BD at age 22-years through the elastic net algorithm **in a population-based birth cohort.**

	Perinatal follow-up visit	11-years follow-up visit	15-years follow-up visit	18-years follow-up visit
Balanced accuracy	0.58	0.59	0.56	0.75
ensitivity	0.60	0.52	0.49	0.72
pecificity	0.57	0.66	0.64	0.77
ositive predictive value	0.09	0.10	0.09	0.18
Negative predictive value	0.95	0.95	0.94	0.97

Table 3. Clinical characteristics at 22-years follow-up visit between the 5th and otherof risk

	Subjects within the 5th quintile (n = 160)	Subjects within the 1st to 4th quintiles(n=591)	Statistics
Attended psychotherapy in the last years (Yes)	21 (17.4%)	47 (10.4%)	$\chi 2(1)= 3.84$, p
Anhedonia†	45 (30.8%)	124 (21.6%)	$\chi 2(1)= 4.95$, p
Drug use lifetime			
LSD	14 (9.4%)	33 (5.6%)	$\chi 2(1)= 2.28$, p
Inhalants	22 (14.8%)	54 (9.0%)	$\chi 2(1)=3.74$, p
Cocaine	44 (29.5%)	147 (24.7%)	$\chi 2(1)= 1.21$, p
Marijuana	77 (51.7%)	272 (45.3%)	$\chi 2(1)= 1.68$, p
MDMA	16 (10%)	27 (4.6%)	$\chi 2(1)= 7.15$, p
Opioids	6 (4.0%)	2 (0.35)	$\chi 2(1)=11.78$,p

†According to the Snaith-Hamilton Pleasure Scale.

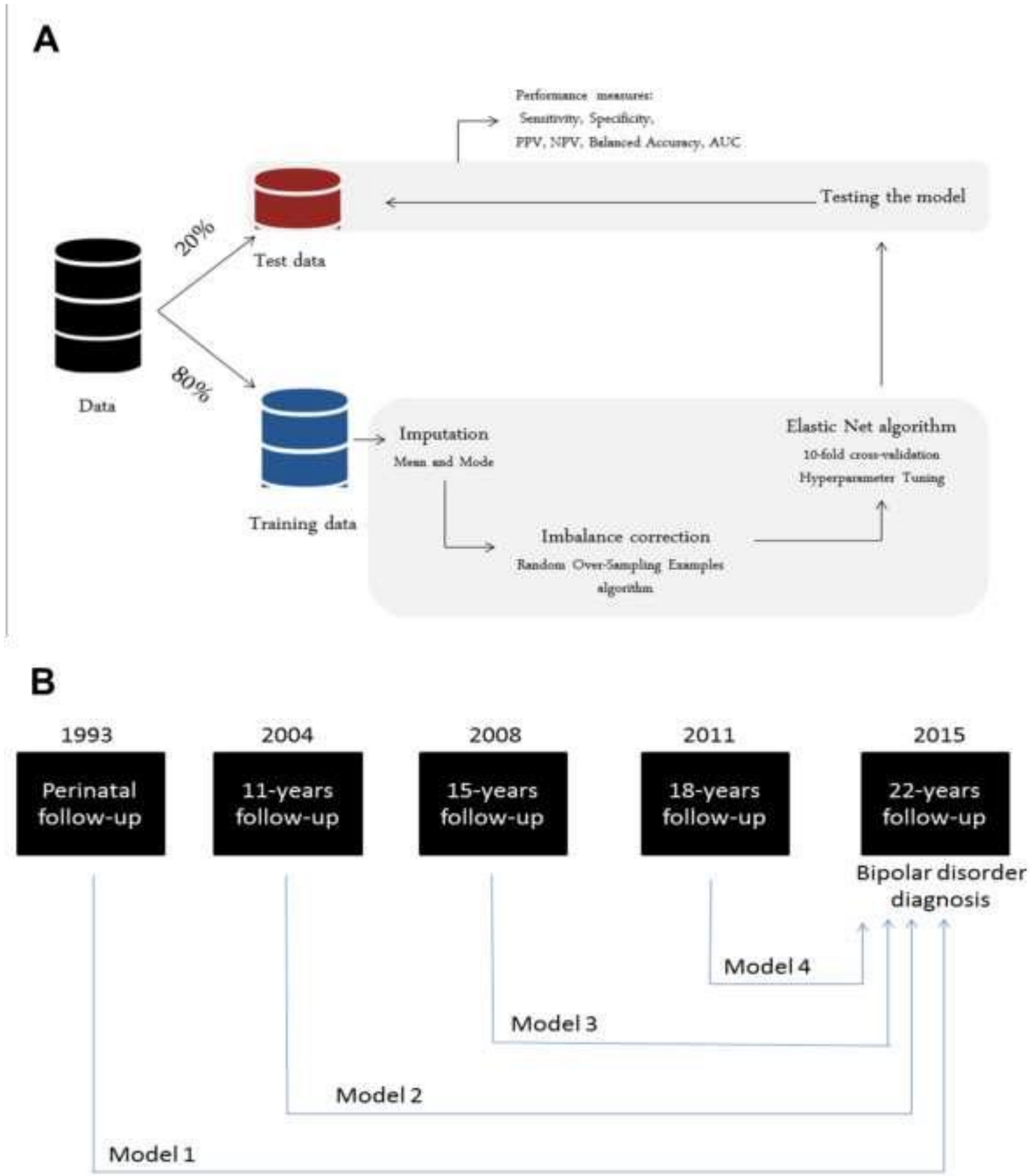

Figure 1. Analytical protocol used in this study. (A) Flow diagram for supervised machine learning protocol with ROSE algorithm as class imbalance solution and Elastic Net algorithm to predict bipolar disorder (BD) in a birth cohort. (B) Flow diagram using each follow-up visit to predict BD at 22 years of age.

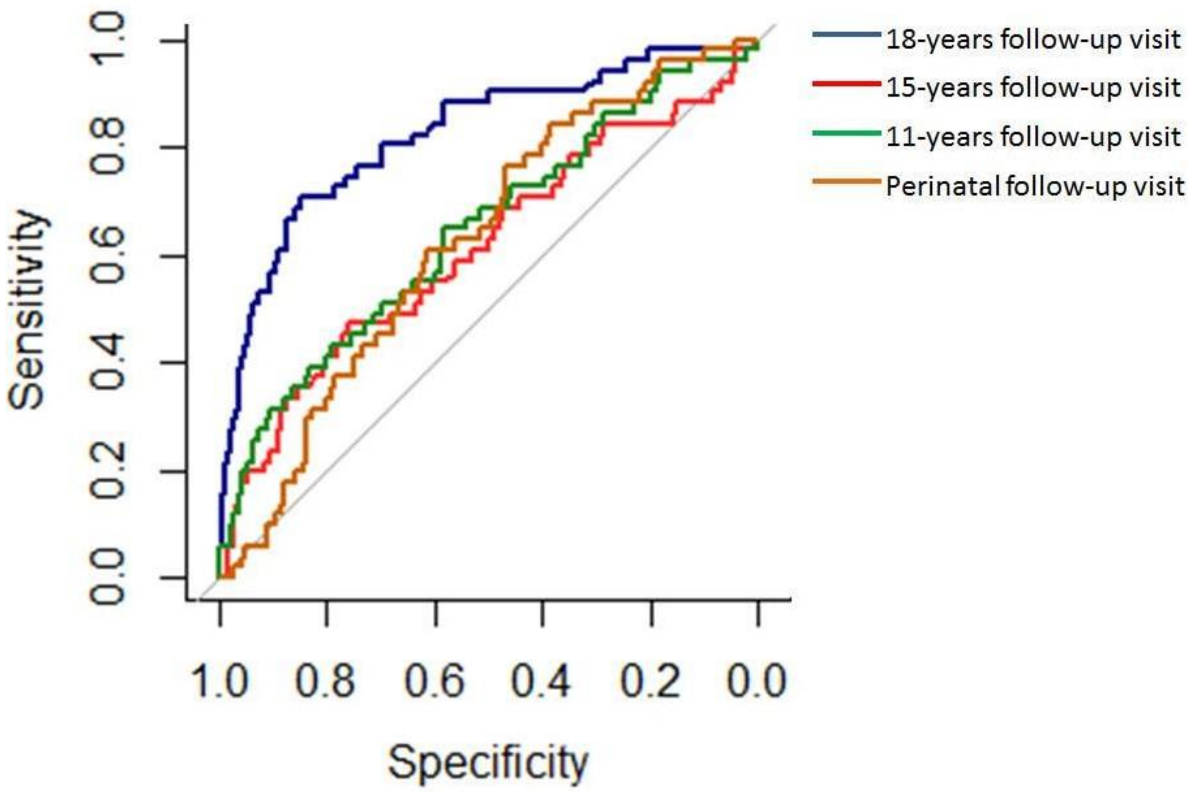

Figure 2. Receiver operating characteristic (ROC) curve for predicting onset of bipolar disorder at 22 years of age through Elastic Net algorithm with 10-fold cross- validation using a population-based cohort study. Each ROC curve means a follow-up visit. Perinatal follow-up: AUC = 0.62 (CI 0.55–0.69); 11-years follow-up: AUC = 0.64 (CI0.55–0.72); 15-years follow-up: AUC = 0.61 (CI 0.52–0.70); 18-years follow-up: AUC = 0.82 (CI 0.75–0.88).

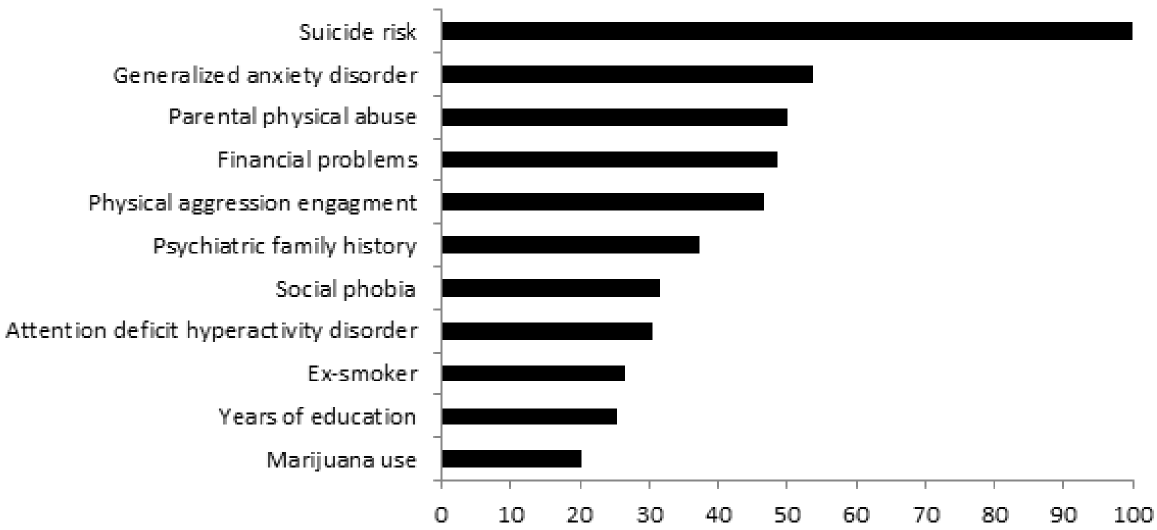

Figure 3. The most important variables used to predict four years before onset of bipolar disorder (BD) at 22 years of age. The bar graph represents weighting factors assigned to each clinical variable over time by Elastic Net algorithm based on their relevance in differentiating subjects with BD from individuals without BD diagnosis.

Supporting Information

Additional Supporting Information may be found in the online version of this article: Fig. S1. Description of the 1993 Pelotas Birth Cohort. Fig. S2. Model performance using Elastic Net algorithm to predict BD including all cutoff between balanced accuracy, sensitivity, specificity, positive predictive value, and negative predictive value. Fig. S3. Correlation plot between continuous variables used to predict BD at 18-years follow-up visit. Fig. S4. Test with 1000 permutations using 18-years follow-up visit. Fig. S5. Estimation error in the prediction accuracy comparing models with diff erent splits between training and testing and cross-validation methods. Fig. S6. Concentration risk of bipolar disorder (BD) by quintile of predictive scores. Table S1. Clinical and demographic variables selected to 'train' the model based on domain expert domain knowledge. Table S2. Percentage of missing values and type of variables at each follow-up visit of the variables used in the model.

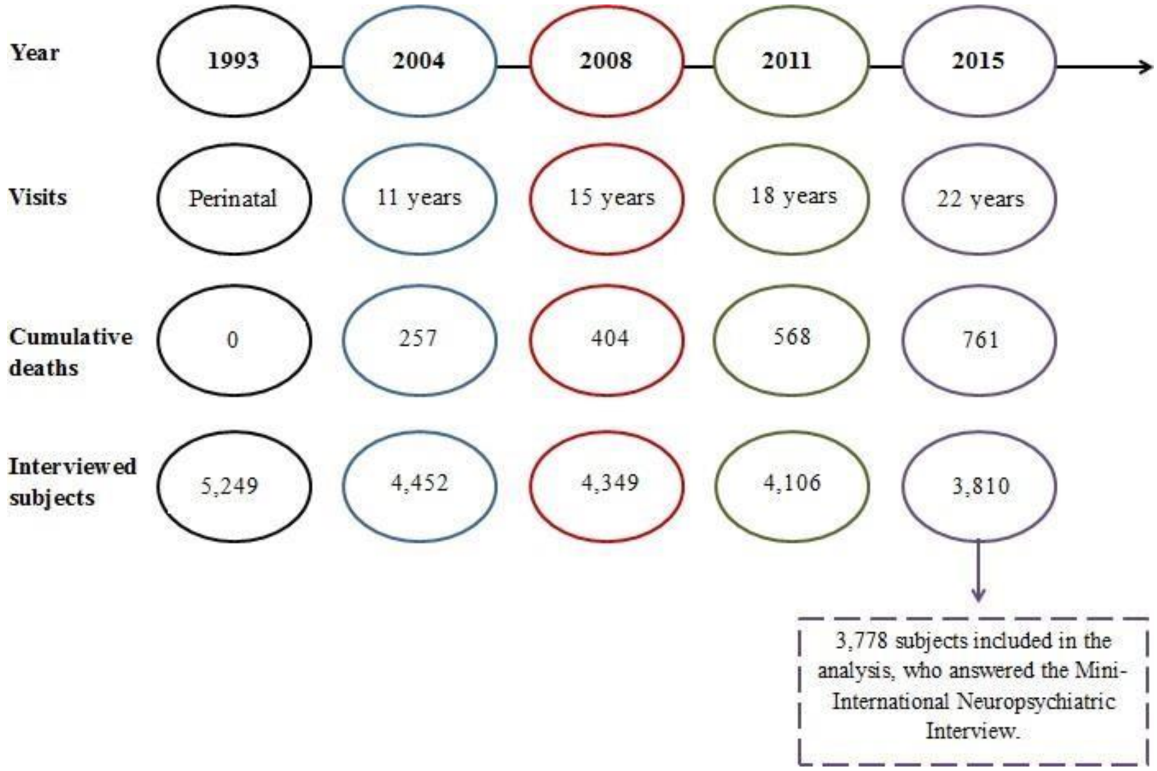

Figure S1 – Description of the 1993 Pelotas Birth Cohort.

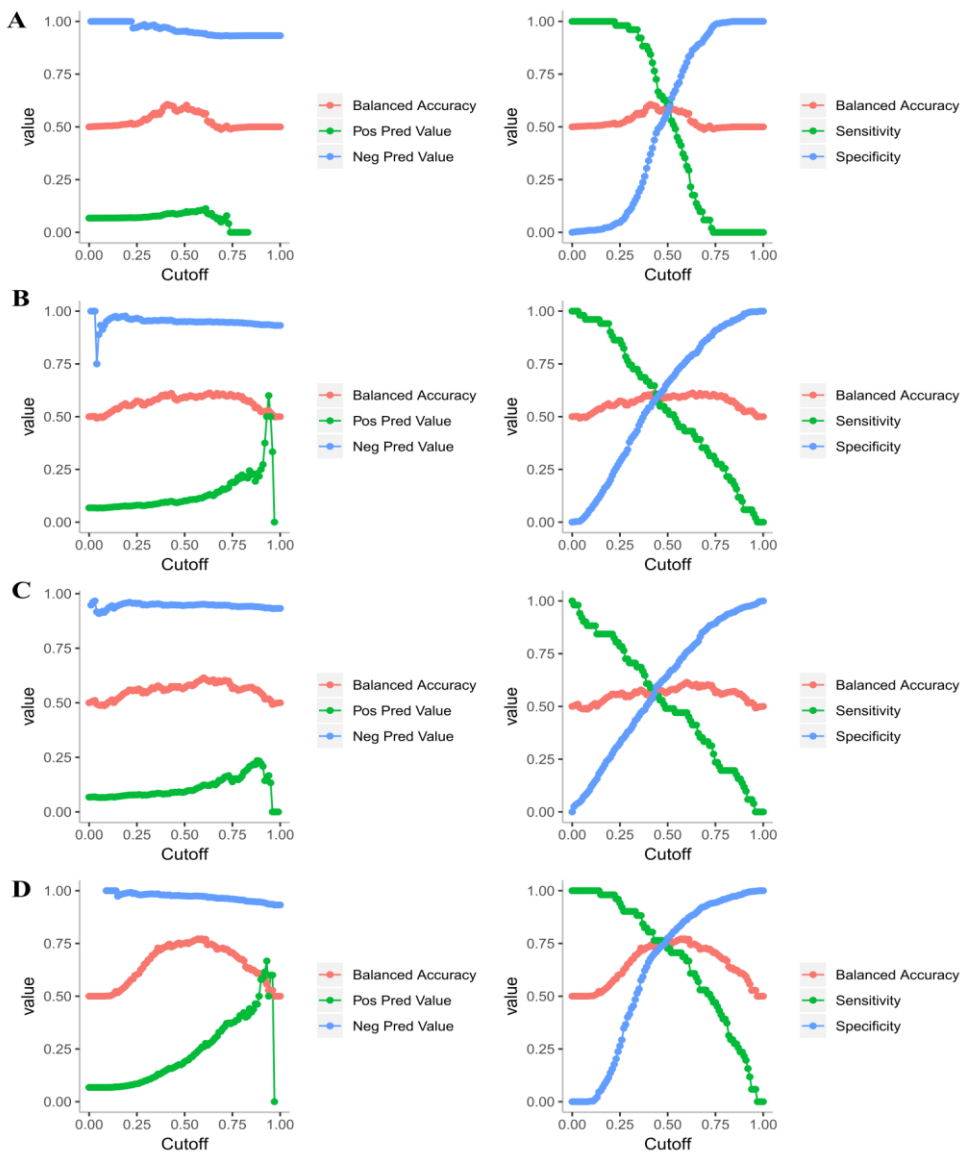

Figure S2. Model performance using Elastic Net algorithm to predict BD including all cutoff between balanced accuracy, sensitivity, specificity, positive predictive value, and negative predictive value. (A) Modelperformance using perinatal follow-up visit. (B) Model performance using 11-years follow-up visit. (C) Model performance using 15-years follow-up visit. (D) Model performance using 18-years follow-up visit.

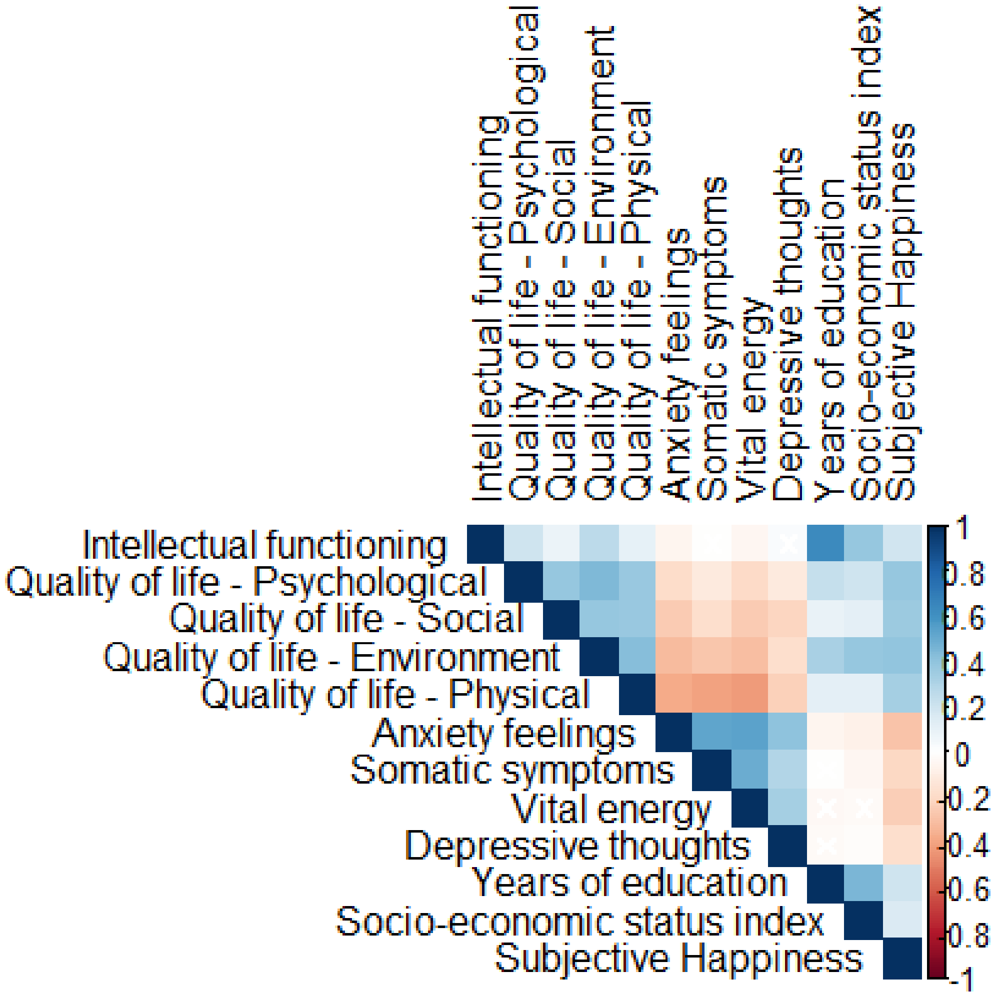

Figure S3. Correlation plot between continuous variables used to predict BD at 18-years follow-up visit.

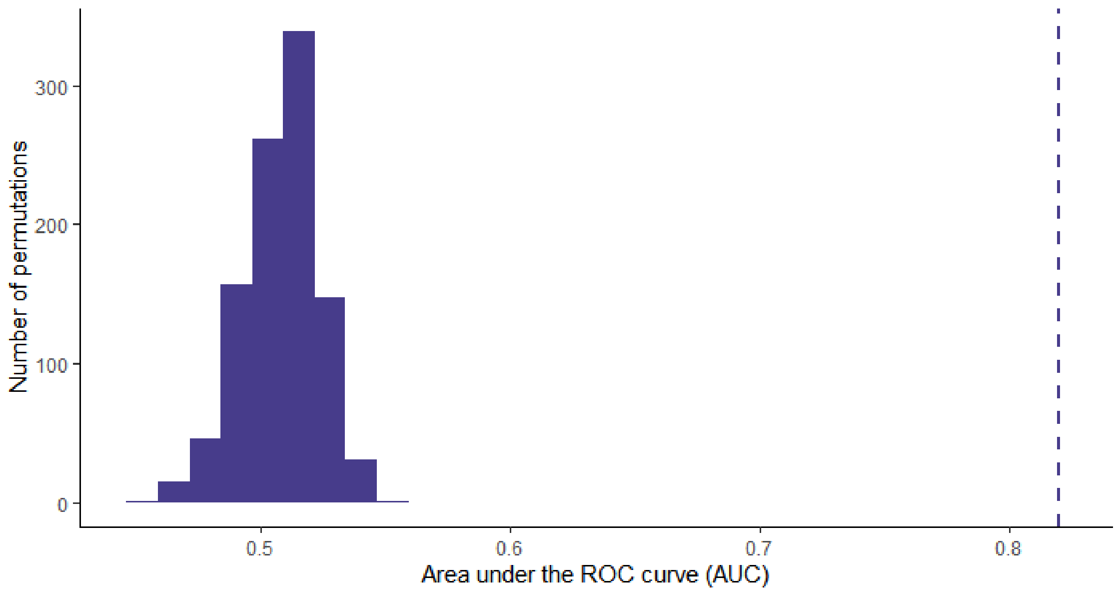

Figure S4. Test with 1,000 permutations using 18-years follow-up visit. The *x*-axis isthe area under the ROC curve (AUC) of each permutation. The blue dash line representsthe AUC of the predictive model with the original dataset at 18-years follow-up visit to predict BD. There were significant differences between permutations and the original predictive model (p < 0·001).

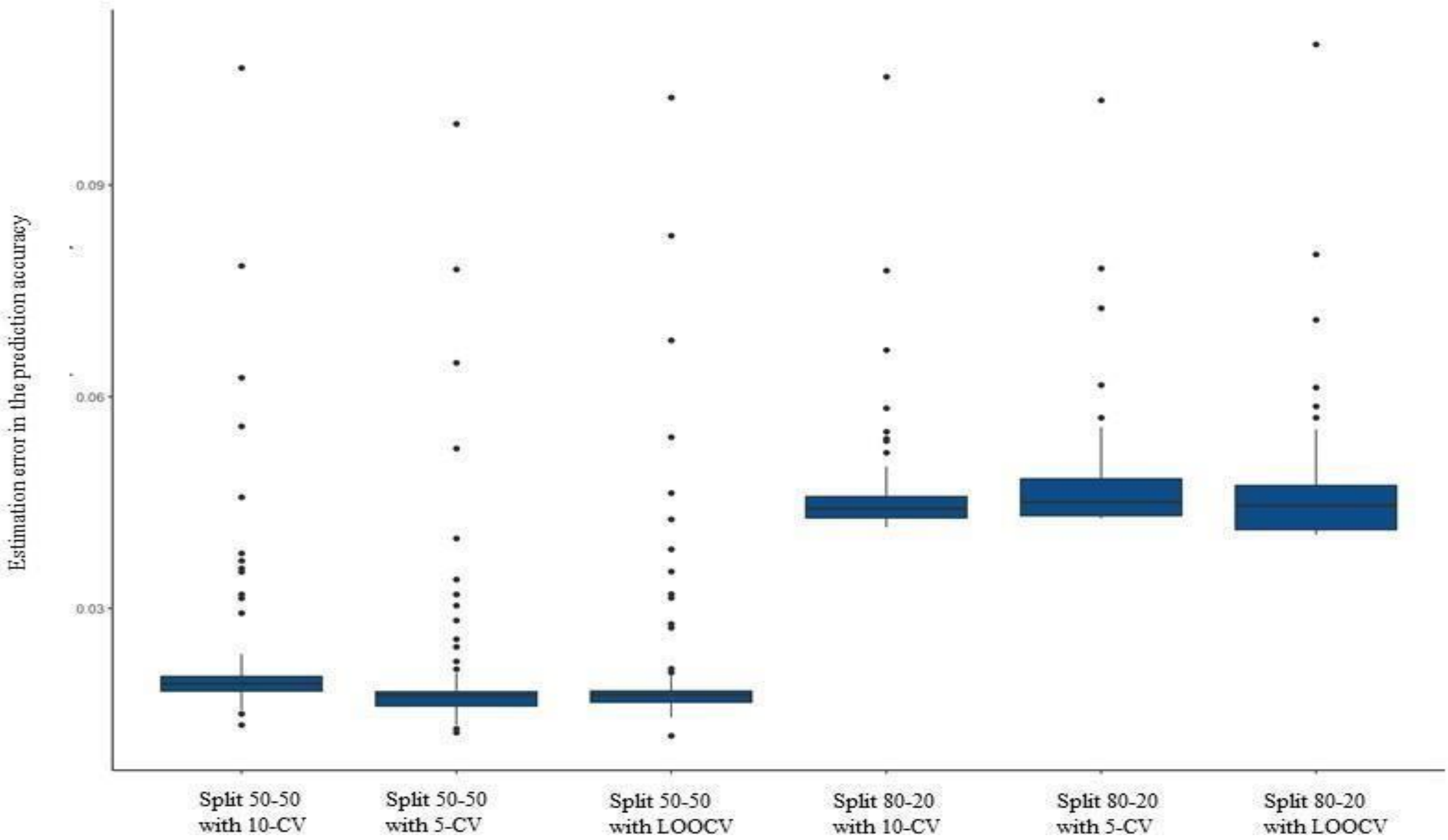

Figure S5. Estimation error in the prediction accuracy comparing models with different splits between training and testing and cross- validation methods. Split 50–50: splitting dataset into training (50% of the whole sample) and test dataset (50%) randomly. Split 80–20: splitting dataset into training (80% of the whole sample) and test dataset (20%) randomly. 10-CV: 10-fold cross-validation. 5- CV: 5-fold cross-validation. LOOCV: leave-one-out cross-validation.

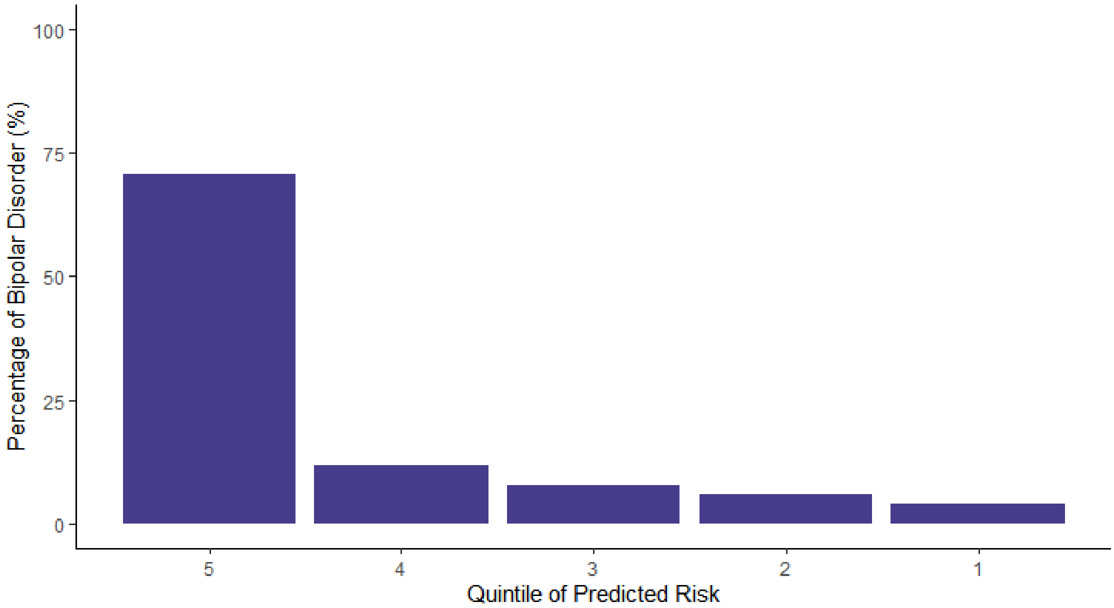

Figure S6. Concentration risk of bipolar disorder (BD) by quintile of predictive scores. Quintiles are five groups of subjects of equal frequency dividing the total sample of 3,748 individuals into groups defined by level of predicted BD risk.

Table S1. Clinical and demographic variables selected to 'train' the model based on domain expert domain knowledge.

Variable	Paper	Type of study	Sample	Findings
Perinatal follow-up visit				
Gender	Birmaher *et al*, 2018[1]	Cohort	BD offspring	Males showed less risk of conversion.
Psychiatric family history	Birmaher *et al*, 2018[1]	Cohort	BD offspring	Familial mania/hipomania was important predictor of BD conversion.
	Hafeman *et al,* 2017[2]	Cohort	BD offspring	Parental age at mood disorder discriminated will develop BD within 5 years.
Parental health problems	Dreier *et al,* 2018[3]	Birth cohort	Population-based	Maternal exposures to fevers and common infections during pregnancy are associated with psychosis-like experiences.
	Suvisaari *et al*, 2013[4]	Birth cohort	Population-based	Obstetric complication such as infections, hypertension, and placental abnormalities was associated with high risk of psychoses.
Smoking during the pregnancy	Talati *et al,* 2013[5]	Birth cohort	Population-based	Prenatal tobacco exposure shows 2-fold greater risk for BD.
	Chudal *et al,* 2015[6]	Nested case control	BD subjects	Smoking during the pregnancy increases 1.14-fold the risk for BD.
Drinking during the pregnancy	Talati *et al,* 2013[5]	Birth cohort	Population-based	Maternal alcohol use during the pregnancy increases 1.99-fold the risk for BD.
Hospitalization during the pregnancy	Al-Haddad et al, 2019[7]	Birth cohort	Population-based	Maternal hospitalization increased the risk for depression.
Mother's age	Keskinen et al, 2013[8]	Birth cohort	Population-based	High maternal age increases 2.6-fold the risk for schizophrenia.
Maternal years of education	Van Meter et al, 2016[9]	Systematic review and Meta-analysis	-	High educational levels of parents increase the risk for BD.
	Drakensmith *et al*, 2016[10]	Birth cohort	Population-based	Maternal education was associated with psychotic experiences.
Birth weight	Talati *et al,* 2013[5]	Birth cohort	Population-based	Offspring birth weight increases 1.89-fold the risk for BD.
	Keskinen et al, 2013[8]	Birth cohort	Population-based	High birth weight increases 11.4-fold the risk for schizophrenia.
Size at birth	Keskinen et al, 2013[8]	Birth cohort	Population-based	High length birth increases 4.1-fold the risk for schizophrenia.
Head size at birth	Pugliese et al, 2019[11]	Cross-sectional	BD sample	A high risk of bipolar disorder was associated with head circumference at birth (OR = 5.40)
Parental social economic status	Agebo *et al,* 2015[12]	Nested case-control	Population-based	Schizophrenia was associated with parental socioeconomic status (OR=8.1).

	Tsuchiya *et al*, 2004[13]	Nested case-control	Population-based	High social economic status of parents was related to increased risk for BD.
11-years follow-up visit				
The Strengths and Difficulties Questionnaire (SDQ)	Birmaher *et al*, 2018[1]	Cohort	BD offspring	Child anxiety and emotional disorders were predictors of BD conversion.
Tobacco smoking	Vermeulen *et al*, 2019[14]	Medelian randomization	Population-based	Smoking initiation (OR= 1.46) and lifetime smoking (OR=1.72) are a casual risk factor for developing BD.
Alcohol use	Starzer *et al*, 2018[15]	Cohort	Population-based	Alcohol-induced psychosis was the most associated with the risk of conversion to BD.
	Duffy *et al*, 2014[16]	Cohort	BD offspring	High-risk offspring had a higher risk of substance use disorder
Illicit drug use	Duffy *et al*, 2012[17]	Cohort	BD offspring	Adolescent substance use is highly associated with early course of BD
Sleep time	Duffy *et al*, 2014[16]	Cohort	BD offspring	High-risk offspring of BD parents had an increased lifetime risk of sleep disorders compared with controls
15-years follow-up visit				
School performance	Van Meter et al, 2016[9]	Systematic review and Meta-analysis	-	Academic difficulties was one the most common prodromal symptoms in BD subjects
Drinking behavior	Starzer *et al*, 2018[15]	Cohort	Population-based	Alcohol-induced psychosis was the most associated with the risk of conversion to BD.
	Duffy *et al*, 2014[16]	Cohort	BD offspring	High-risk offspring had a higher risk of substance use disorder
Socioeconomic status	Tsuchiya *et al*, 2013[18]	Systematic review	-	Higher social class is associated with greater risk for BD conversion.
18-years follow-up visit				
Years of education	Gilman *et al*, 2012[19]	Cohort	Population-based	Less than high school education was a predictor of BD conversion
	Vreeker *et al*, 2016[20]	Cross-sectional	Clinical sample	Patients with BD completed the highest education levels compared to healthy controls.
Severe health problems	Smith *et al*, 2013[21]	Cross-sectional	Clinical sample	BD subjects have one physical condition (OR=1.27), two physical condition (OR=1.45) and three or more physical conditions (OR=1.37) compared to health controls.
Seeking mental health services (in the last year)	Owens *et al*, 2004[22]	Cross-sectional	Psychological autopsy	Mental health services were sought by 56% of subjects prior to suicide.
Death of someone close	Gilman *et al*, 2012[19]	Cohort	Population-based	Past-year problems with one's social support group (OR=1.79) was associated with BD conversion.

	Kessing *et al*, 2004[23]	Case-control	Population-based	Mother or sibling suicide increase the risk for first psychiatric hospitalization with a diagnosis of mania (RR=3.94 and RR=4.72 respectively).
Financial problems	Wege *et al*, 2017[24]	Cohort	Population-based	Unemployment and perceived job insecurityare associated with higher risk of depression (RR= 1.64 and RR=1.48 respectively).
	Gilman *et al*, 2015[25]	Cohort	Population-based	Economic problems increase 1.36-fold of risk for the first-onset mania.
	Butterworth *et al*, 2009[26]	Birth cohort	Population-based	Financial hardship increases the risk for Depression Disorder (OR=2.1).
Variables related to stressful life events: moving house against own will, breaking up, gang conflict where living, feeling of insecurity, victim of robbed	Koenders *et al*, 2014[27]	Cohort	BD sample	Negative life events were associated with severity of mania and depressive episodes.
Physical aggression engagement	Gonda *et al*, 2012[28]	Systematic review	-	Aggressiveness is related to risk for BD.
Parental physical abuse	Gilman *et al*, 2015[25]	Cohort	Population-based	Physical abuse increases 2.23-fold the risk for the first-onset mania.
Smoking (Fagerstrom Test of Nicotine Dependence)	Vermeulen *et al*, 2019[14]	Medelian randomization	Population-based	Smoking initiation (OR= 1.46) and lifetime smoking (OR=1.72) are a casual risk factor for developing BD.
The Alcohol Use Disorders Identification Test (AUDIT)	Starzer *et al*, 2018[15]	Cohort	Population-based	Alcohol-induced psychosis was the most associated with the risk of conversion to BD.
	Duffy *et al*, 2014[16]	Cohort	BD offspring	High-risk offspring had a higher risk of substance use disorder
Quality of life (World Health Organization Quality-of-Life Scale - WHOQOL)	Perlis *et al*, 2009[29]	Cohort	BD samples	Quality of life was worse in early-onset BD subjects.
Domains of Self-Reporting Questionnaire (SRQ-20)	Duffy *et al*, 2013[30]	Cohort	BD offspring	High emotionality (HR = 1.11) and anxious symptoms (HR=2.13) were associated with BD conversion.
	Birmaher *et al*, 2018[1]	Cohort	BD offspring	Mood liability symptoms was one of the most predictors of BD conversion (AUC 0.71)
Subjective well-being (Subjective Happiness Scale - SHS)	Gruber *et al*, 2009[31]	Cross-sectional	At risk sample	Subjects at high risk for mania showed elevated positive emotion.
	Gruber *et al*, 2011 [32]	Experimental design	BD sample	BD individuals reported high positive emotion compared to healthy controls.
Suicide risk	Pompili *et al*, 2013[33]	Systematic review	-	The suicide risk among BD is 20 to 30 times higher than the general population.
Generalized anxiety disorder (GAD)	Hafeman *et al*, 2017[2]	Cohort	BD offspring	Anxiety symptoms were associated with BD conversion.

	Meier *et al*, 2018[34]	Birth cohort	Population-based	The rate of BD was high in individuals with prior diagnosis of ADHD or anxiety disorder only. However, the combination of anxiety and ADHD increased the risk of BD 30-fold compared to those with no ADHD or anxiety.
Social phobia	Gilman *et al*, 2012[19]	Cohort	Population-based	History of social phobia (OR=2.20) was associated with BD conversion.
	Duffy *et al*, 2013[30]	Cohort	BD offspring	Social phobia was the second most incident anxiety disorder in high-risk BD offspring
Attention deficit hyperactivity disorder (ADHD)	Duffy *et al*, 2007[35]	Cohort	BD offspring	Offspring of lithium non-responders had high rates of ADHD.
	Meier *et al*, 2018[34]	Birth cohort	Population-based	The rate of BD was high in individuals with prior diagnosis of ADHD or anxiety disorder only. However, the combination of anxiety and ADHD increased the risk of BD 30-fold compared to those with no ADHD or anxiety.
Intellectual functioning of the Wechsler Adult Intelligence Scale (WAIS-III).	Urfer-Parnas *et al*, 2010[36]	Cohort	Population-based	Psychiatric in-patients have lower pre-morbid intellectual functioning than healthy controls.
	Smith *et al*, 2015[37]	Birth cohort	Population-based	Higher intellectual functioning at age 8 years is associated with lifetime manic features at age 22-23 years

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Table S2. Percentage of missing values and type of variables at each follow-up visit of the variables used in the model.

Variable	Percentage of missing data	Type of variable
Perinatal follow-up visit		
Gender	0	Categorical
parental health problems	0	Categorical
smoking and drinking during pregnancy	0	Categorical
hospitalization during pregnancy	0	Categorical
mother's age	0	Continuous
maternal years of education	0	Continuous
birth weight	0.1	Continuous
size at birth	0.08	Continuous
Head size at birth	0.07	Continuous
parental socioeconomic status	1.8	Categorical
psychiatric family history	4.7	Categorical
11-years follow-up visit		
Gender	0	Categorical
parental socioeconomic status	0.04	Categorical
psychiatric family history	4.7	Categorical
hours of sleep	4.8	
parental health problems	5.1	Categorical
smoking behavior	5.1	Categorical
Drinking behavior	6	Categorical
illicit drug use	6	Categorical
Strengths and Difficulties Questionnaire (SDQ)	6	Continuous
15-years follow-up visit		
Gender	0	Categorical
psychiatric family history	4.7	Categorical
school performance	5.9	Categorical
parental socioeconomic status	6	Categorical
Strengths and Difficulties Questionnaire (SDQ)	6	Continuous
Tobacco smoking	6	Categorical
Alcohol drinking	6	Categorical
18-years follow-up visit		
Gender	0	Categorical
Socioeconomic status	0.7	Continuous
Years of education	0.1	Continuous

Severe health problems	6	Categorical
seeking mental health services (in the last year)	6	Categorical
death of someone close	6	Categorical
financial problems	6	Categorical
Variables related to stressful life events: moving house against own will, breaking up, gang conflict where living, feeling of insecurity	6	Categorical
physical aggression engagement	6	Categorical
parental psychological abuse	6	Categorical
victim of theft	6	Categorical
psychiatric family history	4.7	Categorical
Drug use		
Marijuana use	4	Categorical
Cocaine use	4	Categorical
Inhalant use	2.4	Categorical
Hallucinogen use	6	Categorical
Tobacco Smoking (Fagerstrom Test for Nicotine Dependence)	6	Categorical
Alcohol drinking (Alcohol Use Disorders Identification Test [AUDIT])	6	Categorical
Quality of life (World Health Organization Quality of Life scale [WHOQOL])	6	Continuous
Self-Reporting Questionnaire (SRQ-20)	6	Continuous
Subjective well-being (Subjective Happiness Scale [SHS])	6	Continuous
psychiatric conditions according to the MINI		
Suicide risk	0	Categorical
Generalized anxiety disorder (GAD)	6	Categorical
Social phobia	6	Categorical

Attention deficit hyperactivity disorder (ADHD)	6	Categorical
Intellectual functioning of the Wechsler Adult Intelligence Scale (WAIS-III)	6	Continuous

9.2 Artigo não publicado

Premorbid intelligence quotient and school failure as risk markers for bipolar disorder and major depressive disorder

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Abstract

Objectives: Identifying intelligence quotient(IQ) and the number of school failures as risk factors for Bipolar Disorder (BD) and Major Depressive Disorder (MDD) before the formal diagnosis in a birth cohort study.

Methods: We included 3,580 participants from the Pelotas population-based birth cohort study with available data at 22 years old and no previous diagnosis of a mood disorder. We developed regression models controlling for potential confounders to assess the impact of IQ and school failure obtained at 18 years old on a subsequent diagnosis of BD and MDD at 22 years old, comparing individuals without mood disorders as comparators.

Results: A total of 158 (4.4%) participants presented a diagnosis of BD and 441 (12.3%) of MDD, according to the DSM-IV criteria. Having low and borderline IQ (below 70) at 18 years-old was a risk marker for participants with BD (Adjusted Odds Ratio [AOR] 1.75, 95%CI: 1.00–3.09, $p<0.05$) and superior IQ (above 120) for individuals with MDD (AOR 2.16, 95%CI: 1.24–3.75, $p<0.001$). The number of school failures increased the risk for BD (AOR 1.23, 95%CI: 1.11–1.41, $p<0.001$) but not for subjects with MDD. The number of school failures was a significant marker for BD type 1(AOR 1.36, 95% CI: 1.17–1.58, $p<0.001$) but not in individuals with BD type 2 or those without a mood disorder.

Conclusion: The present study shows that BD has a distinct premorbid intellectual performance compared to MDD. These findings contribute to a better understanding of the illness trajectories and inform risk scoring tools to predict mood disorders.

Key words: bipolar disorder, major depressive disorder, risk markers, depression, school failure, intellectual functioning, intelligence quotient**,** cognition**.**

Introduction

Mood disorders are chronic conditions estimated to affect nearly 500 million people worldwide (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Major Depressive Disorder (MDD) is the 2nd leading cause of disability in the United States, while Bipolar Disorder (BD) ranks 18th (Murray *et al.*, 2013). The onset of both disorders typically occurs during adulthood, and there is growing interest in understanding preceding factors and risk markers that increase the vulnerability for developing these conditions (Silva Ribeiro *et al.*, 2020; Kieling *et al.*, 2021; Weavers *et al.*, 2021). In this sense, little is known about premorbid measures of intelligence, asits associations with a prospective diagnosis of BD and MDD remain equivocal in the literature (Trotta *et al.*, 2015; Scult *et al.*, 2017). Further elucidation on this relationship could contribute to a better understanding of the illness trajectories and inform risk scoring tools.

A few longitudinal studies have approached this matter. Using populational data from Sweden, previous research examined registries from over a million men and found both low and high intelligence quotient (IQ) at 18 years of age to be associated with an increased risk for BD in adulthood (Gale *et al.*, 2013). Similarly, excellent and poor school performance at age 16 were linked to a later onset of the diagnosis when compared to average performance (MacCabe *et al.*, 2010; Kendler *et al.*, 2016b). Another nationwide analysis found an association between low IQ obtained at 18 to 20 years-old with an increased risk for an admission for depression across the lifespan (Lager *et al.*, 2017). Nevertheless, these reports have relied on national registries on hospitalization to identify cases of mood disorders, and may be prone to considerable selection bias. This issue could be addressed by using birth cohorts, as they establish diagnoses on the basis of symptoms elicited on follow-up interviews (Gonçalves *et al.*, 2018; Canova and Cantarutti, 2020). Indeed, a few studies were performed using such methodology, and data from 1,037 people in New Zealand suggested an association of low childhood IQ with increased risk of MDD in adulthood (Koenen *et al.*, 2009). However, birth cohorts thus far have been generally undersampled to gauge association effects for an infrequent event such as BD (Koenen *et al.*, 2009; Betts *et al.*, 2016).

To address the limitations of prior efforts, the present study used data from the Pelotas birth cohort (Gonçalves *et al.*, 2014, 2018) to investigate the potential role of two surrogate measures of intelligence, namely IQ and the number of school failures, as premorbid markers of BD and MDD. Our research hypothesis is that low IQ and school failures may be a risk marker for the developmentof both conditions.

Methods

Participants

We used data from the 1993 Pelotas Birth Cohort, a prospective population-based Brazilian birth study (Gonçalves *et al.*, 2018). All 5,265 births that took place in 1993 were eligible for the study, and a total of 5,249 newborns were included following agreement by the mother. Data collection was performed at baseline and multiple timepoints (11, 15, 18, and 22 years of age). The entire cohort was sought for evaluation at these ages but there are other data collection points with subsamples. The last wave of data collection took place between October 2015 and July 2016, including 3,810 subjects (retention rate = 76.3%, including those who are known to be dead) with a mean age of 22.6 years. Out of these participants, we excluded 62 participants for a previous diagnosis of BD and 148 individuals for a previous diagnosis of MDD at age 18. Additionally, we excluded 20 subjects due to missing data, resulting in a final sample size of 3,580 for analyses. A local research ethics committee at Federal University of Pelotas approved the study protocol. Participants signed informed consent forms and all data was anonymized. Further details regardingthe study design can be found elsewhere (Gonçalves *et al.*, 2018). All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Assessment and definition of outcome variables

Trained psychologists assessed participants at the ages of 18 and 22 using the Mini-International Neuropsychiatric Interview (M.I.N.I) (Sheehan *et al.*, 1998). The diagnosis of BD and MDD were established according to DSM-IV criteria. For this study, only incident diagnosis of BD and MDD at age 22 were considered as outcome variables, and we excluded participants diagnosed at age 18 with either condition. This timeframe was selected since IQ and the number of school failures were assessed at the age of 18 years.

Assessment and definition of risk marker variables

IQ and school failure, both assessed at age 18, were defined as risk markers. We estimated IQ through an abbreviated version of the Wechsler's Adult Intelligence Scale (WAIS-III) with four subscales: similarities, arithmetic, picture completion, and digit-symbol coding. Then, we inserted into the model as an ordinal variable according to the Brazilian version coded in four levels: low/borderline (below 70), low average (80 - 89), average (90 - 109), high average (110 - 119), and superior (above 120) (Wechsler, 2004).

Sociodemographic variables obtained at age 18 were inserted in the statistical models as covariates: sex (male and female), maternal years of education, socioeconomic status (divided intofive quintiles according to a wealth index based on a principal component analysis using a list of assets whose the first and last quintile correspond the poorest and wealthiste family incomes, respectively) (Crespo *et al.*, 2021; Oliveira *et al.*, 2021), and skin color (coded in three levels: White, Black, and Brown). To control for the number of school failures, we also added school dropouts last year as a covariate. Physical trauma in the last year was also considered as a covariate in the model, defined as being a victim of robbery and/or physical aggression and coded in two levels (present or absent).

Statistical analyses

Statistical analyses were performed in R (version 4.1.0) and RStudio (version 2021.09.0+351). We conducted the Shapiro-Wilk test to verify the normal distribution of continuous variables. Furthermore, we used Kruskall-Wallis test with Bonferroni post-hoc test for multiplecomparison and χ^2 tests (when appropriate) to compare the groups. We developed regression models to verify the impact of IQ (at 18-years follow-up visit) as risk marker for BD at 22-years visit. In the first model, we performed a binomial logistic regression model comparing subjects with BD and participants without mood disorders to test IQ as a predictor for BD. In the second model, we compared participants with BD, with MDD, and without mood disorders. The third model compared individuals with BD type I, with BD type II, and without mood disorders using multinomial logistic regressions.

Furthermore, we analyzed the number of school failures until 18 years-old as a predictor for BD at 22 years-old, controlling for IQ, ethnicity, maternal years of education, socioeconomic status, and physical trauma. We compared participants with BD and without mood disorders through a binomial logistic regression. Following this, we built a multinomial regression model testing participants with BD, with MDD, and without mood disorders. Then, we compared whether there are differences between individuals with BD type I, with BD type II, and without mood disorders. Statistical significance was $p < 0.05$ (two-tailed) for all tests. All results from regression models are expressed as odds ratio – OR (95% CI) and adjusted odds ratio – AOR (95% CI).

Results

From 3,580 included participants, 158 (4.4%) were diagnosed with BD and 441 (12.3%) with MDD at 22 years-old (Table 1). According to the Brazilian version's Wechsler's Intelligence Scales for Adults (WAIS-III), 6.8% of subjects with MDD had a superior IQ while 4.1% of non-mood disorder participants presented a superior IQ ($X^2(8)=30.71$, $p< 0.01$). Otherwise, 16.7% of individuals with BD had a low or borderline IQ and only 8.7% of those with MDD showed low or borderline IQ. The Kruskall-Wallis test displayed a significant group effect comparing IQ and the number of school failures four years before the formal diagnosis (18-years follow-up visit) among subjects with BD, with MDD and without mood disorders ($H(2)=18.91$, $p < 0.001$). The post-hoc test demonstrated that participants with BD (Median [1st - 3rd quartile]) (92.5 [83.5 - 102]) had lower IQ compared to individuals with MDD (98 [88 - 107.5]) ($p < 0.001$), and individuals without mood disorders (98 [88 - 105]) ($p < 0.001$). Otherwise, there was no difference in IQ between individuals with MDD and without mood disorder ($p = 1$).

The same pattern was found with respect to the number of school failures at 18-years follow-up visit after the post hoc test. Participants with BD displayed a higher number of school failures compared to participants with MDD ($p<0.001$) and without mood disorders ($p<0.001$).

Having a low or borderline IQ increases risk for BD (OR 2.29, 95% CI: 1.39 – 3.63, $p < 0.001$) whilst an above average IQ was a protective factor (OR 0.46, 95% CI: 0.2 – 0.91, $p = 0.04$) compared to unaffected volunteers. The other ranges did not have association with BD (Supplementary Table 1). When we compared MDD, BD, and unaffected participants, individuals with a superior IQ at 18 years had a nearly twofold increased risk of MDD (OR 1.81, 95% CI: 1.15 – 2.84, $p < 0.01$) and a low or borderline IQ increased risk of BD (OR 2.31, 95% CI: 1.43 – 3.74, $p < 0.001$) (Supplementary Table 2).

After controlling for confounder variables, the adjusted odds ratio (AOR) showed that individuals with a low or borderline IQ at 18 years had a nearly twofold increased risk of BD (AOR 1.76, 95% CI: 1.20 – 3.03, $p < 0.05$) at 22 years compared to unaffected volunteers (Supplementary Table 3). Although, when we compared participants with BD, with MDD, and without mood disorders, a superior IQ was a risk marker for MDD (AOR 2.16, 95% CI: 1.24 – 3.75, $p < 0.001$) and a low or borderline IQ remained a risk marker for BD (AOR 1.75, 95% CI: 1.00 – 3.09, $p < 0.05$) (Table 2). We found low or borderline IQ was a risk factor for BD type I (OR 2.44, 95% CI: 1.34 – 4.45, $p < 0.001$) (Supplementary Table 4). Nevertheless, after adjusted analysis for confounders, there were no IQ differences between participants with BD type I, with BD type II, and without mood disorders (Supplementary Table 5).

In relation to school failures at 18-years follow-up visit (Supplementary Table 6), individuals with BD were significantly more likely than subjects without mood disorders to show a higher number of school failures (AOR: 1.22, 95% CI: 1.08 – 1.38, $p < 0.001$)(Supplementary Table 6). The number of school failures and no school dropout were not significant for MDD but those were significant for BD (number of school failures - AOR: 1.23, 95% CI: 1.11 – 1.41, $p < 0.001$; no school dropout AOR: 0.51, 95% CI: 0.33 – 0.80, $p < 0.01$) (Table 3). The number of school failure (AOR: 1.36, 95% CI: 1.17 – 1.58, $p < 0.001$) was a significant risk factor and a lack of drop out (AOR: 0.48, 95% CI: 0.27 – 0.83, $p < 0.01$) was a protective factor for BD type I in relation to BD type II and volunteers without mood disorders (Supplementary Table 7).

Discussion

In the present study, we drew on data from the Pelotas birth cohort to investigate the association between premorbid measures of IQ and school failure (obtained at 18 years) and a subsequent diagnosis of BD and MDD (established at 22 years old), including individuals without mood disorders as a control group. The main findings were: (a) low or borderline IQ at 18 years old increased the risk of a BD diagnosis at 22 years old; (b) higher IQ at 18 years old increased the risk of a MDD diagnosis at 22 years old; (c) individuals with BD were significantly more likely than subjectswithout mood disorders to have a higher number of school failures; (d) the number of school failure isa risk factor and no school drop out is a protective factor for BD type I. These findings contribute to the understanding of risk markers in the trajectory of BD and MDD by suggesting marked differences between these disorders. To the extent of our knowledge, this is the first population-based birth cohortstudy assessing the association between IQ/school failures collected four years before the formal diagnosis and subjects with BD, MDD, and without mood disorders.

With respect to BD, previous reports corroborate an association with low premorbid IQ but results are conflicting. A prospective cohort study of more than one million in-patient men described that both low and high intelligence scores had been associated with an increased risk of hospital admissions for BD (Gale *et al.*, 2013). Additionally, a similar study used national registry data from inpatient and outpatient services by comparing them with intelligence scores at 18 years-old and school performance (2016a). In this case, no association has been found between IQ and a subsequent diagnosis of BD (2016a). Nonetheless, these studies present limitations, as they relied on registries from mental health services to identify individuals with BD, and one of the samples was composed exclusively by hospitalized men (Gale *et al.*, 2013). This introduces a series of biases, as more severe manifestations of illness are captured in analyses, misrepresenting outpatients and underdiagnosed individuals, therefore limiting generalizability. Furthermore, individuals requiring inpatient care are also more susceptible to psychosis, which is argued to be a trandiagnosis marker of premorbid low IQ and could thus confound the association (Betts *et al.*, 2016; Kloiber *et al.*, 2020).

It is important to mention that birth cohort studies avoid this kind of selection bias by predetermining a sample of individuals who will be followed up over an extended period of time. In this direction, a study examined data from 1,037 participants of the Dunedin cohort and found high IQ to be a risk marker of adult mania (2009). However, only eight individuals met the diagnosis, compromising results. Additionally, a prospective Australian pre-birth cohort study that followed 7,223 mothers did not find an association between cognitive tests in 5-years-old offspring with subsequent symptoms of mania during early adult life, and low cognitive performance was only foundto predict psychosis (2016). It is speculated that it was not possible to find an association between cognitive tests and BD in adulthood because the authors used cognitive variables in early childhood. Recent cohort studies have shown that BD can be identified a few years before the first episode (Birmaher *et al.*, 2018; Rabelo-da-Ponte *et al.*, 2020). Furthermore, sample sizes were limited, and therefore symptom domains were used instead of established diagnosis of disorders. As such, the present study was the first birth cohort sufficiently powered to uncover an association between low IQand a subsequent diagnosis of BD.

MDD is generally associated with low premorbid IQ, which is contrary to our findings. A population-based cohort using Swedish registries of 50,087 male subjects found low premorbid IQ (obtained at age 18 to 20) to increase the risk of hospitalization for severe depression (Zammit *et al.*, 2004). Using similar methods, another study examined data from 49,321 Swedish men and found high IQ to be a protector for first time hospitalization for depression across the lifespan (Lager *et al.*, 2017). In both studies, only severe manifestations of depression had been captured, and subjects with underlying diagnosis other than MDD were possibly included, compromising generalizability. In contrast, in a study with greater external validity, the Dunedin birth cohort from New Zealand analyzed data from 1,037 participants and found low childhood IQ to be related with an elevated risk for adult depression (Koenen *et al.*, 2009). However, only 147 individuals met the criteria of a depressive episode, relative to triple sample size (441 individuals) in the present study.

The association of a high number of school failures and a subsequent diagnosis of BD is also corroborated by previous reports. A prospective study using national registries from Sweden analyzed data from 996,865 participants and found an association between poor school achievement at 16 years old and a posterior diagnosis of BD established at inpatients or outpatients services (2016a). In our study, the number of school failures closely resembles school achievement, as the students were not able to obtain sufficient grades to pass the next school year. Similarly, another Swedish cohort study with 713,876 participants matched school grades with a posterior discharge for BD with psychotic symptoms, showing both excellent and poor school performance to be associated with elevated risk for BD (2010). However, the sample was restricted to males and subjects with psychotic symptoms (2010). Endorsing this finding, a register-based nationwide cohort study following 505,688 individuals born in Denmark showed that individuals who did not complete the exams at term (when turning 17 years old) had a higher risk for BD and BD type I, and low performance in mathematics ina compulsory schooling test was especially associated with increased risk for BD (Pedersen *et al.*, 2018). As such, this finding is replicated in an independent sample using a different cohort methodology (2010).

An important strength of our study was to use a birth cohort design, as it is a robustmethodology for elucidating risk markers over the course of illness. This way, we attenuate the selection bias of nationwide studies who rely on health services registries to identify cases (Kendler *etal.*, 2016a; Pedersen *et al.*, 2018), especially if analyses are restricted to hospitalization records (Zammit *et al.*, 2004; MacCabe *et al.*, 2010; Gale *et al.*, 2013; Lager *et al.*, 2017). Moreover, we utilized a sample size sufficiently powered to grasp association effects for both MDD and BD, which was not possible in previous studies with similar objectives (2009; 2016). Another relevant strength was the use of the WAIS-III, a gold-standard scale to assess IQ. Moreover, we used an independent sample from an upper middle income country while previous evidence on this topic comes mainly from data collected in high income countries (Zammit *et al.*, 2004; Koenen *et al.*, 2009; MacCabe *et al.*, 2010; Gale *et al.*, 2013; Betts *et al.*, 2016; Kendler *et al.*, 2016a; Lager *et al.*, 2017; Pedersen *etal.*, 2018). This way, we addressed the necessity of replicating findings in heterogeneous scenarios.

With respect to limitations in the present study, we could not distinguish which participants with BD also presented with psychosis. Psychosis has been implicated in decreased IQ scores across a range of diagnosis (Barnett *et al.*, 2012; Betts *et al.*, 2016; Kloiber *et al.*, 2020), and its effect on cognition may manifest even before symptomatic presentation (Woodberry *et al.*, 2010; Bang *et al.*, 2015; Catalan *et al.*, 2021). Therefore, controlling for psychosis may further clarify potential moderators between IQ and risk factors for BD. Furthermore, we could only identify 158 cases of BD, comprising 92 individuals with Type 1 and 66 participants with Type 2, respectively. Distinguishing between subtypes is methodologically prudent, as a growing body of evidence supports different signatures for Type 1 and Type 2 (Wang *et al.*, 2011; Kapczinski *et al.*, 2017; Song *et al.*, 2018; Coleman *et al.*, 2020). In the present study, we found having a low or borderline IQ is a risk markerfor BD type 1 but the finding does not hold after controlling for confounders. We could only identifya difference in the number of school failures after controlling for confounders, which was a significant risk marker for BD type 1 in relation to BD type 2 and subjects without mood disorders. Future longitudinal studies should replicate our results using independent samples with greater statistical power, as well as explore possible mechanisms implicated in these associations.

In conclusion, we investigated the association of premorbid IQ and school failure through data from the Pelotas 1993 population-based birth cohort. Individuals diagnosed with BD at 22 years- old had both higher numbers of school failure and lower IQ measures at 18 years old compared to individuals with MDD and without mood disorders. To the extent of our knowledge, this is the first time a report using a birth cohort was sufficiently powered to elucidate risk factors for the diagnosis of mood disorders, contributing to the understanding of trajectories of BD and MDD.

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Declarations of interest

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Table 1. Sociodemographic and clinical characteristics of individuals with BD, MDD, and without mood disorders.

	No mood disorders (n=2,981)	MDD (n=441)	BD (n=158)	Statistics
Sex				
Female, n(%)	1,464 (40.9)	314 (8.8)	79 (2.2)	$X^2(2)=75.32$, $p< 0.01$
Skin color, n(%)				$X^2(4)=23.26$, $p< 0.001$
White	1,830 (56.9)	255 (7.9)	65 (2)	
Black	402 (12.5)	55 (1.7)	32 (1)	
Brown	466 (14.5)	75 (2.3)	38 (1.2)	
Marital status*, n (%)				$X^2(6)=19.24$, $p< 0.01$
Married	474 (15.9)	49 (11.1)	32 (20.3)	
Divorced	12 (0.4)	4 (0.9)	0 (0)	
Single	2,495 (83.7)	387 (87.1)	126 (79.7)	
Widower	0 (0)	1 (0.2)	0 (0)	
Bipolar I Disorder, n(%)	-	-	92 (2.6)	-
Bipolar II Disorder, n(%)	-	-	66 (1.8)	-
Intellectual functioning (IQ), n(%)†				
Low or borderline	215 (7.9)	32 (8.7)	24 (16.7)	$X^2(8)=30.71$, p 0.01
Low average	489 (17.9)	69 (17.9)	33 (22.9)	
Average	1,572 (57.5)	202 (52.5)	76 (52.8)	
Above average	347 (12.7)	56 (14.5)	8 (5.6)	
Superior	112 (4.1)	26 (6.8)	3 (2.1)	
Number of school failure at 18-years follow-up visit ‡	2 [0 — 3]	1.5 [0 — 3]	2 [1 — 3]	$H(2)=24.58$, p 0.001

School dropout (last year) at 18-years follow-up visit, n(%)	418 (12.7)	57 (1.7)	39 (1.2)	$X^2(2)=14.02$, p 0.001

*Data collected at 22-years follow-up visit
‡ Values expressed as median [1st ‑3rd quartile]. It was performed Kruskall Walis test with Bonferroni post hoc test
†The percentages are represented within groups. All values within each column should be 100%.

Table 2. The adjusted odds ratio for subjects with BD and MDD at 22-year follow-up visit comparing individuals without mood disorders, assessing IQ four years before a formal diagnosis.

	Major Depressive Disorder AOR (95% CI)	Bipolar Disorder AOR (95% CI)
Intellectual Functioning (IQ)		
Low or threshold	1.01 (0.63 – 1.62)	1.75 (1.00 – 3.09)*
Below average	1.18 (0.86 – 1.61)	1.38 (0.88 – 2.16)
Above average	1.31 (0.90 – 1.90)	0.59 (0.25 – 1.41)
Superior	2.16 (1.24 – 3.75)**	0.76 (0.18 – 3.23)
Sex		
Female	2.35 (1.81 – 3.04)***	1.22 (0.83 – 1.78)
Ethnicity		
Black	1.07 (0.77 – 1.51)	1.75 (1.09 – 2.81)*
Brown	1.12 (0.82 – 1.54)	1.89 (1.21 – 2.95)**
Maternal years of education	1.02 (0.99 – 1.06)	0.98 (0.93 – 1.03)
Economic status		
2nd quintile	0.68 (0.47 – 0.98)	0.96 (0.57 – 1.60)

3rd quintile	0.74 (0.51 – 1.08)	0.88 (0.50 – 1.55)
4th quintile	0.61 (0.41 – 0.90)	0.80 (0.44 – 1.44)
5th quintile	0.79 (0.52 – 1.19)	0.66 (0.30 – 1.36)
Physical trauma	1.09 (0.83 – 1.43)	1.59 (1.07 – 2.36)*

*p < 0.05, ** p < 0.01, *** p < 0.001

Table 3. The adjusted odds ratio for subjects with BD and MDD at 22-year follow-up visit compared to individuals without mood disorders, assessing the number of school failures four years before a formal diagnosis.

	MDD AOR (95% CI)	BD AOR (95% CI)
Number of school failure	1.05 (0.96 – 1.14)	1.23 (1.11 – 1.41)***
No school drop out (last year)	0.91 (0.64 – 1.28)	0.51 (0.33 – 0.80)**
Sex		
Female	2.45 (1.88 – 3.20)***	1.44 (0.97 – 2.15)
Skin color		
Black	1.01 (0.72 – 1.43)	1.94 (1.20 – 3.13)**
Brown	1.07 (0.78 – 1.47)	1.98 (1.26 – 3.10)**
Maternal years of education	1.04 (1.00 – 1.08)*	1.00 (0.95 – 1.06)

Economic status		
2^{nd} quintile	0.68 (0.47 – 0.98)	0.96 (0.57 – 1.63)
3^{rd} quintile	0.78 (0.54 – 1.14)	0.98 (0.55 – 1.75)
4^{th} quintile	0.66 (0.44 – 0.98)*	0.89 (0.48 – 1.65)
5^{th} quintile	0.86 (0.56 – 1.31)	0.76 (0.36 – 1.60)
Physical trauma	1.13 (0.84 – 1.46)	1.51 (1.01 – 2.26)**

*$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

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Supplementary Table 1. The odds ratio for subjects with BD at 22-year follow-up visit comparing subjects without mood disorders, assessing IQ four years before a formal diagnosis.

	Bipolar Disorder OR (95% CI)
Intellectual functioning (IQ)	
Low or borderline	2.29(1.39 – 3.63)***
Low average	1.38 (0.89 – 2.08)
Above average	0.46 (0.2 – 0.91)
Superior	0.51 (0.12 – 1.41)

*p < 0.05, ** p < 0.01, *** p < 0.001

Supplementary Table 2. The odds ratio for subjects with BD and MDD at 22-year follow-up visit comparing subjects without mood disorders, assessing IQ four years before a formal diagnosis.

	BD OR (95% CI)	MDD OR (95% CI)
Intellectual functioning (IQ)		
Low or borderline	2.31 (1.43 – 3.74)***	1.16 (0.77 – 1.73)
Low average	1.40 (0.91 – 2.13)	1.10 (0.82 – 1.47)
Above average	0.47 (0.22 – 0.99)*	1.26 (0.91 – 1.73)
Superior	0.55 (0.17 – 1.78)	1.81 (1.15 – 2.84)**

*p < 0.05, ** p < 0.01, *** p < 0.001

Supplementary Table 3. The adjusted odds ratio for subjects with BD at 22-year follow-up visit comparing subjects without mood disorders, assessing IQ four years before a formal diagnosis.

	Bipolar Disorder AOR (95% CI)
Intellectual functioning (IQ)	
Low or borderline	1.76 (1.20 – 3.03) *
Low average	1.36 (0.86 - 2.10)
Above average	0.58 (0.22 - 1.27)
Superior	0.68 (0.11 - 2.30)
Sex	
Female	1.06 (0.73 - 1.55)
Skin color	
Black	1.75 (1.08 - 2.77) *
Brown	1.85 (1.18 - 2.86) **
Maternal years of education	0.98 (0.93 – 1.04)
Economic status	
2nd quintile	1.01 (0.60 – 1.68)
3rd quintile	0.92 (0.52 – 1.61)
4th quintile	0.86 (0.47 – 1.56)
5th quintile	0.69 (0.32 – 1.39)
Physical trauma	1.55 (1.04 – 2.29) *

*p < 0.05, ** p < 0.01, *** p < 0.001

Supplementary Table 4. The odds ratio for subjects with BD - type I and BD - type II at 22-year follow-up visit comparing individuals without mood disorders, assessing IQ four years before a formal diagnosis.

	BD – type I OR (95% CI)	BD – type II OR (95% CI)
Intellectual Functioning (IQ) *Low or borderline*	2.44 (1.34 – 4.45)***	2.12 (0.997 – 4.52)
Below average	1.36 (0.78 – 2.34)	1.45 (0.76 – 2.75)
Above average	0.40 (0.144 – 1.13)	0.58 (0.2 – 1.67)
Superior	0.62 (0.149 – 2.61)	0.45 (0.06 – 3.35)

*p < 0.05, ** p < 0.01, *** p < 0.001

Supplementary Table 5. The adjusted odds ratio for subjects with BD - type I and BD - type II at 22-year follow-up visit comparing individuals without mood disorders, assessing IQ four years before a formal diagnosis.

	BD – type I AOR (95% CI)	BD – type II AOR (95% CI)
Intellectual Functioning (IQ)		
Low or borderline	1.50 (0.72 – 3.14)	2.24 (0.96 – 5.21)
Below average	1.26 (0.71 – 2.25)	1.55 (0.78 – 3.08)
Above average	0.33 (0.07 – 1.41)	1.01 (0.34 – 3.01)
Superior	0.68 (0.09 – 5.15)	1.01 (0.13 – 7.81)
Sex		
Female	1.53 (0.93 – 2.52)	0.89 (0.5 – 1.60)
Skin color		
Black	1.44 (0.77 – 2.69)	2.29 (1.13 – 4.64)
Brown	1.66 (0.93 – 2.95)	2.19 (1.11 – 4.34)
Maternal years of education	0.97 (0.91 – 1.04)	0.99 (0.91 – 1.07)
Economic status		
2nd quintile	0.76 (0.40 – 1.45)	1.47 (0.63 – 3.41)
3rd quintile	0.66 (0.32 – 1.37)	1.41 (0.57 – 3.50)
4th quintile	0.51 (0.23 – 1.13)	1.51 (0.60 – 3.78)
5th quintile	0.56 (0.22 – 1.42)	0.93 (0.29 – 3.01)

Physical trauma	**1.67 (1.01 – 2.79) ***	1.50 (0.82 – 2.73)

*p < 0.05, ** p < 0.01, *** p < 0.001

Supplementary Table 6. The adjusted odds ratio for subjects with BD at 22-year follow-up visit compared to individuals without mood disorders, assessing the number of school failures four years before a formal diagnosis.

	Bipolar Disorder AOR (95% CI)
Number of school failures	1.25 (1.11 – 1.40)***
No school drop out (last year)	0.53 (0.34 – 0.82) ***
Sex	
Female	1.24 (0.84 – 1.85)
Skin color	
Black	1.94 (1.19 – 3.10) **
Brown	1.96 (1.25 – 3.05) **
Maternal years of education	1.00 (0.94 – 1.06)
Economic status	
2nd quintile	1.02 (0.60 – 1.72)
3rd quintile	1.02 (0.57 – 1.81)
4th quintile	0.97 (0.52 – 1.77)
5th quintile	0.78 (0.36 – 1.61)
Physical trauma	1.48 (0.98 – 2.20)

*p < 0.05, ** p < 0.01, *** p < 0.001

10. PRÊMIOS E EDITAIS

Nome	Instituição	Ano	Observação
Doutora do sanduíche	Erasmus Programme	2021	Desenvolvido e obtido durante o doutorado
International Travel Grant Award	International Brain Research Organization (IBRO)	2020	Desenvolvido e obtido durante o doutorado
Samuel Gershon Junior Investigator Awards	International Society for Bipolar Disorders (ISBD)	2019	Obtido durante o doutorado devido à pesquisa do mestrado

11. DIVULGAÇÃO CIENTÍFICA

Nome da entrevista	Jornal	Ano	Endereço
Doctors develop system which can predict Bipolar Disorder 4 years before onset	European College of Neuropsychopharmacology	2020	https://www.ecnp.eu/Informati onandnews/ecnp-press-office/congress-press-release
Novel Tool May Predict Bipolar Disorder Long Before Onset	MedScape	2020	https://www.medscape.com/vi ewarticle/937644#vp_1
Estudo observa brasileiros por 22 anos e cria sistema para prever transtorno bipolar	G1	2020	https://g1.globo.com/ciencia-e-saude/noticia/2020/09/14/estud o-observa-brasileiros-por-22- anos-e-cria-sistema-para- prever-transtorno-bipolar.ghtml

Egresso da UFC faz parte de grupo que mostrou eficácia do plasma convalescente no tratamento de pacientes com covid-19	UFC notícias	2020	https://egressos.ufc.br/2020/09/11/egresso-da-ufc-faz-parte- de-grupo-que-mostrou- eficacia-do-uso-do-plasma- convalescente-no-tratamento- de-pacientes-com-covid-19/
Pesquisa usa ferramenta virtual para prever suicídio	Record TV	2018	https://www.recordtvrs.com.br/rio-grande-record/videos/pesquisa-usa- ferramenta-virtual-para-prever-suicidio-31102018

12. CONSIDERAÇÕES FINAIS

Essa tese de doutorado teve como resultado a produção de dois artigos científicos. O primeiro foi publicado pela *Acta Psychiatrica Scandinavica* e o segundo está em revisão na *Psychological Medicine*. O primeiro artigo cujo título é "**Early identification of bipolar disorder among young adults – a 22-year community birth cohort**" teve como objetivo identificar precocemente TB em uma coorte de nascimentos. Foram avaliados 3810 sujeitos na visita de 22 anos de idade, mas foram incluídos, nesse artigo científico, 3778 participantes. Através de algortimos de ML, foi possível detectar pessoas que desenvolverão TB quatro anos antes do diagnóstico, isto é, na coleta de dados realizada aos 18 anos de idade. O modelo de ML teve boas medidas de desempenho, ou seja, o algortimo foi capaz de prever adequadamente quem terá TB quatro anos antes do diagnóstico formal. Dentre as variáveis mais importantes para identificá-los precocemente foi risco de suicídio, diagnóstico de transtorno de ansiedade generalizada, abuso físico parental, problemas financeiros e entre outros. Posteriormente, foram estratificados os indivíduos em alto e baixo risco de desenvolver TB a partir das probabilidades preditas pelo modelo e achou-se que os sujeitos em alto risco, na visita de 22 anos, apresentavam sintomas de anedonia e usaram drogas como MDMA e opióides no último ano.

Do ponto de vista clínico, é altamente relevante o desenvolvimento de instrumentos para diagnóstico precoce do TB, uma vez que há uma lacuna entre o primeiro episódio de humor e o início do tratamento adequado. Esse período está associado há maiores chances de mortes por súicídio e longos períodos sem receber o tratamento adequado podem estar associado a piores desfechos funcionais e maior refratariedade ao tratamento (Gonda *et al.*, 2012; Passos *et al.*, 2016). Dessa forma, sua identificação precoce possibilitará a aplicação de intenverções preventivas com o objetivo de reduzir o risco de desfechos desfavoráveis associados ao TB quando não tratado adequadamente. Futuros estudos devem replicar esses achados em amostra independentes oriundas de diferentes países, maiores períodos de acompanhamento bem como adicionar variáveis de distintos níveis biológicos como neuroimagem estruturais e funcionais, escores de risco poligênico e multi-omics. Assim, poder-se-á ter uma avaliação global das pessoas com TB e desenvolver modelos de IA com maior acurácia e menor falso negativo.

O segundo artigo é intitulado **"Premorbid intelligence quotient and school failure as risk markers for bipolar disorder and major depressive disorder"** e está em *under review* no periódico *Psychological Medicine.* Um dos principais achados foi que ter um QI baixo ou limítrofe aos 18 anos e número de repetência escolar foi um marcador de risco para o desenvolvimento de TB aos 22 anos de idade, ou seja, quatro anos antes do diagnóstico, enquanto que um QI alto foi um marcador de risco para Transtorno Depressivo Maior, mas não o número de repetência escolar. O número de repetência escolar e o QI baixo ou limítrofe foram marcadores de risco para TB-I e não para TB-II.

Ademais, compreender o funcionamento cognitivo pré-mórbido permite o desenvolvimento de terapêuticas focadas na reabilitação cognitiva e psicossocial dessas pessoas bem como no aperfeiçoamento de intervenções biológicas que possam ter um efeito na cognitição. É crucial que haja mais estudos longitudinais de coortes de nascimentos para investigar todo percurso clínico e cognitivo de pessoas com TB antes e após o primeiro episódio de humor, pois permanece inconclusivo se os prejuízos neuropsicológicos após o início do transtorno são devidos aos episódios de humor ou se essas pessoas apresentam déficits pré-mórbidos ou se é uma combinação destes fatores.

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