**UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL FACULDADE DE MEDICINA PROGRAMA DE PÓS-GRADUAÇÃO EM PSIQUIATRIA E CIÊNCIAS DO COMPORTAMENTO**

DISSERTAÇÃO DE MESTRADO

# Identificando a Depressão Precocemente na Adolescência: um Estudo de Neuroimagem Estrutural

Fernanda Rohrsetzer Cunegatto

Orientador: Prof. Dr. Christian Kieling

Porto Alegre, setembro de 2022

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Dissertação apresentada ao Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento como requisito parcial para obtenção do grau de Mestre.

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## SUMÁRIO

**Lista de Abreviaturas e siglas**

ACC - Anterior Cingulate Cortex

CEN - Central Executive Network

DMN - Default Mode Network

DTI - Diffusion Tensor Imaging

EEG - Eletroencefalograma

ENIGMA - Enhancing Neuroimaging Genetics Through Meta-Analysis

eTIV - Volume intracraniano Total Estimado

FDR - False Discovery Rate

FWHM - Full Width at Half Maximum

fMRI - functional magnetic resonance imaging

GLM - General Linear Model

GM - Gray Matter

GTs - Grupos de Trabalho

HICs - High Income Countries

ICV - Volume Intracraniano

IDEA - Identifying Depression Early in Adolescence

IDEA-RS - Escore de Risco Identificando a Depressão no Início da Adolescência

IDEA-RiSCo - Coorte Estratificada de Risco para Identificação de Depressão no Início da Adolescência

LCR - Líquido Cefalorraquidiano

MRI - Ressonância Magnética (Magnetic Resonance Imaging)

OFC - Orbitofrontal Cortex

PFC - Prefrontal Cortex

RNM - Ressonância Magnética Nuclear

ROI - Regions of Interest

SBM - Surface Based Morphometry

SCN - Structural Covariance Network

sMRI - Structural Magnetic Resonance Imaging

SN - Salient Network

TDM - Transtorno Depressivo Maior

VBM - Voxel-Based Morphometry

WM - White Matter

## Resumo

**Introdução:** O transtorno depressivo maior (TDM) tem uma incidência importante na adolescência e representa uma das principais causas de carga e incapacidade nessa faixa etária. Além disso, são inúmeros fatores que estabelecem uma causa para o TDM e da mesma forma são múltiplos os caminhos da predisposição ao desenvolvimento do transtorno. Assim, identificar características cerebrais associadas ao risco e à ocorrência precoce do TDM representam importantes oportunidades para compreender os mecanismos associados ao início da depressão. Sendo assim, a partir de um escore de risco composto para estimar a probabilidade individual de desenvolver depressão maior entre adolescentes brasileiros (IDEA-RS), incluímos 150 adolescentes brasileiros entre 14-16 anos de idade na *Coorte Estratificada de Risco para Identificação de Depressão no Início da Adolescência* (IDEA-RiSCo), uma amostra bem caracterizada de adolescentes de baixo risco e alto risco para depressão e com TDM atual. **Objetivos:** Explorar diferenças cerebrais morfométricas regionais associadas ao risco e presença de depressão na adolescência através de uma abordagem baseada em vértices e na organização estrutural das redes de covariância. **Métodos:** Foram analisados dados transversais de neuroimagem estrutural da amostra IDEA-RiSCo associada ao risco e presença de depressão por meio de uma abordagem baseada em vértices com medidas de volume cortical, área de superfície e espessura. Foram examinadas diferenças entre grupos em volumes subcorticais e foram exploradas diferenças na organização de redes de covariância estrutural entre os grupos. **Resultados:** De agosto de 2018 a dezembro de 2019, 150 participantes (50% do sexo feminino) realizaram exames de ressonância magnética: destes, 50 estavam no grupo LR, 50 no grupo HR e 50 no grupo MDD. A média de idade foi de 15,6 anos e não houve diferenças significativas na proporção de adolescentes que se auto identificaram como brancos nos três grupos. Neste momento não foram observadas diferenças significativas entre os grupos em nenhuma das comparações acima. Tendo em vista que os dados analisados são transversais, espera-se a ausência de diferenças morfométricas significativas associadas ao risco e presença de depressão na adolescência, conforme relatado em estudos anteriores. **Conclusão:** O presente trabalho se propôs a apresentar resultados transversais de dados de neuroimagem estrutural de adolescentes brasileiros com alto ou baixo risco de depressão ou vivenciando um episódio depressivo. Neste momento, não encontramos diferenças significativas na estrutura cerebral entre os grupos de risco/TDM. O seguimento deste projeto certamente irá agregar mais informações acerca do desenvolvimento da estrutura cerebral e possíveis alterações relacionadas ao risco e presença de depressão na adolescência.


Palavras-chave: adolescência, escore de risco, depressão, neuroimagem/estrutural

## Abstract

**Introduction:** Major depressive disorder (MDD) is highly prevalent in adolescence and one of the main causes of burden and disability in this age group. In addition, there are numerous factors that establish a cause for MDD and, in the same way, there are multiple paths of predisposition to the development of the disorder. Thus, identifying brain characteristics associated with the risk and early occurrence of MDD represents important opportunities to understand the mechanisms associated with the onset of depression. Therefore, based on a composite risk score to estimate the individual probability of developing major depression among Brazilian adolescents (IDEA-RS), we included 150 Brazilian adolescents between 14-16 years of age in the Risk Stratified Cohort for the Identification of Early Depression of Adolescence (IDEA-RiSCo), a well-characterized sample of low-risk (LR) and high-risk (HR) for depression and with current depression (MDD). **Objectives:** To explore regional morphometric brain differences associated with the risk and presence of depression in adolescence through an approach based on vertices and on the structural organization of covariance networks. **Methods:** Cross-sectional structural neuroimaging data from the IDEA-RiSCo sample associated with the risk and presence of depression were analyzed using a vertex-based approach with measurements of cortical volume, surface area and thickness. Differences between groups in subcortical volumes were examined and differences in the organization of structural covariance networks between groups were explored. **Results:** From August 2018 to December 2019, 150 participants (50% female) underwent MRI scans: of these, 50 were in the LR group, 50 in the HR group and 50 in the MDD group. The mean age was 15.6 years and there were no significant differences in the proportion of adolescents who self-identified as white in the three groups. At this time, no significant differences were observed between the groups in any of the above comparisons. Considering that the analyzed data are cross-sectional, it is expected the absence of significant morphometric differences associated with the risk and presence of depression in adolescence, as reported in previous studies. **Conclusion**: The present study aimed to present cross-sectional results of structural neuroimaging data from Brazilian adolescents with high or low risk of depression or experiencing a depressive episode. At this time, we found no significant differences in brain structure between risk/MDD groups. The follow-up of this project will certainly add more information about the development of the brain structure and possible changes related to the risk and presence of depression in adolescence.


Keywords: adolescence, risk score, depression, neuroimaging/structural

## 1. Apresentação

Este trabalho consiste na dissertação de mestrado intitulada *"Identificando a Depressão Precocemente na Adolescência: um Estudo de Neuroimagem Estrutural"* apresentada ao Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento da Universidade Federal do Rio Grande do Sul (UFRGS). O trabalho é apresentado em sete partes, na ordem que segue:

2. Introdução;
3. Base conceitual e revisão da literatura,
3.1. Depressão na infância e adolescência,
3.2. Caracterização de risco,
3.3. Exame de ressonância magnética;
3.3.1 Morfometria cerebral por Ressonância Magnética;
3.3.2 Freesurfer;
3.3.3 Covariância estrutural;
3.4 Achados neuroimagem estrutural e depressão;
4. Objetivos;
4.1 Objetivo geral;
4.2 Objetivos específicos;
5. Considerações éticas;
6. Artigo;
7. Conclusões e considerações finais;
8. Referências bibliográfica
9. Anexos

## 2. Introdução

No mundo todo, o Transtorno Depressivo Maior (TDM) é uma das principais causas de carga relacionada à doença e à incapacidade entre adolescentes (1, 2) e uma maneira de reduzir essa carga poderia ser, em diminuir o número de novos casos, ou seja, reduzir a incidência (3). Considerando que a causa da depressão é multifatorial e que, da mesma forma, são múltiplos os caminhos da predisposição ao desenvolvimento do transtorno, identificar características cerebrais associadas ao risco elevado e à ocorrência precoce do TDM representam importantes oportunidades para compreender os mecanismos associados ao início da depressão (4, 5).

Nesse contexto, nos últimos anos, estudos de neuroimagem, como a ressonância magnética estrutural (sMRI - sigla em inglês) exploraram alterações na estrutura cerebral associadas ao risco e à presença de TDM em adolescentes (6-11). No entanto, os achados dos estudos são altamente heterogêneos (6-9, 11, 12). A maioria das investigações de morfometria cerebral concentraram-se principalmente em regiões cerebrais específicas (ROIs), o que pode ter contribuído para as inconsistências nos achados (13, 14). Por exemplo, se uma região específica é medida, outras estruturas cerebrais são ignoradas e possíveis efeitos permanecem não detectados em outras partes do cérebro (15). Estudos que investigaram alterações neuroanatômicas em amostras com adolescentes em risco elevado para TDM também apresentam inconsistência nos achados, como volumes maiores, menores ou semelhantes na amígdala, hipocampo e putâmen no grupo de alto risco em comparação ao grupo de baixo risco (16-19). Alterações na espessura

cortical também foram descritas em amostras de adolescentes em alto risco para TDM embora os resultados desses estudos também tenham sido inconsistentes e tenham tido tamanhos de efeito relativamente pequenos (20-22).

Evidências de pesquisas em neuroimagem também apoiam a visão de que as diferenças na estrutura cerebral relacionadas ao TDM não ocorrem somente em regiões cerebrais isoladas, mas também são caracterizadas em termos de redes cerebrais estruturais alteradas (23). Por exemplo, os componentes dos sistemas neurais que provavelmente estão subjacentes ao MDD incorporam quatro redes: rede afetiva límbica, a rede de recompensa frontal-estriatal, a rede de modo padrão e uma rede de controle cognitivo dorsal (24). A caracterização dessa conectividade em nível de sistemas pode ser considerada em vários níveis de análise e um desses níveis é a covariância estrutural (25, 26).

As várias propriedades organizacionais das redes derivadas da covariância estrutural foram caracterizadas usando a teoria dos grafos. Embora a interpretação neurobiológica dessas associações permaneça vaga, foi levantada a hipótese de refletir influências genéticas e plásticas, incluindo o tempo de maturação (27, 28). As redes de covariância estrutural do cérebro foram exploradas em alguns estudos entre adultos com TDM e controles saudáveis (23, 29-31). No entanto, nenhum estudo explorou as redes de covariância estrutural cerebral em adolescentes em risco e com TDM. Além de fornecer uma melhor compreensão dos substratos neurais da depressão, a análise de covariância estrutural em adolescentes em risco e com depressão também seriam úteis para encontrar potenciais marcadores cerebrais de vulnerabilidade para prevalência do transtorno (22, 32).

Diferenças metodológicas nos *pipelines* de processamento usados para derivar medidas estruturais de sMRI entre os estudos também podem ter contribuído para a inconsistência dos resultados (32). Por exemplo, um foco maior foi dado para análise de espessura cortical baseada em região em comparação a estimativas mais precisas como a espessura cortical baseada em vértice (33). Embora as duas abordagens sejam eficazes para estimar os índices de morfologia cortical, elas fornecem informações em diferentes escalas (34). A análise por vértice é usada para calcular parâmetros morfológicos locais para cada ponto (vértice) da superfície cortical, enquanto a análise por região é usada para analisar a organização cortical em larga escala a nível de área com base no parcelamento cortical (35). Além disso, a variabilidade nos critérios de inclusão e exclusão, podem contribuir para esses achados díspares (36).

Outro possível contribuinte para a heterogeneidade dos achados é que a maioria dos estudos que investigaram correlatos neurobiológicos de fatores de risco para o início da depressão se concentrou em fatores únicos para atribuir o status de risco, (por exemplo, o histórico familiar de depressão) (37, 38). Entretanto, o foco em fatores de risco únicos resulta na dependência de apenas uma fonte de informação para a estratificação dos indivíduos em termos de alto e baixo risco. Por exemplo, adolescentes sem histórico familiar do transtorno (geralmente classificados como de baixo risco em muitos estudos) podem ter uma alta probabilidade de desenvolver TDM com base em outros fatores de risco (por exemplo, a experiência de maus-tratos durante a infância) (39).

Considerando esse cenário, recentemente, nosso grupo desenvolveu um escore de risco composto para estimar a probabilidade individual de desenvolver

depressão maior entre adolescentes brasileiros (40). O *Identifying Depression Early in Adolescence Risk Score* (IDEA-RS) compreende apenas variáveis sociodemográficas que podem ser facilmente obtidas diretamente do adolescente (41). Usando o IDEA-RS, recentemente incluímos 150 adolescentes no estudo *Identifying Depression Early in Adolescence Risk Stratified Cohort* (IDEA-RiSCo) (42), uma amostra bem caracterizada de adolescentes de baixo risco, alto risco e com TDM do Brasil. Portanto, é dentro dessa perspectiva que a presente dissertação se insere, especificamente no estudo de caráter exploratório das diferenças cerebrais morfométricas regionais associadas ao risco e presença de depressão através de uma abordagem baseada em vértices e na organização estrutural das redes de covariância entre os grupos.

## 3. Base conceitual e revisão da literatura

### 3.1. Depressão na adolescência

Nas duas últimas décadas, a depressão entre adolescentes vem sendo reconhecida como um importante problema de saúde mental (2, 43). De acordo com estudos epidemiológicos (44-46), a depressão está associada a prejuízos nas relações sociais, piora no desempenho escolar e um risco aumentado de mortalidade precoce por suicídio (47, 48).

Enquanto os estudos apontam para uma ocorrência relativamente baixa de episódios depressivos em pré-escolares – afetando aproximadamente 1% a 2,5% dessa população – durante a adolescência (36), as estimativas de prevalência se assemelham àquelas encontradas na população adulta, com 4,5 a 7,7% dos jovens apresentando um episódio depressivo em um período de 12 meses (36, 49, 50). Já ao longo da adolescência, o risco acumulado para a ocorrência de um episódio depressivo aumenta de 5% para 10% (51, 52). Além disso, a prevalência do transtorno na proporção de meninas é o dobro quando comparada à população de meninos, mantendo-se assim ao longo da vida adulta (53).

Muitos fatores podem contribuir para esse aumento na prevalência de depressão, uma vez que a adolescência é um período crucial para o desenvolvimento humano, marcado por diversas mudanças biológicas, psicológicas e sociais (52, 53). O entendimento sobre quais fatores estão envolvidos na fisiopatologia da depressão e de como a doença é expressa nessa população se torna necessário, pois essa identificação pode contribuir para o desenvolvimento de

intervenções precoces, reduzindo o impacto da depressão no âmbito familiar, social e acadêmico, podendo assim, diminuir o risco de comportamento suicida, abuso de substâncias e a persistência do transtorno ao longo da vida (54, 55).

### 3.2 Caracterização de risco

Quando se fala em fatores de risco, principalmente no campo da pesquisa em psiquiatria e saúde mental, muitas vezes se investiga um único fator de risco por vez (por exemplo, pobreza, maus-tratos, discriminação) na tentativa de identificar mecanismos associados à fisiopatologia do transtorno (42). Mesmo com os significativos avanços na identificação de marcadores de risco de depressão individuais, confiar em fatores de risco únicos pode ser um equívoco na identificação de indivíduos de alto e baixo risco. A título de exemplo, adolescentes sem histórico familiar do transtorno (frequentemente classificado como de baixo risco em muitos estudos) podem na realidade estar em alto risco de desenvolver depressão devido à experiência de outros fatores de risco (por exemplo, maus-tratos na infância) (42).

A maioria das amostras atuais em pesquisa em saúde mental contrasta casos e controles (não-casos), sendo os últimos geralmente definidos pela ausência de um transtorno psiquiátrico atual (42). No entanto, especialmente entre os indivíduos mais jovens, os não-casos podem apresentar uma série de fatores de risco que os tornam propensos a desenvolver um transtorno no futuro, levando a um grau elevado de ruído e heterogeneidade nesses desenhos típicos. O uso de escores de risco derivados de múltiplos fatores de risco representa uma estratégia lógica para não presumir que adolescentes sem o transtorno sejam um grupo homogêneo, permitindo assim que pesquisadores se concentrem especificamente

não apenas em indivíduos com risco extremamente alto, mas também extremamente baixo de desenvolver depressão (42). Pensando no desenvolvimento e aplicação de métodos de pesquisa de ponta normalmente empregados em países de alta renda (HICs, sigla em inglês), o consórcio *Identifying Depression Early in Adolescence* (IDEA) é uma iniciativa multinacional para melhorar a identificação precoce do TDM em adolescentes (42). Pesquisadores do Brasil, Nepal, Nigéria, Reino Unido e Estados Unidos desenvolveram um escore composto para estimar a probabilidade individual de desenvolver depressão maior entre adolescentes brasileiros (40, 56-58). O escore de risco IDEA (IDEA-RS) (41) compreende apenas variáveis sociodemográficas que podem ser facilmente obtidas diretamente do adolescente para facilitar a tradução em prática: sexo biológico, cor da pele, uso de drogas, reprovação escolar, isolamento social, envolvimento em brigas, relacionamento com a mãe, relacionamento com o pai, relação entre os pais, maus-tratos na infância e fuga de casa (42). Entre adolescentes de 15 anos no Brasil, o IDEA-RS apresentou bom desempenho discriminativo (estatística C de 0,78) para estratificar indivíduos de alto e baixo risco para desenvolver depressão aos 18 anos de idade (40).

### 3.3. Exame de ressonância magnética

O exame de ressonância magnética é uma técnica de imagem baseada nos princípios da ressonância magnética nuclear (RMN) que detecta sinais de prótons de moléculas de água e fornece medidas precisas da anatomia e fisiologia do cérebro sem o uso de radiação ionizante (59-61). Nas últimas décadas, a utilização desse método na pesquisa tomou grandes proporções, principalmente na investigação dos transtornos psiquiátricos, procurando explicar os aspectos

neuroanatômicos e funcionais envolvidos na etiologia e/ou fisiologia dos transtornos mentais (62). Além disso, a RMN também forneceu informações valiosas sobre a anatomia e fisiologia do cérebro em desenvolvimento de jovens saudáveis, bem como daqueles com doenças neuropsiquiátricas (61, 63, 64).

A depressão na adolescência tornou-se recentemente um foco em estudos de neuroimagem na busca pela identificação de mecanismos neurobiológicos subjacentes a esse transtorno no cérebro em desenvolvimento, pois isso pode ser essencial para otimizar o tratamento e a prevenção da depressão em adolescentes e suas trajetórias clínicas negativas (65, 66). As sequências de varredura de ressonância magnética comumente usadas por pesquisadores incluem imagens estruturais de alta resolução (3D-T1), que representam a espessura da massa cinzenta em volume e morfologia cerebral; imagem por tensor de difusão (DTI - sigla em inglês), que descreve a microestrutura da substância branca; e imagem de ressonância magnética funcional (fMRI - sigla em inglês), que indica a atividade neuronal na região do cérebro (67).

### 3.3.1 Morfometria cerebral por Ressonância Magnética

O estudo da morfometria cerebral e sua caracterização podem ser realizados *in vivo* com ressonância magnética de alta resolução combinada com métodos de neuroanatomia computacional (68). Os métodos para estimar a morfologia cortical a partir de imagens de ressonância magnética (MRI - sigla em inglês) podem ser amplamente categorizados como baseados em voxels (VBM - sigla em inglês) ou baseados em superfície (SBM - sigla em inglês) (34). Ambos os métodos requerem uma segmentação inicial para separar a substância cinzenta (*Gray-Matter, GM*), a

substância branca (White-Matter, WM) e o líquido cefalorraquidiano (LCR - sigla em inglês) (69).

A VBM é uma das técnicas automatizadas mais utilizadas e computacionalmente muito eficientes para examinar padrões de alterações cerebrais (15, 69). A VBM funciona diretamente na grade de voxels e compara diferentes cérebros voxel por voxel após os campos de deformação terem sido usados para normalizar espacialmente as imagens (70, 71). No entanto, são considerados menos precisos devido à limitada resolução da grade de voxels, menos robustos ao ruído e à segmentação incorreta, pois normalmente não possuem os mecanismos necessários para avaliar e corrigir erros topológicos (72).

A SBM foi desenvolvida para representar o córtex cerebral anatomicamente usando um modelo de superfície composto por uma malha triangulada com base no limite da substância branca ou no limite da superfície pial (73-75), que é então deformado para encontrar o limite oposto. Com o córtex fechado no tronco cerebral, a superfície resultante é topologicamente equivalente a uma esfera (69, 76). A SBM permite que se separe a espessura cortical, área de superfície e dobras para examinar como cada um desses índices contribui para a variabilidade na anatomia cortical (77). Em geral, a análise baseada em superfície fornece uma distinção mais clara entre o sulco e o giro do que a VBM (73). Abaixo uma figura ilustrativa sobre as diferenças entre a VBM e SBM (77).

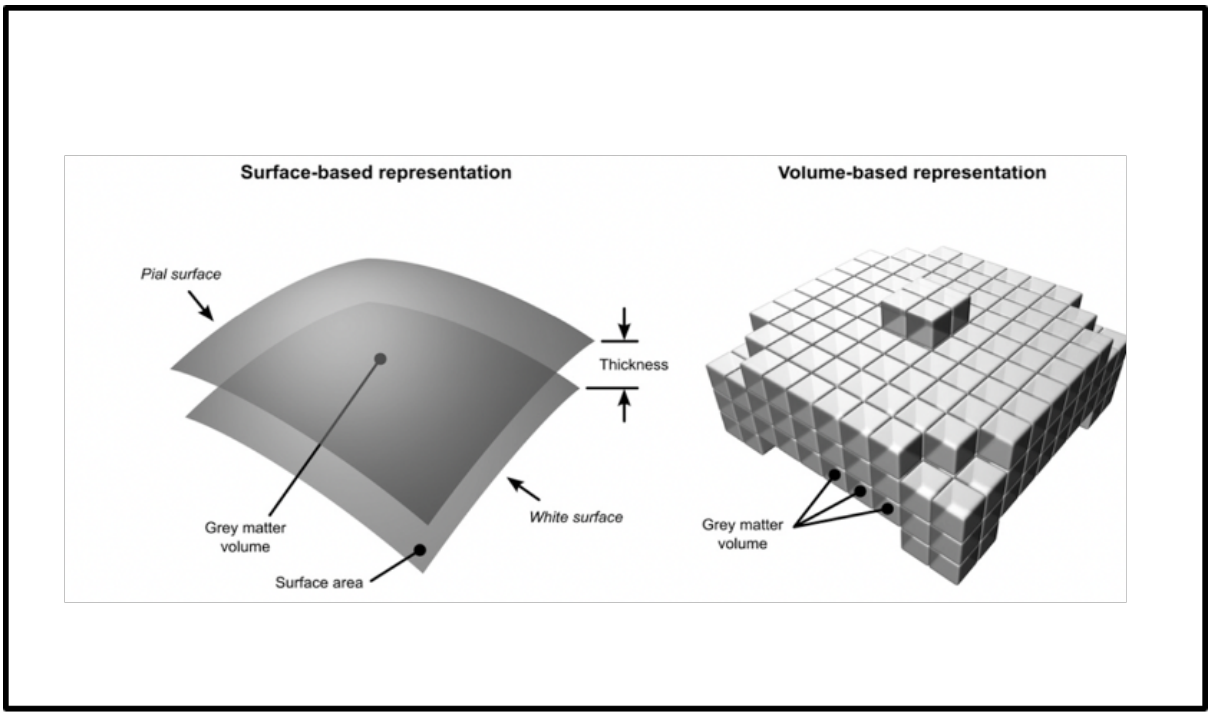


**Figura. 1**. Relação geométrica entre espessura cortical, área da superfície e volume da substância cinzenta. Na SBM, o volume de matéria cinzenta é uma função quadrática das distâncias nas superfícies e uma função linear da espessura. Na VBM, apenas os volumes podem ser medidos diretamente e exigem que os efeitos de volume parciais (não representados) sejam considerados. Figura extraída de winkler et al., 2011)

A automação de técnicas de segmentação cerebral desenvolvidas continuamente nas últimas décadas tem contribuído substancialmente para os avanços na área de neuroimagem com softwares de análise de imagem cada vez melhores (78). Entre as ferramentas mais complexas de segmentação e parcelamento, o FreeSurfer (FS) detém a posição de ferramenta padrão-ouro para a medição da espessura e volume cortical de um amplo espectro de estruturas neuroanatômicas (61, 79).

### 3.3.2 Freesurfer

O FreeSurfer é um método amplamente utilizado, documentado e disponível gratuitamente (http://surfer.nmr.mgh.harvard.edu/) para a análise e visualização de dados de neuroimagem estrutural e funcional de estudos transversais ou longitudinais (80). O FreeSurfer calcula várias métricas de morfometria em dois fluxos de processamento: um fluxo baseado em superfície e um fluxo baseado em volume. A reconstrução baseada na superfície cortical é fundamentada em modelos geométricos da superfície cortical e na identificação das bordas entre certos tipos de tecidos (detalhes estão descritos em Dale et al., 1999) (74, 81). O limite/fronteira entre a pia-máter e a substância cinzenta cortical forma a superfície pial, enquanto o limite/fronteira entre a substância cinzenta e branca cortical representa a superfície branca (82). O córtex é ainda modelado como uma superfície com uma malha de triângulos. Cada ponto de encontro de triângulos (chamado de vértice) tem coordenadas exatas que permitem várias manipulações não lineares, como inflação, normalização espacial e análise de grupo. Essas reconstruções permitem diferenciar volume cortical, espessura, área de superfície, curvatura média e padrões de girificação local (82). Para a espessura cortical o FreeSurfer calcula a distância entre a superfície pial e a superfície branca (76). Já o volume cortical representa o produto da espessura cortical e área de superfície. O índice de girificação local quantifica a girificação em cada vértice na superfície e é calculado de forma 3D usando uma região circular de interesse (ROI; 20 a 25 mm) em torno de cada vértice (83).

A reconstrução baseada em volume foi desenvolvida independentemente do fluxo baseado em superfície(84, 85). O FreeSurfer rotula cada voxel no tecido

cortical e subcortical em uma máscara do cérebro sem crânio, dependendo da intensidade do voxel e dos mapas de probabilidade. Consequentemente, o volume das estruturas subcorticais (como, núcleo caudado, tálamo, putâmen, globo pálido, amígdala e hipocampo), substância cinzenta e branca cerebelar, substância cinzenta cortical e substância branca cerebral é calculado (82). O FreeSurfer também calcula o “volume intracraniano total estimado” (eTIV; também chamado de volume intracraniano ou ICV), usando um modelo representativo do atlas, que representa “a expansão (ou contração) do volume cerebral total necessária para registrar cada indivíduo ao modelo” (86).

### 3.3.3 Covariância estrutural

O cérebro é um conectoma que coleta arquiteturas de rede por organizações fragmentadas e aglutinadas (87). O conectoma do cérebro humano pode ser separado em conectividade funcional com base no processo de sinal (88, 89) conectividade estrutural baseada em tratos de fibra (90-92) e conectividade de covariância com base na análise de covariância estrutural (91, 93). A covariância estrutural é uma abordagem que examina se a alteração anatômica em uma região se correlaciona com as alterações em outras regiões do cérebro (94). A conectividade de covariância, principalmente referida como rede de covariância estrutural (SCN - sigla em inglês) construída por imagens morfológicas, pode ser usada para medir os padrões topológicos sincronizados de regiões cerebrais com base em associações estatísticas inter-regionais de diferentes descritores morfológicos (por exemplo, espessura cortical, volume de matéria cinzenta e área de superfície) (25, 26).

As várias propriedades organizacionais das redes derivadas de covariância estrutural foram caracterizadas usando a teoria dos grafos (95). De acordo com a teoria dos grafos, as redes cerebrais estruturais podem ser descritas como grafos compostos de nós (vértices) que denotam elementos neurais (neurônios ou regiões cerebrais) que são ligados por arestas que representam conexões físicas (sinapses ou projeções axonais) (87).

Evidências de pesquisas de neuroimagem também apoiam a visão de que as diferenças estruturais cerebrais relacionadas ao TDM não ocorrem em regiões cerebrais isoladas, mas também são caracterizadas em termos de redes cerebrais estruturais alteradas (23). Por exemplo, os componentes dos sistemas neurais que provavelmente estão subjacentes ao TDM incorporam quatro redes: uma rede afetiva límbica ventral que parece estar associada ao processamento e regulação das emoções (66), uma rede de recompensa frontal-estriatal que foi sugerida para explicar a anedonia (96), a rede de modo padrão parece estar associada à experiências internalizantes e à ruminação depressiva (97) e a uma rede de controle cognitivo dorsal que se acredita estar subjacente a déficits cognitivos relacionados ao processamento emocional (98-100). Embora a interpretação neurobiológica dessas associações permaneça vaga, foi levantada a hipótese de refletir influências genéticas e de plasticidade cerebral, incluindo o tempo de maturação (27, 28).

As redes de covariância estrutural do cérebro foram exploradas em alguns estudos entre adultos com TDM e controles saudáveis (23, 29, 30, 101, 102). Padrões alterados na rede de regulação emocional em pacientes com MDD foram

relatadas por Wu et al., (2017) (101) através no aumento da força de correlação do volume da massa cinzenta entre o giro angular e a amígdala, bem como uma diminuição da força da correlação do volume da massa cinzenta entre o lado direito giro angular e o córtex cingulado posterior. Outros estudos também relataram alterações em redes estruturais, como (a) rede do lobo temporal medial envolvendo principalmente o hipocampo e giro parahipocampal foi significativamente correlacionada com a gravidade dos sintomas individuais no grupo MDD (29); (b) rede neural de todo o cérebro com diminuição da força do nó hipocampal do corno direito, indicando conectividade diminuída com o resto do cérebro no grupo MDD (31); (c) rede de modo padrão, cortical pré-frontal ventromedial e redes de saliência com menor integridade estrutural em indivíduos com TDM (102); e (d) organização da rede de espessura cortical interrompida em pacientes com MDD. Os nós com centralidade anormal incluíram áreas no núcleo da rede de modo padrão (DMN – sigla em inglês), ou seja, rede de saliência (SN – sigla em inglês) e rede executiva central (CEN – sigla em inglês). No entanto, nenhum estudo explorou as redes de covariância estrutural cerebral em adolescentes em risco e com TDM (103).

A Análise de redes de covariância estrutural cerebral (SCNs) (redes construídas com base em correlações estatísticas dos índices morfológicos entre regiões cerebrais) pode fornecer informações abrangentes a nível de rede e fornecer pistas para a identificação de biomarcadores de desenvolvimento alterado que contribuem para o surgimento de transtornos de humor (104). Além de fornecer uma melhor compreensão dos substratos neurais associados à depressão, tais análises em adolescentes em risco para o transtorno também podem ser úteis na

identificação de potenciais marcadores cerebrais associados à vulnerabilidade para TDM (98, 105).

### 3.4 Achados neuroimagem estrutural e depressão na adolescência

Nos últimos anos, estudos de neuroimagem forneceram achados de alterações estruturais cerebrais associadas ao TDM em adolescentes (6-9, 11, 106), com investigações de morfometria focando principalmente em regiões específicas do cérebro e encontrando resultados altamente heterogêneos (107, 108). Por exemplo, enquanto alguns estudos identificaram alterações no volume da amígdala e do hipocampo, outros relataram alterações na área cortical, espessura e volume de algumas regiões, como córtex pré-frontal (PFC - sigla em inglês), córtex orbitofrontal (OFC - sigla em inglês), córtex cingulado anterior (ACC - sigla em inglês) (6, 7, 109, 110). Da mesma forma, estudos que investigaram alterações neuroanatômicas em amostras com adolescentes com risco de depressão sugerem volumes maiores, menores ou iguais de amígdala, hipocampo e putâmen no grupo de alto risco em relação ao grupo de baixo risco (16, 17, 111, 112). Alterações na espessura cortical também foram descritas em amostras de adolescentes com alto risco para TDM (20-22). Diferenças metodológicas nos pipelines de processamento usados para derivar medidas estruturais de sMRI entre estudos podem contribuir para resultados inconsistentes (32, 113). Com o objetivo de reduzir a heterogeneidade no processamento de dados de ressonância magnética, O grupo *Enhancing Neuroimaging Genetics Through Meta-Analysis* (ENIGMA), surgiu como uma importante ferramenta de padronização e harmonização de processamento de dados de neuroimagem (114).

O grupo ENIGMA é um consórcio internacional de neuroimagem com colaboração de mais de 1.400 cientistas de 43 países que estudam o cérebro humano (115, 116). Fundado em 2009, os primeiros estudos do ENIGMA identificaram variantes genéticas comuns que contribuíram para variações normais na estrutura cerebral. Atualmente o ENIGMA conta com mais de 50 grupos de trabalho (GTs) reunindo dados, recursos e conhecimentos em todo o mundo para responder a perguntas fundamentais em neurociência, psiquiatria, neurologia e genética (117). Os GTs são divididos em 2 grupos: os grupos técnicos, que apoiam a análise harmonizada de diferentes tipos de dados relacionados ao cérebro coletados em todo o mundo; e grupos clínicos que estudam diferentes distúrbios e condições em psiquiatria e neurologia, bem como alguns comportamentos (por exemplo, esquizotipia e comportamentos antissociais). Como alternativa à centralização de dados, o ENIGMA trabalha como um “consórcio distribuído”, solicitando aos grupos que elaborem protocolos padronizados e harmonizados de pré-processamento de dados de ressonância magnética, de forma a unificar os dados com o objetivo de diminuir a heterogeneidade de fatores metodológicos entre os locais onde os estudos são realizados (117).

Todos os locais aplicam os mesmos *pipelines* de pré-processamento para obter estimativas de espessura e área de superfície para regiões corticais de interesse (ROIs) e estimativas de volume para ROIs subcorticais (117). Os protocolos harmonizados estão em uso para análise padronizada de dados de sMRI, DTI, fMRI e EEG em estado de repouso, bem como vários tipos de dados epigenéticos (114).

Como parte do consórcio ENIGMA, em 2012 foi fundado o grupo de trabalho ENIGMA-TDM com o objetivo inicial de identificar alterações cerebrais estruturais e funcionais associadas ao TDM que possam ser detectadas e replicadas de forma confiável em inúmeras diferentes amostras em todo o mundo; e identificar os fatores demográficos, genéticos, clínicos, psicológicos e ambientais que afetam essas associações (115, 116). Desde que foi estabelecido até setembro de 2019, o ENIGMA-TDM já incluía 35 instituições de pesquisa participantes (totalizando 45 coortes de estudo) de 14 países diferentes em seis continentes (117, 118). As análises morfométricas cerebrais realizadas pelo ENIGMA-TDM foram baseadas em dados de RMN de 1.728 pacientes com TDM e 7.199 controles para volumes subcorticais e de 2.148 pacientes com TDM e 7.957 controles para medidas corticais. O grande tamanho da amostra disponível no ENIGMA-TDM potencializa o poder estatístico necessário para investigar alterações cerebrais estruturais de todo o cérebro (119).

## 4. Objetivos

### 4.1. Objetivo geral

Apresentar dados transversais de neuroimagem estrutural da fase inicial do estudo *Identifying Depression Early in Adolescence Risk Stratified Cohort* (IDEA-RiSCo) de adolescentes definidos como de baixo risco e de alto risco para desenvolver o TDM, bem como aqueles adolescentes em episódio depressivo atual.

### 4.2. Objetivos específicos

- Investigar possíveis diferenças regionais morfométricas cerebrais entre os grupos de risco a partir de uma abordagem baseada em vértices espacialmente imparciais que fornece medidas de volume cortical, área de superfície e espessura cortical.

- Identificar as regiões subcorticais com possíveis anormalidades de imagem entre os grupos de risco, com relevância estatística.

- Explorar possíveis diferenças na organização das redes de covariância estrutural entre os grupos de risco.

## 5. Considerações éticas

O protocolo do estudo foi aprovado pelo comitê de ética em pesquisa do Hospital de Clínicas de Porto Alegre e pela Comissão Nacional de Ética do Brasil (projeto 50473015.9.0000.5327).

## 6. Conclusões e considerações finais

No presente trabalho, envolvendo uma amostra de adolescentes bem caracterizada para o risco e presença de depressão, apresentamos os resultados basais de dados de neuroimagem estrutural de adolescentes brasileiros com alto ou baixo risco de depressão ou vivenciando um episódio depressivo. Até o momento, a maioria dos estudos se concentrou em fatores de risco únicos para caracterizar grupos de risco de depressão (38). Após o desenvolvimento, pelo nosso grupo de pesquisa, de um escore composto de 11 variáveis sociodemográficas para analisar o risco de depressão, conseguimos criar uma coorte em que três grupos estão claramente definidos: baixo risco, alto risco e TDM. O escore foi validado em amostras do Nepal, Nova Zelândia, Nigéria e Reino Unido (40, 56-58), confirmando sua capacidade de estratificar adolescentes de alto e baixo risco além do acaso. Assim, esta coorte estratificada de risco é ideal para o estudo de correlatos neurobiológicos de risco e presença de depressão (41, 42).

A partir desta estratificação de risco, examinamos as diferenças regionais no volume cortical (CV) com base em dois componentes, espessura cortical (CT) e área de superfície (SA) e volume subcortical. Além disso, exploramos as diferenças entre os grupos no volume subcortical. No entanto, não encontramos diferenças significativas entre os grupos em nenhuma dessas comparações. Tendo em vista que os dados analisados são transversais, espera-se a ausência de diferenças morfométricas significativas associadas ao risco e presença de depressão na adolescência, conforme relatado em estudos anteriores (120-122).

Em relação à rede de covariância estrutural, houve indicação de aumento do índice de centralidade de intermediação do hipocampo na rede do grupo HR em

relação à rede do grupo MDD e do grupo LR após a correção do FDR para comparações múltiplas. O índice de centralidade betweenness quantifica teoricamente o envolvimento do nó (região) no fluxo de informação através da rede e define o número de caminhos mais curtos que cruzam um determinado nó (123, 124). Um nó com um índice de centralidade de betweenness mais alto teria mais controle sobre a rede, pois mais informações passam por esse nó, o que implica comunicações mais eficientes e caminhos de transferência de informações mais curto entre o hipocampo e outras regiões (125). Como o hipocampo é a região chave do sistema límbico e envolvido no processo de formação da memória, estresse e regulação emocional (121, 126), especulamos que o grupo de alto risco pode usar utilizando de padrões compensatórios para lidar com a alta carga de sofrimento e com isso o hipocampo parece ficar mais sensibilizado. De toda forma, esses resultados preliminares devem ser interpretados com cautela até que sejam replicados no seguimento ou em pesquisas futuras.

Embora o estudo tenha um desenho transversal, ele se destaca por apresentar dados de ressonância magnética estrutural de uma amostra de adolescentes do Brasil, país de média renda, especialmente considerando que nove em cada dez crianças e adolescentes no mundo vivem em áreas de baixa e média renda (127, 128). Outro ponto forte do estudo, é a aplicação de um método inovador de estratificação de risco, que contou com múltiplas variáveissimultaneamente. Além disso, a avaliação clínica minuciosa com psiquiatras de crianças e adolescentes que entrevistaram o adolescente e seu cuidador individualmente possibilitou uma amostra bem caracterizada de adolescentes de baixo risco, alto risco e em episódio depressivo atual (42).

Infelizmente devido a natureza transversal dos resultados aqui apresentados, nenhuma inferência sobre causalidade pode ser extraída desses resultados. A estratégia de investigação, propositadamente desenhada para identificar extremos empíricos em termos de risco para desenvolver TDM, por sua natureza também limita outras amostras de adolescentes – um aspecto especial a ser considerado aqui é a alta carga de fatores de risco no grupo TDM. A caracterização cuidadosa de grupos mais homogêneos resultou em um tamanho de amostra limitado – embora não menor do que a maioria dos estudos de locais individuais publicados até agora (38).

O presente trabalho se propôs a apresentar resultados transversais de dados de neuroimagem estrutural de adolescentes brasileiros com alto ou baixo risco de depressão ou vivenciando um episódio depressivo. Neste momento, não encontramos diferenças significativas na estrutura cerebral entre os grupos de risco/TDM. Esses resultados dialogam com achados de estudos transversais que não encontraram evidências de associações significativas entre adolescentes em risco e com TDM na estrutura cerebral (19, 129-133).

O seguimento deste projeto certamente irá agregar mais informações acerca do desenvolvimento da estrutura cerebral e possíveis alterações relacionadas ao risco e presença de depressão. Dada a evidência de que o escore de risco IDEA é capaz de estratificar corretamente o risco em várias amostras, os resultados sugerem que, com um período de acompanhamento relativamente curto, é possível identificar mudanças na estrutura cerebral ao longo do desenvolvimento da doença (19, 134).

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## 8. Anexos

**Anexo A**: Identifying Depression Early in Adolescence Risk Stratified Cohort (IDEA RiSCo), artigo no qual o presente estudo está inserido.

**Anexo A:**

frontiers in Psychiatry

ORIGINAL RESEARCH
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# The Identifying Depression Early in Adolescence Risk Stratified Cohort (IDEA-RiSCo): Rationale, Methods, and Baseline Characteristics

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**Background:** The characterization of adolescents at high risk for developing depression has traditionally relied on the presence or absence of single risk factors. More recently, the use of composite risk scores combining information from multiple variables has gained attention in prognostic research in the field of mental health. We previously developed a sociodemographic composite score to estimate the individual level probability of depression occurrence in adolescence, the Identifying Depression Early in Adolescence Risk Score (IDEA-RS).

**Objectives:** In this report, we present the rationale, methods, and baseline characteristics of the Identifying Depression Early in Adolescence Risk Stratified Cohort (IDEA-RiSCo), a study designed for in-depth examination of multiple neurobiological, psychological, and environmental measures associated with the risk of developing and with the presence of depression in adolescence, with a focus on immune/inflammatory and neuroimaging markers.

**Methods:** Using the IDEA-RS as a tool for risk stratification, we recruited a new sample of adolescents enriched for low (LR) and high (HR) depression risk, as well as a group of adolescents with a currently untreated major depressive episode (MDD).

Methods for phenotypic, peripheral biological samples, and neuroimaging assessments are described, as well as baseline clinical characteristics of the IDEA-RiSCo sample.

**Results:** A total of 7,720 adolescents aged 14–16 years were screened in public state schools in Porto Alegre, Brazil. We were able to identify individuals at low and high risk for developing depression in adolescence: in each group, 50 participants (25 boys, 25 girls) were included and successfully completed the detailed phenotypic assessment with ascertainment of risk/MDD status, blood and saliva collections, and magnetic resonance imaging (MRI) scans. Across a variety of measures of psychopathology and exposure to negative events, there was a clear pattern in which either the MDD group or both the HR and the MDD groups exhibited worse indicators in comparison to the LR group.

**Conclusion:** The use of an empirically-derived composite score to stratify risk for developing depression represents a promising strategy to establish a risk-enriched cohort that will contribute to the understanding of the neurobiological correlates of risk and onset of depression in adolescence.

**Keywords: depression, adolescence, risk score, cohort, neurobiology**

## INTRODUCTION

Major advances have been accomplished in healthcare through the identification of factors that increase or decrease the probability of an individual developing a negative outcome (1). In the field of cardiovascular medicine, for example, the identification of a set of risk factors has enabled the implementation of multiple preventative strategies that have ultimately translated into decreased burden of heart disease (2). A crucial aspect of this approach is the combination of multiple factors into one single, composite score—e.g., the Framingham Risk Score aggregates information from six variables to estimate the 10-year risk of coronary disease (3).

There is a dire need to reduce the burden associated with depressive disorders globally (4). Differently from other branches of medicine, however, research in the field of psychiatry and mental health has often examined a single risk factor at a time (e.g., poverty, child maltreatment, discrimination) in the effort to identify mechanisms associated with the disorder's pathophysiology. Despite unquestionable advances in the identification of individual markers of depression risk—notably the role of a positive family history of depression in increasing the probability of the disorder in the offspring—a broader, more comprehensive approach is likely to be required in the context of multifactorial disorders such as depression (5).

The incidence of depression peaks in adolescence (6), which implies not only a substantial disease-related burden early in life, but also an important window of opportunity for prevention. Universal approaches addressing entire groups of adolescents have been less successful than selective and indicated interventions focusing on those who are at high-risk because of the presence of either proximal risk factors or subclinical symptoms (7). To further advance targeted preventive interventions, however, an important challenge that remains is the characterization of who is at high risk, as well as which neurobiological, psychological, and environmental mechanisms are associated with the development of depression (8). Crucially, relying on single risk factors can be potentially misleading in the identification of high- and low-risk individuals, as, for instance, an adolescent with no family history of the disorder (frequently assigned as being at low risk) can actually be at an increased risk for developing depression due to the experience of other risk factors (e.g., childhood maltreatment) (9).

In fact, the ability to move beyond a binary approach to risk (i.e., absent/present) to incorporate a dimensional perspective is another opportune advantage of using composite scores. Most of the current samples in mental health research contrast cases and non-cases, with the latter usually defined by lack of a current psychiatric disorder. However, especially among younger individuals, non-cases may have a number of risk factors that make them likely to develop a disorder in the future, leading to a high degree of noise and heterogeneity in these typical designs. The use of risk scores derived from multiple risk factors therefore does not assume adolescents without the disorder as a homogenous group, allowing researchers to specifically focus on individuals at extremely high, but also at extremely low risk for developing depression.

In that sense, efforts have been proposed in terms of using composite scores to stratify risk, with great attention recently directed to the use of genetic information (10). Polygenic risk scores (PRS) are calculated as the sum of genetic risk variants for a specific trait or disorder weighted according to previous genome-wide association studies. Considering that non-genetic factors also contribute to the etiology of depression (5, 11), the case for what has been termed a "polysocial risk score" could also be made, modeling the combination of socio-environmental factors to capture individual-level risk of developing the disorder (12). As suggested by many PRS studies, a focus on extreme strata (e.g., below the lowest and above the highest deciles) could potentially allow for the characterization of more homogeneous groups.

As part of the Identifying Depression Early in Adolescence (IDEA) international consortium (8), our group has developed a composite score to estimate individual-level probability of developing major depression among Brazilian adolescents (13). The IDEA risk score (IDEA-RS) comprises only sociodemographic variables that can be easily obtained directly from the adolescent to facilitate translation into practice: biological sex, skin color, drug use, school failure, social isolation, fight involvement, relationship with mother, relationship with father, relationship between parents, childhood maltreatment, and ran away from home (**Figure 1**). Among 15-year-old adolescents in Brazil, the IDEA-RS exhibited good discriminative performance (C-statistic of 0.78) to parse individuals at high- and at low-risk for developing depression at age 18 (13). External validation indicated that the IDEA-RS was also able to predict the occurrence of depression in samples from other countries and continents (13–15).

As a further step, we here present the Identifying Depression Early in Adolescence Risk Stratified Cohort (IDEA-RiSCo), established to investigate neurobiological features associated with the risk of developing depression and with the presence of depression in adolescence, with a focus on immune/inflammatory and neuroimaging markers. Using the IDEA-RS as a tool for risk stratification, we recruited a new sample of adolescents enriched for low and high depression risk, as well as a group of adolescents with a currently untreated major depressive episode. Methods for phenotypic, peripheral biological samples, and neuroimaging assessments are described, as well as baseline clinical characteristics of the IDEA-RiSCo sample. Additionally, we present adolescents' perspectives on taking part in this study.

# METHODS

## Ethics Approval

This study was approved by the Brazilian National Ethics in Research Commission (CAAE 50473015.9.0000.5327). Adolescents provided written assent and their primary caregivers written consent prior to entering the study. Approval for the school screening phase was obtained from the 1st Regional Education Bureau, in charge of public state schools in the city of Porto Alegre. All participants received feedback with findings from the diagnostic assessment and were referred for care in the Brazilian public health system if clinically indicated. Situations of imminent risk of self-harm or maltreatment were referred to emergency care or protective services following Brazilian legislation. Participants received no financial incentive for taking part in the study, but were compensated for expenses related to their participation (e.g., travel). Approval was also obtained from the Ethics Committee at King's College London for secondary data analysis for biological measures.

## Ascertainment and Group Assignment

In this report, we present cross-sectional data from the baseline stage of the IDEA-RiSCo study, following the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines (16). Individuals at low- and at high-risk for developing depression were identified using the IDEA-RS questions (**Supplementary Material 1**). The IDEA-RS was initially developed and validated on a sample of adolescents aged 15 years old to estimate the probability of a diagnosis of major depressive disorder at age 18 (13) in the Pelotas 1993 Birth Cohort Study (17). For the present study, 14 to 16-year-old adolescents (to resemble the developmental stage in which the IDEA-RS was originally devised) were screened in 101 public state schools located in the city of Porto Alegre, Brazil (see **Supplementary Materials 2, 3** for detailed procedures). The answers to the questions were aggregated to create a continuous score (i.e., the IDEA-RS) for each adolescent who participated in the screening stage of the study. Using cut-offs for the IDEA-RS based on the Pelotas 1993 Birth Cohort Study (13), we *a priori* operationalized risk strata for recruitment of participants into the new cohort: low-risk (LR) adolescents were those scoring equal to or below the 20th percentile of the IDEA-RS; and high-risk (HR) adolescents were those scoring equal to or above the 90th percentile of the IDEA-RS. We allowed a larger stratum in the LR group as the absolute risk difference between the 10th and the 20th percentiles was minimal. Importantly, as the probability of depression is known to be higher in females in comparison to males, we opted to generate sex-specific IDEA-RS in order to guide the recruitment of this risk-enriched sample. According to IDEA-RS in Pelotas, the probabilities of depression for the 20th and the 90th percentiles were 1.87 and 8.39% for girls and 1.12 and 3.37% for boys. Of note, these estimates refer to the probability of presenting a depressive episode exactly at age 18 years, as in the Pelotas 1993 Cohort Study only the point-prevalence of a current unipolar depressive episode was assessed. This means that the lifetime probabilities of MDD are likely higher for all groups.

In addition to the LR and HR groups, we also recruited a third group of adolescents with major depressive disorder (MDD). To allow for two-by-two comparisons between groups, adolescents with MDD were also required a score equal to or above the 90th percentile of the IDEA-RS. Thus, LR and HR groups were similar in showing no lifetime history of any depressive disorder, but markedly different regarding the IDEA-RS. Conversely, HR and MDD groups were similar regarding IDEA-RS, but while HR participants showed no evidence of depression at any time, those in the MDD group had to be in a current unipolar depressive episode at the time of the assessment.

To optimize the recruitment process and increase the probability that diagnostic criteria for depression were met in the MDD group, but not in the LR and HR groups, during the school screening adolescents also completed the Patient Health Questionnaire—adolescent version (PHQ-A) (18). Adolescents with a PHQ-A $\leq 6$ were considered for further assessment for the LR/HR groups, and those with a PHQ-A $\geq 10$ for the MDD group. Importantly, PHQ-A cutoffs were necessary but not sufficient for group assignment, as, for instance, the absence of a lifetime history of depressive disorders was also required for the LR/HR groups, and this was only determined during clinical assessment.

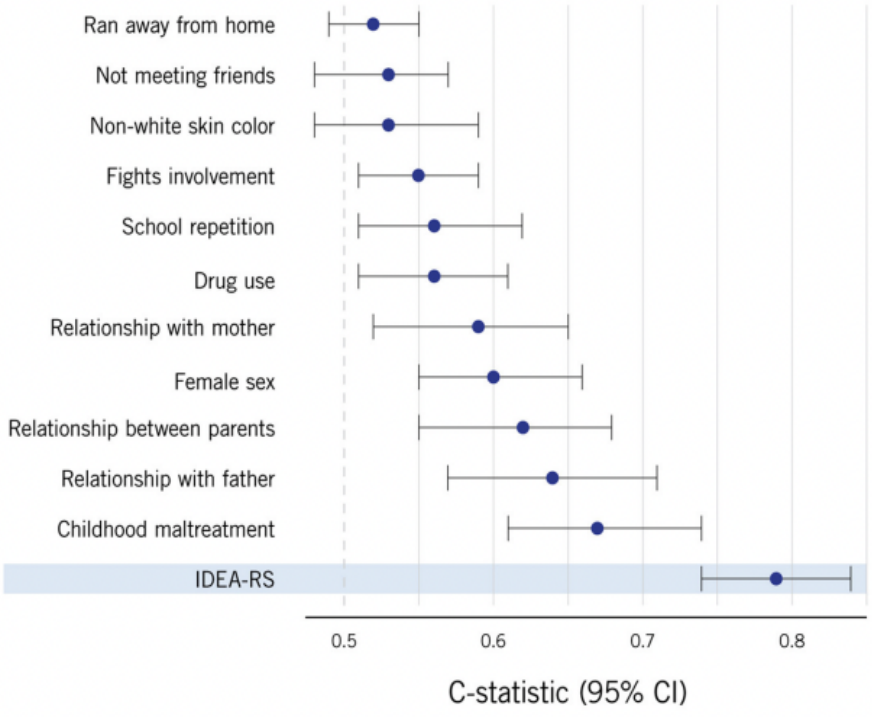


**FIGURE 1 |** Discriminative ability of each individual Identifying Depression Early in Adolescence Risk Score (IDEA-RS) variable, as well as the combined statistic for the IDEA-RS in the last line. Generated using data from the Pelotas 1993 Birth Cohort (13).

Based on school screening information, participants meeting criteria for further assessment were invited to the Clinical Research Center at Hospital de Clínicas de Porto Alegre (HCPA). Clinical assessment was conducted by board-certified child and adolescent psychiatrists who individually interviewed both the adolescent and their primary caregiver and were unaware of the participant's risk group status. Absence of a lifetime history of depressive disorders (including dysthymia) for the LR and HR groups and presence of a current depressive episode for the MDD group were determined using the Brazilian Portuguese translation of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (19). Clinicians received prior inter-reliability training on the K-SADS-PL, and for each participant a clinical formulation and best estimate diagnoses were generated and subsequently reviewed by an experienced child and adolescent psychiatrist (CK) to confirm diagnoses and assure uniformity in participant assignment. Participants in all three groups were excluded if they met lifetime diagnostic criteria for autism spectrum disorder, bipolar disorder, eating disorders, post-traumatic stress disorder, schizophrenia, or substance use disorders. Additional exclusion criteria are listed in **Supplementary Material 2**.

## Phenotypic Assessment

Youth assigned to LR, HR, or MDD groups underwent further phenotypic assessment. Comorbid diagnoses were assessed using the K-SADS-PL (19). Whereas the module on mood disorders was applied to both adolescents and caregivers, other domains were assessed primarily using information obtained from adolescents (anxiety, obsessive-compulsive, trauma-related, eating, and substance use disorders) or caregivers (schizophrenia/psychosis and neurodevelopment/disruptive disorders). Adolescents' IQ was estimated using the Wechsler Abbreviated Scale of Intelligence (WASI) (20, 21). Caregivers were asked about the adolescent's family history of depression—information was collected on parents, grandparents, and siblings and summarized in a family liability index that estimates the proportion of affected family members, adjusting for relatedness (22). Pubertal stage was determined by adolescent self-report using the Tanner Puberty Staging Scale (23). Further psychological and socio-environmental assessments included self- and clinician-based instruments as described in **Table 1**, **Supplementary Material 4**.

Anthropometric measurements were performed right after the clinical evaluation. Axillary temperature (°C) was measured using an electronic thermometer. Weight (kg) was measured using an electronic scale, with individuals wearing light clothes and without shoes. Height (cm) was measured using a stadiometer. Waist circumference (cm) was measured with a non-stretching tape at the midpoint between the iliac crest and the lowest rib margin.

## Collection of Blood and Saliva Samples

On the same day of clinical/phenotypic assessment, once the risk/MDD status was ascertained, participants underwent collection of blood and saliva samples (**Figure 2**). Only

**TABLE 1** | Domains and instruments used for phenotypic characterization of the IDEA-RiSCo sample.

| Domain | Instrument |
|---|---|
| **Adolescents** | |
| Overall psychopathology | DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure, Child (CCSM-C) (24, 25) |
| Depression | Mood and Feelings Questionnaire—Child (MFQ-C) (26, 27) |
| Anhedonia | Snaith-Hamilton Pleasure Scale (SHAPS) (17, 28) |
| Irritability | Affective Reactivity Index—Child (ARI-C) (29, 30) |
| Suicidality | Columbia-Suicide Severity Rating Scale (C-SSRS) (31) |
| Anxiety | Spence Children's Anxiety Scale (SCAS-C) (32, 33) |
| Insomnia | Insomnia Severity Index (ISI) (34, 35) |
| Reflexive functioning | Reflective Functioning Questionnaire for Youth (RFQY) (36, 37) |
| Resilience | Adapted Resilience Scale (ARS)* (38, 39) |
| Positive attributes | Youth Strengths Inventory—Adolescent (YSI-A) (40, 41) |
| Parental bonding (separate measures for mother and father) | Parental Bonding Instrument (PBI) (42) |
| Maltreatment/trauma history | Child Trauma Questionnaire (CTQ) (43, 44) |
| Recent life events | Life Events Questionnaire (LEQ)* (45) |
| Physical activity | Patient-Centered Assessment and Counseling for Exercise Plus Nutrition* (PACE+) (46) |
| **Primary caregivers** | |
| Overall psychopathology | DSM-5 Self-Rated Level 1 Cross-Cutting Symptom Measure, Parent (CCSM-P) (24) |
| Depression | Mood and Feelings Questionnaire—Parent (MFQ-P) (26, 27) |
| Irritability | Affective Reactivity Index—Parent (ARI-P) (29, 30) |
| Anxiety | Spence Children's Anxiety Scale—Parent (SCAS-P) (32, 33) |
| Positive attributes | Youth Strengths Inventory—Parent (YSI-P) (40, 41) |
| Socioeconomic status | Brazil socioeconomic classification index (ABEP) (47) |
| Caregiver's depression | Mood and Feelings Questionnaire—Adult (MFQ-A) (26, 27) |
| **Combined information (adolescent + caregiver)** | |
| Depression | Children's Depression Rating Scale Revised (CDRS-R) (48, 49) |
| Clinical global impression | Clinical Global Impression (CGI) (50) |
| Global functioning | Children's Global Assessment Scale (CGAS) (51, 52) |

** Instruments for which we performed the translation into Brazilian Portuguese following the steps described in* ***Supplementary Material 4****. IDEA-RiSCo, Identifying Depression Early in Adolescence Risk-Stratified Cohort.*

participants for whom blood and saliva samples were successfully collected were included in the cohort.

Briefly, procedures included a previous instruction not to change their eating habits the day before the blood and saliva collection, and to take any medications as usual. Participants were also required to avoid excessive fasting (over 24 h); to avoid intake of any kind of food, natural water, coffee, tea, juice, milk, or other drinks at least 2 h before the collection; and to avoid smoking or chewing gum during the period between awakening and sample collection. The following samples were collected, processed, and stored at −80°C: serum from whole blood (6.0 mL of blood using a vacutainer tube without any anticoagulant); plasma from EDTA whole blood (6.0 mL of blood using a K3EDTA anticoagulant tube); RNA (2.5 mL of blood using PAXGene tubes, PreAnalitix, Qiagen/BD Company). Peripheral blood mononuclear cells (PBMC) were collected from whole blood (4.0 mL of blood collected in 2 Vacutainer EDTA tubes) by the density gradient centrifugation method using Histopaque®-1077 reagent (Sigma-Aldrich) according to manufacture instructions. The cells were kept frozen in liquid nitrogen with a cryoprotectant solution (bovine fetal serum F4135-Gibco and 10% DMSO-D2650-Sigma Aldrich). Saliva samples were collected using Oragene RNA tubes (RE-100) supplied by DNA Genotek (Ottawa, Ontario, Canada). A total of 2.0 mL of unstimulated saliva was collected by directly spitting into the tubes; once collected, Oragene RNA tubes were stored at −20°C.

All samples were shipped using a courier specialized for transferring biological samples. Four serum, four plasma, and two PBMC cryovials were sent in a single batch to The Maurice Wohl Clinical Neuroscience Institute Laboratory at King's College London, United Kingdom. One PAXGene tube and saliva samples were sent in two batches to IRCCS Istituto Centro San Giovanni di Dio Fatebenefratelli in Brescia, Italy. The remaining two serum and plasma cryovials and one PAXGene tube were kept as a backup in Brazil.

## Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) was performed on the same day, following collection of blood and saliva samples. Only participants who were able to successfully complete the entire MRI procedure were included in the cohort. Both structural and functional images were acquired on a 3T Ingenia scanner

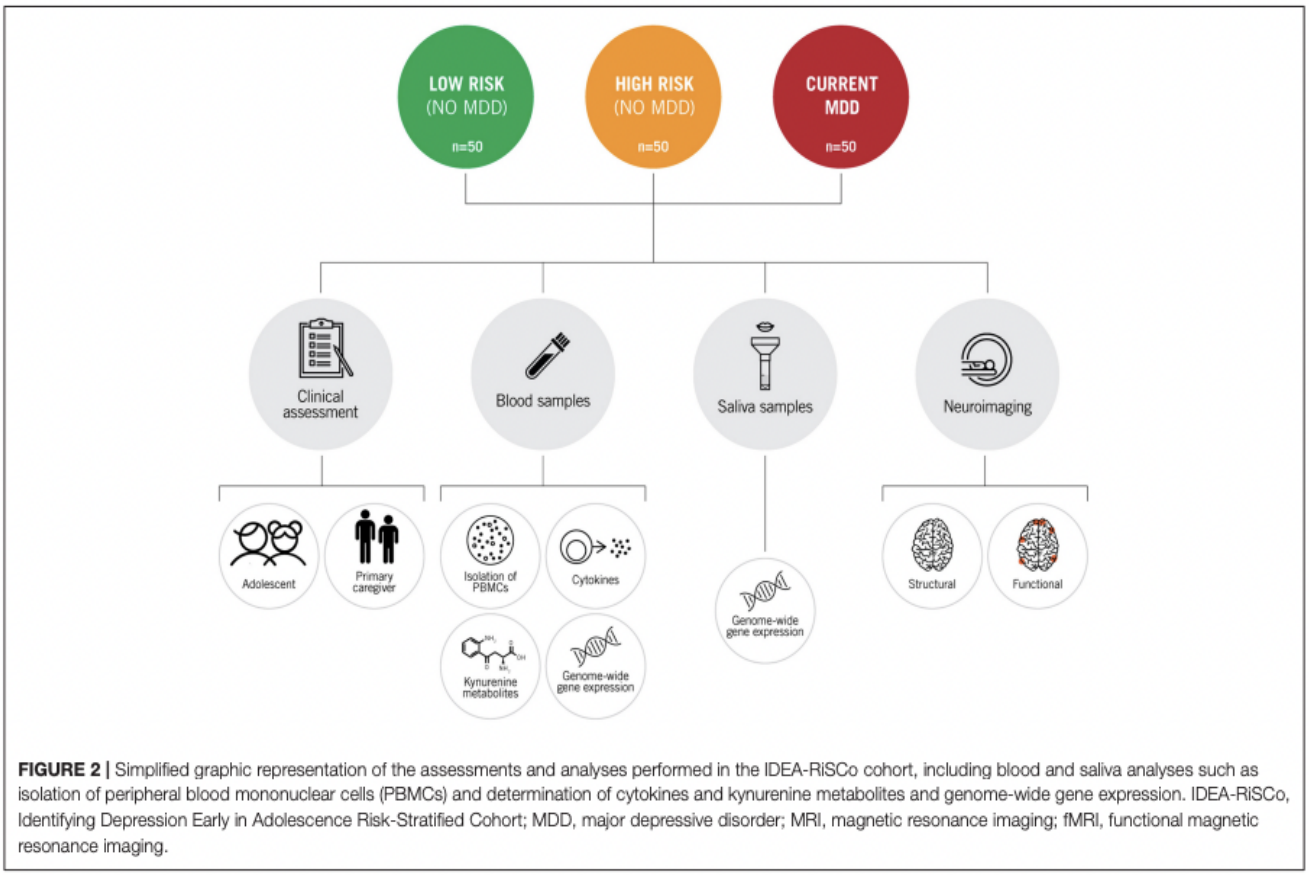


**FIGURE 2 |** Simplified graphic representation of the assessments and analyses performed in the IDEA-RiSCo cohort, including blood and saliva analyses such as isolation of peripheral blood mononuclear cells (PBMCs) and determination of cytokines and kynurenine metabolites and genome-wide gene expression. IDEA-RiSCo, Identifying Depression Early in Adolescence Risk-Stratified Cohort; MDD, major depressive disorder; MRI, magnetic resonance imaging; fMRI, functional magnetic resonance imaging.

(Koninklijke Philips N.V., The Netherlands), software version 5.3.1, at Hospital de Clínicas de Porto Alegre.

Before entering the MRI suite, participants were asked to remove all metal objects from their body (e.g., earrings, piercings, rings, watches). They received instructions regarding scanning procedures (including the request to keep their head still during the scan) and scanning duration. A 30-s demonstration for each task was provided. Finally, they were informed about loud banging noises during scanning, and that communication with the experimenter would be possible at any time during the scan. Once they entered the MRI room, participants were positioned in the scanner. Images were acquired in the same order for every participant—structural, gambling task, face-matching task, and resting-state (**Figure 3**; see **Supplementary Material 5** for data acquisition parameters).

## Tasks

The gambling task was adapted from Barch et al. (53) and translated into Brazilian Portuguese. The task was to guess whether the number behind a question mark was higher or lower than 5 by using two one-button boxes with the left and right index fingers. After each guess, participants received pre-determined feedback consisting of reward (i.e., correct guess), punishment (i.e., incorrect guess), and neutral feedback (i.e., the number is 5). The task included four runs, each with 2 blocks consisting primarily of reward trials (i.e., 6 out of 8 trials) and blocks consisting primarily of punishment trials (i.e., 6 out of 8 trials) in each run. The task consisted of 4 runs with different orders of reward and punishment blocks, which were counterbalanced across participants. Each block took 28 s and consisted of 8 trials, which contained a question mark (1.5 s) and feedback (1 s). Participants conducted at least 10 practice trials before the actual task.

The face-matching task was adapted from Hariri et al. (54) and translated into Brazilian Portuguese. During the task, participants viewed a trio of faces or shapes and had to select which of two stimuli on the bottom row matched the target stimuli on the top row by pressing a button with their left or right index finger. This task included counterbalanced presentation of 10 face blocks, including 5 facial expressions (i.e., angry, fearful, happy, sad, and neutral faces) and 11 shapes blocks. Face and shape blocks were alternatively presented and the order of face blocks was counterbalanced across participants. Each block included 6 trials. Face blocks included 2 blocks of 5 facial expressions (i.e., angry, fearful, happy, sad, neutral). Each block took 26 s and consisted of 6 trials with 2 s of stimuli presentation.

## Task-based fMRI Data Analysis

After preprocessing (**Supplementary Material 6**), we estimated generalized linear models (GLM) to examine neural activity and connectivity during reward processing (i.e., reward vs. punishment) and emotional face processing (i.e., angry faces vs. shapes, fearful faces vs. shapes, happy faces vs. shapes, sad faces vs. shapes, and neutral faces vs. shapes), and we generated

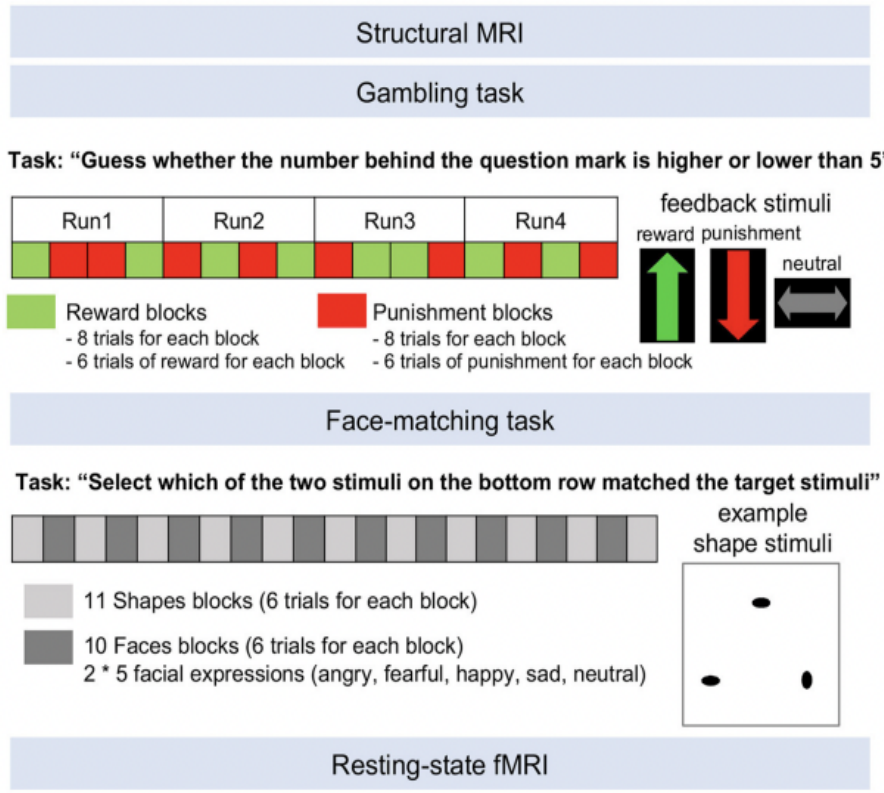


**FIGURE 3 |** MRI data acquisition procedure. After structural images were acquired, functional images were acquired during a gambling task, face-matching task, and resting-state. The gambling task consisted of counterbalanced presentation of reward and punishment blocks. The face-matching task consisted of counterbalanced presentation of shapes and faces blocks. Feedback stimuli for the gambling task and an example shape stimulus for the face-matching task are presented. During the resting-state fMRI scan, participants were instructed to let their minds wander.

contrast maps (**Figure 4**). The contrast maps of each individual will be carried forward into group-level random-effects models and will be used to examine differences in neural activity between the LR, HR, and MDD groups in future research papers.

### Resting-State fMRI Data Analysis

The resting-state functional connectivity (rsFC) images were preprocessed and denoised using the CONN toolbox (https://web.conn-toolbox.org). In future papers, we plan to conduct three types of analyses to examine differences in rsFC between the LR, HR, and MDD groups: (1) seed-based connectivity analysis that examines the connectivity between a seed region (e.g., amygdala, posterior cingulate cortex) and other regions in the whole brain, (2) ROI-to-ROI analysis that examines the connectivity of all nodes within a specific network, and (3) graph theory analysis that examines the topological properties of a network (e.g., how much a particular node is efficiently connected with other nodes of the network) (**Figure 4**).

## Sample Size Calculation

One of the major goals for this study is to examine both concurrent and prospective (in planned longitudinal follow-ups that are underway) associations between risk status, depression symptoms, and neurobiological features. In prior work (55), an IDEA investigator had examined differences in threat-related amygdala function in adolescents at high familial risk for depression compared to those at lower risk, and with high exposure to recent life stress compared to low exposure to recent life stress. In that research, models that included age, family history, and recent life stress as predictors explained 11% total variance in amygdala function. Thus, for the IDEA-RiSCo sample, we conducted a power analysis using an expected effect size of partial $\eta^2 = 0.10$. Assuming this effect size and an F-test with 3 groups stratified by sociodemographic risk and MDD status, we estimated we would need at least 90 participants (30 in each group) to identify an effect of this size with at least 80% power. Additionally, prior research has shown that neural activity predicts depression/internalizing symptoms with effect sizes of partial $r^2 = \sim 0.05–0.30$ (29, 56–59). We computed a power analysis using G*Power based on partial $r^2 = 0.10$ and obtained a required sample size of 73 to achieve 80% power to detect significant associations between neural activity and continuously-measured depression symptoms. Based on these power analyses, we determined a sample size of at least 90 participants would be required to test our primary hypotheses. We also assumed there would be ∼10% data loss in the MRI data due to quality control procedures, which would require a total sample of 100 participants to achieve a final sample of 90 participants meeting all quality control criteria. Because we also planned to follow participants longitudinally and assumed some

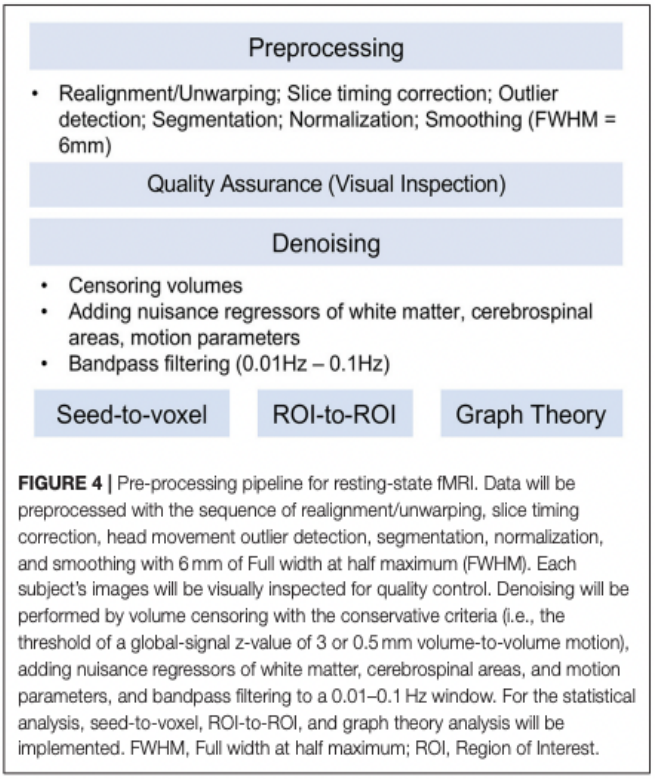


**FIGURE 4 |** Pre-processing pipeline for resting-state fMRI. Data will be preprocessed with the sequence of realignment/unwarping, slice timing correction, head movement outlier detection, segmentation, normalization, and smoothing with 6 mm of Full width at half maximum (FWHM). Each subject's images will be visually inspected for quality control. Denoising will be performed by volume censoring with the conservative criteria (i.e., the threshold of a global-signal z-value of 3 or 0.5 mm volume-to-volume motion), adding nuisance regressors of white matter, cerebrospinal areas, and motion parameters, and bandpass filtering to a 0.01–0.1 Hz window. For the statistical analysis, seed-to-voxel, ROI-to-ROI, and graph theory analysis will be implemented. FWHM, Full width at half maximum; ROI, Region of Interest.

loss of data due to attrition and MRI quality control at the second longitudinal scan, we determined our final sample size for the baseline data collection to be 150 participants (50 LR, 50 HR, and 50 MDD).

## Data Management and Statistical Analyses

All clinical data were collected and managed using the Research Electronic Data Capture (REDCap) system hosted at Hospital de Clínicas de Porto Alegre (60, 61).

Sample characteristics are presented using descriptive statistics, Kruskal-Wallis, two proportion *Z*-test, and network analysis. The Kruskal-Wallis non-parametric test was used for mean comparisons, as all distributions of the instruments were non-normal. Two-proportion *Z*-tests were used to compare the proportions of risk score variables in the Porto Alegre vs. Pelotas samples (62). Network analysis was performed using the Mixed Graphic Model, which estimates networks from data with dichotomous, categorical, discrete and continuous variables (62). All statistical analyses were performed using R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) through RStudio. A $p < 0.05$ was considered the threshold for statistical significance. The Tidyverse package (63) was used for data manipulation. The ggplot2 package was used for plotting figures (64). The "bootnet" package (65) and "mgm" method (corresponding to the Mixed Graphic Model) were used for network analysis. This model allows simultaneous analysis of different types of variables (e.g., categorical, dichotomized, and continuous). The "cor_auto" method, which automatically computes an appropriate correlation matrix for polychoric and polyserial correlations, was used to calculate correlations between variables. To visualize the networks, the qgraph package with the layout = "string" function was used, corresponding to the Fruchterman-Reingold algorithm for approximation of variables. Network structure and connectivity were compared with the Network Comparison Test (NCT) (66).

## Qualitative Component

Qualitative data collection on the study experience is an extension of a broader IDEA qualitative study on feasibility and acceptability of early detection of depression among adolescents in global settings (67). Qualitative interviews aimed to explore the experience of adolescents diagnosed with depression while taking part in the clinical evaluation. These participants were sampled by convenience, as the recruitment began at the final stages of the IDEA-RiSCo baseline assessment: the last 10 included adolescents who met criteria for a formal DSM-5 diagnosis of depression were invited to participate. They were first approached by the interviewers after the clinical evaluation and were invited to participate in two semi-structured interviews: one immediately after the clinical evaluation and the second 2 weeks later. This interview focused on understanding the adolescents' reaction to receiving a diagnosis of depression, but also explored the experience of participating in the clinical evaluation, having their blood and saliva collected and doing the fMRI, and their comprehension of the study's aims and objectives. Both interviews were audio recorded and later transcribed. The final analysis included 8 adolescents, as two were excluded due to incompleteness of their second interview.

One-on-one interviews were conducted in Brazilian Portuguese by two researchers (AV and SB, who had previous training and experience in qualitative research) and took place in a private room in the same setting as the remainder of the research protocol. Coding was done by both researchers using Framework Analysis (FA) (40) and this process was supervised by a third senior researcher (CK). The creation of the codes was inductive—we used line-by-line coding of two initial interviews to create a framework of codes that was later adapted and expanded until no new codes emerged (68). Additionally, constant comparison methods (69) and discussions with the research team were used to refine and create the final codebook. The full dataset was coded by two researchers using NVivo version 12 (70). Inter-rater reliability was assessed using Cohen's Kappa with 0.7 indicating adequate agreement (71). Afterward, code queries were generated in NVivo, and code summaries were written to capture adolescents' perspectives and experiences. Results highlight the main aspects of participation, presenting the number of adolescents who endorsed such views and following the steps of the described research protocol.

# RESULTS

## The IDEA-RS in Porto Alegre and Its Comparison to Pelotas

Between July 2018 and November 2019, 7,720 adolescents (54.93% females) were screened in 101 schools (for details,

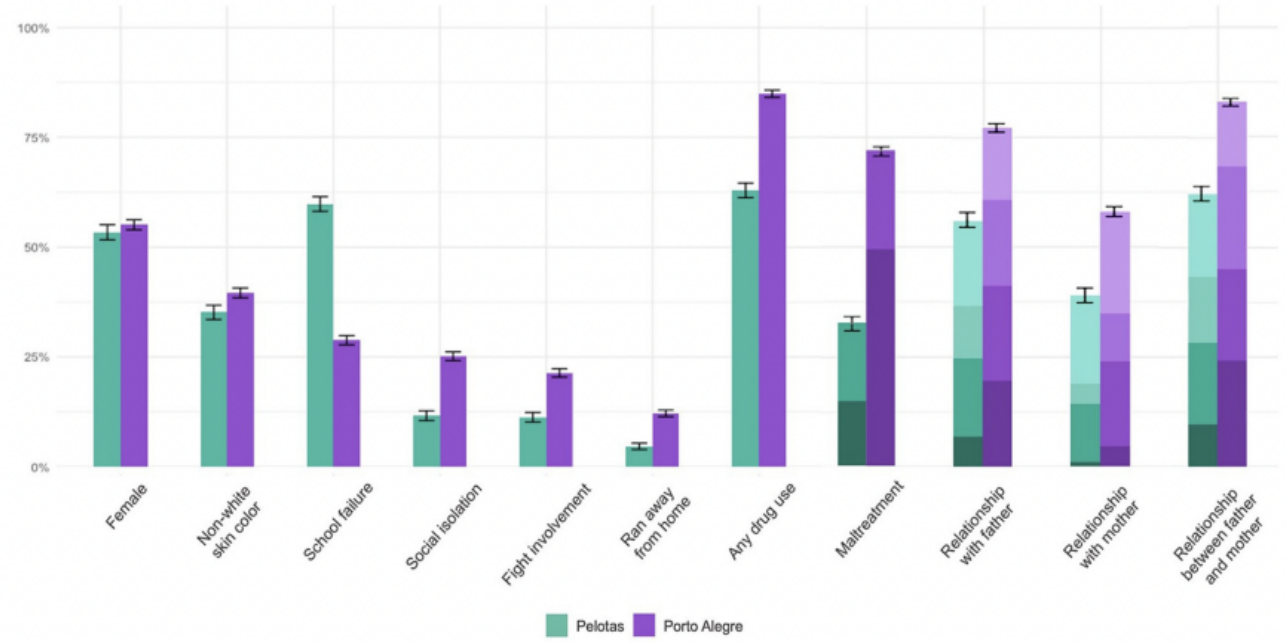


**FIGURE 5 |** Prevalence of risk variables in Pelotas (2008) vs. Porto Alegre (2018–9). Proportions do not reach 100% because the figure only shows responses that indicate risk for the variables (i.e., non-involvement in fights or non-use of drugs are not shown). 95% confidence intervals are shown in dichotomous variables. In ordinal variables darker shades (bottom) indicate greater severity. The maltreatment variable is divided into "severe" (darkest green or purple) and "probable," while relationship variables are divided into "bad" (darkest green or purple), "regular," "good," and "very good." $n = 3,290$ (Pelotas) and $n = 7,229$ (Porto Alegre) adolescents with complete Identifying Depression Early in Adolescence risk score (IDEA-RS) questionnaires.

see **Supplementary Material 3**). A comparison of the IDEA-RS in Porto Alegre and Pelotas, where the risk score was originally developed, indicated a higher average probability of developing a depressive episode within 3 years in Porto Alegre (5.30%) in relation to what was observed in Pelotas (3.39%). **Supplementary Material 7** shows the probability of depression in 3 years for girls and boys in Porto Alegre and Pelotas.

Individual IDEA-RS variables were more prevalent in Porto Alegre than in Pelotas (**Figure 5**), with two exceptions: biological sex, which was not significantly different in the two samples, and school failure, which was more prevalent in Pelotas. The higher prevalence of school failure could be expected in the population-based Pelotas sample, as opposed to the school-based Porto Alegre sample, which included only students around the expected grade for age.

To further explore potential similarities and differences of the IDEA-RS in Pelotas vs. Porto Alegre, we performed a network analysis to assess the associations among variables in both samples. We observed a similar pattern of positive and negative associations between the 11 nodes in the two networks (**Figure 6**). There was no evidence of significant differences in terms of connectivity (summarized by global strength, which is taken as the weighted absolute sum of all edges in the network) (72) or structure (calculated by the distance measure *M*, which is based on the maximum difference in edge weights of the observed networks) (73), suggesting comparability between the Pelotas and the Porto Alegre samples. A detailed description of the network analysis results can be found in **Supplementary Material 8**.

## Characteristics of Adolescents Included in the IDEA-RiSCo

School screening in Porto Alegre confirmed higher IDEA-RS for girls (7.34%) in comparison to boys (2.78%). The mean PHQ-A score was 9.52, with higher scores also observed for girls (11.51 vs. 7.07 in boys). To reach the target sample size, 260 clinical assessments were conducted at Hospital de Clínicas de Porto Alegre. The distribution of IDEA-RS and PHQ-A for all boys and girls screened in schools appears in **Figure 7**, which also shows the 150 adolescents included in the IDEA-RiSCo sample. Following study design, both LR and HR adolescents exhibited lower mean PHQ-A scores in comparison to those with MDD. Likewise, mean IDEA-RS was lower for the LR in comparison to HR and MDD groups. In terms of age, there was a small but significant difference between groups, with the LR group being slightly younger than the HR and MDD groups. Detailed statistics are presented in **Table 2**.

As shown in **Table 3**, there were no significant differences in the proportion of adolescents who self-identified as having white skin color across the three groups. School failure, drug use, and involvement in fights were less common in the LR group in comparison to both HR and MDD. Conversely, a history of running away from home was reported more frequently by those in the MDD group in comparison to both LR and HR. Adolescents in the LR group rated both their relationship with their father and between their parents more favorably than the adolescents in the HR and MDD groups. In terms of the relationship with mothers, there was a

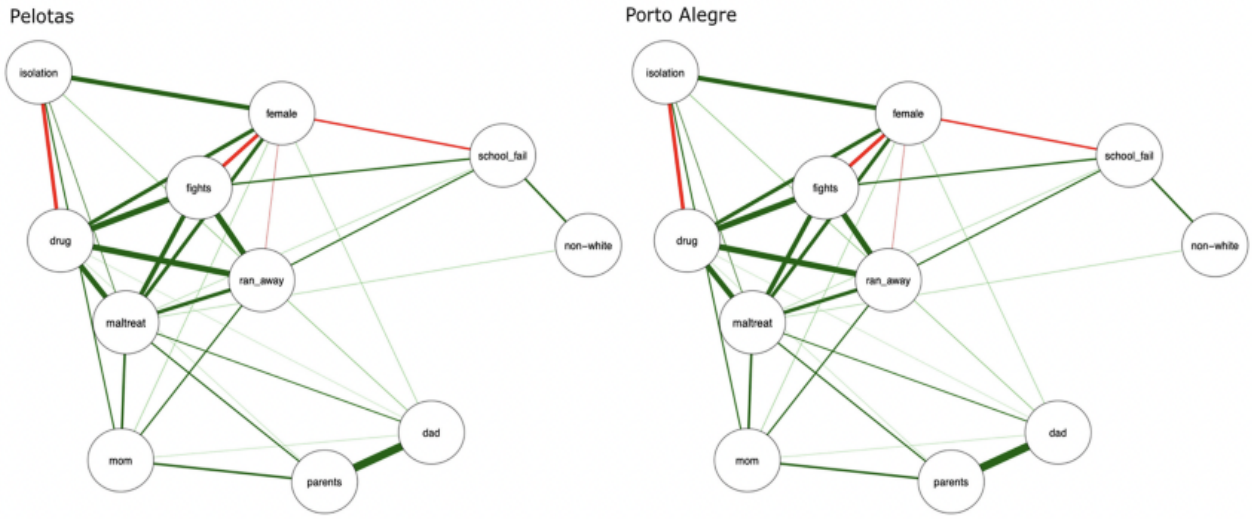


**FIGURE 6 |** Network analysis of variables that are part of the IDEA-RS by cohort. Structure of Pelotas and Porto Alegre Identifying Depression Early in Adolescence risk score (IDEA-RS) networks with 11 nodes, each representing one of the risk score's variables. The green linkage lines between variables represent positive correlations. The red linkage lines represent negative correlations. Thicker lines represent greater strength of the correlation, which is based on the weighted network analysis. non-white, non-white skin color; drug, any drug use; school_fail, history of school failure; isolation, social isolation; fights, fight involvement; mom, relationship with mother; dad, relationship with father; parents, relationship between parents; maltreat, childhood maltreatment; ran_away, ran away from home.

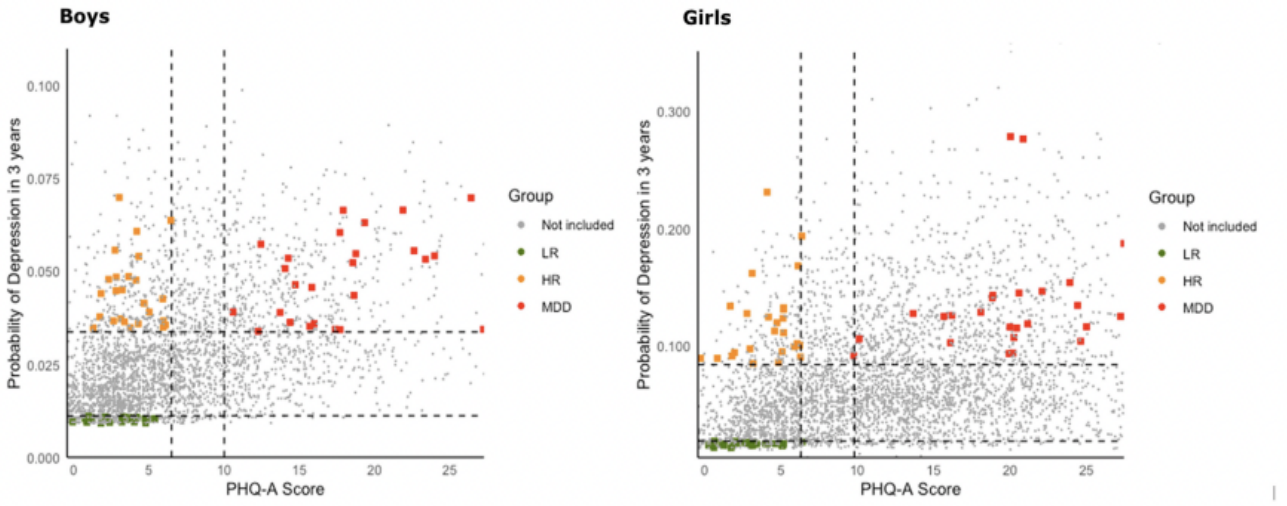


**FIGURE 7 |** Adolescents screened at schools and included in the Identifying Depression Early in Adolescence Risk Stratified Cohort (IDEA-RiSCo). Vertical dotted lines show the Patient Health Questionnaire—adolescent version (PHQ-A) cutoffs, and horizontal dotted lines show the Identifying Depression Early in Adolescence risk score (IDEA-RS) cutoffs. Low risk (LR) adolescents appear in the lower left quadrant (PHQ-A≤6 and IDEA-RS≤20th percentile); high risk (HR) adolescents in the upper left quadrant (PHQ-A≤6 and IDEA-RS≥90th percentile); and adolescents with current major depressive disorder (MDD), in the upper right quadrant (PHQ-A≥10 and IDEA-RS≥90th percentile). Gray dots representing the students who did not meet inclusion criteria are spread over all quadrants.

stepwise decrease from LR to HR to MDD—a similar pattern was observed for the proportion of adolescents who reported regularly meeting friends. Whereas all LR participants fell into the "no maltreatment" category, three quarters and almost all of those in the HR and MDD groups were classified, respectively, as having experienced "severe maltreatment."

**Figures 8**, **9** exhibit the results of phenotypic measures in the three groups based on reports by adolescents and primary caretakers, respectively. As shown in the figures, there was a stepwise increase from LR to HR to MDD across a variety of phenotypic measures: adolescent-reported (MFQ-C) and clinician-rated (CDRS-R) depressive symptomatology, clinical impression (CGI), and overall functioning (CGAS), as well as in specific measures of anhedonia (SHAPS) and irritability (ARI-C). A pattern in which the MDD group differed from both LR and HR groups emerged in relation to adolescent-rated suicidality (C-SSRS), anxiety (SCAS-C), insomnia (ISI), and positive attributes (YSI-A); as well as in caregiver-rated depression (MFQ-P),

**TABLE 2 |** Phenotypic characteristics of the IDEA-RiSCo sample.

| | Low risk ($n = 50$) Mean (SD)[a] | High risk ($n = 50$) Mean (SD)[a] | MDD ($n = 50$) Mean (SD)[a] | Group differences[b] |
|---|---|---|---|---|
| Adolescent self-report | | | | |
| Age (years) | 15.36 (0.81) | 15.76 (0.83) | 15.80 (0.75) | LR < (HR = MDD) |
| IDEA-RS (%) | 1.33 (0.32) | 8.21 (4.61) | 9.24 (5.60) | LR < (HR = MDD) |
| PHQ-A | 2.82 (1.53) | 3.96 (1.59) | 18.82 (4.48) | (LR = HR) < MDD |
| MFQ-C | 6.74 (4.84) | 12.8 (8.36) | 41.2 (11.11) | LR < HR < MDD |
| SHAPS | 5.66 (3.93) | 10.66 (5.54) | 14.52 (6.79) | LR < HR < MDD |
| ARI-C | 1.54 (2.07) | 3.18 (2.73) | 8.4 (3.83) | LR < HR < MDD |
| C-SSRS (lifetime) | 0.00 (0.00) | 1.72 (3.91) | 14.64 (5.81) | (LR = HR) < MDD |
| SCAS-C | 23.02 (11.03) | 25.46 (11.27) | 47.66 (20.45) | (LR = HR) < MDD |
| ISI | 2.44 (3.12) | 3.44 (2.81) | 10.96 (4.72) | (LR = HR) < MDD |
| RFQ-Y | 9.94 (1.58) | 9.74 (1.57) | 8.94 (1.87) | LR > MDD |
| YSI-A | 27.8 (3.75) | 25.7 (5.52) | 21.7 (5.51) | (LR = HR) > MDD |
| PBI (mother) | | | | |
| Care | 31.69 (5.42) | 26.60 (6.79) | 21.66 (8.60) | LR > HR > MDD |
| Overprotection | 13.08 (5.76) | 16.08 (5.67) | 18.94 (8.25) | LR < (HR = MDD) |
| PBI (father) | | | | |
| Care | 29.90 (6.36) | 21.13 (7.79) | 14.56 (8.56) | LR > HR > MDD |
| Overprotection | 10.38 (5.58) | 14.36 (6.86) | 18.74 (10.05) | LR < (HR = MDD) |
| CTQ | 29.16 (3.35) | 38.08 (8.23) | 51.56 (13.16) | LR < HR < MDD |
| LEQ | | | | |
| Positive events | 1.00 (0.93) | 0.92 (0.99) | 0.76 (0.94) | |
| Neutral events | 0.52 (0.68) | 0.46 (0.84) | 0.70 (1.16) | |
| Negative events | 1.24 (1.27) | 1.58 (1.39) | 3.04 (2.06) | (LR = HR) < MDD |
| ARS | 46.80 (4.80) | 43.40 (7.24) | 36.44 (9.44) | (LR = HR) > MDD |
| PACE+ | 3.17 (2.31) | 2.55 (2.08) | 2.11 (2.06) | |
| Caregiver report | | | | |
| MFQ-P (parent on child) | 6.26 (8.37) | 8.64 (7.74) | 20.46 (12.30) | (LR = HR) < MDD |
| ARI-P | 1.24 (2.44) | 2.58 (3.39) | 6.68 (4.82) | (LR = HR) < MDD |
| SCAS-P | 13.62 (11.74) | 14.00 (9.61) | 21.16 (12.54) | (LR = HR) < MDD |
| YSI-P | 39.30 (7.40) | 37.56 (6.77) | 32.24 (7.93) | (LR = HR) > MDD |
| ABEP | 31.88 (9.78) | 25.27 (7.63) | 26.78 (9.28) | LR > (HR = MDD) |
| MFQ-A (parent self-report) | 12.34 (14.59) | 15.68 (13.01) | 20.82 (14.22) | LR < MDD |
| Family liability index | 0.13 (0.18) | 0.20 (0.16) | 0.24 (0.21) | LR < (HR = MDD) |
| Combined (adolescent + caregiver) | | | | |
| CDRS-R | 19.3 (2.85) | 22.6 (5.44) | 50.94 (9.79) | (LR = HR) < MDD |
| CGI-S | 1.32 (0.55) | 1.82 (0.75) | 3.76 (0.66) | (LR = HR) < MDD |
| CGAS | 90.00 (6.67) | 83.52 (8.57) | 55.52 (8.78) | LR > HR > MDD |
| Other | | | | |
| WASI (IQ) | 90.06 (10.16) | 88.04 (8.57) | 88.64 (9.76) | |
| Body mass index | 22.61 (5.46) | 22.4 (4.84) | 22.75 (3.87) | |
| Body temperature | 35.88 (0.59) | 36.01 (0.51) | 36.07 (0.62) | |
| Afternoon evaluations, *n* (%) | 30 (60.00) | 31 (62.00) | 30 (60.00) | |

[a]*Unless noted as n (%).* [b]*For a $p < 0.05$, comparisons between low risk (LR) vs. high risk (HR), LR vs. major depressive disorder (MDD), and HR vs. MDD, as indicated. ABEP, Brazil socioeconomic classification index; ARI-C, Affective Reactivity Index–Child; ARI-P, Affective Reactivity Index–Parent; ARS, Adapted Resilience Scale; CDRS-R, Children's Depression Rating Scale Revised; CGAS, Children's Global Assessment Scale; CGI-S, Clinical Global Impression–Severity scale; C-SSRS, Columbia-Suicide Severity Rating Scale; CTQ, Child Trauma Questionnaire; IDEA-RS, Identifying Depression Early in Adolescence Risk Score; IDEA-RiSCo, Identifying Depression Early in Adolescence Risk-Stratified Cohort; ISI, Insomnia Severity Index; LEQ, Life Events Questionnaire; MFQ-A, Mood and Feelings Questionnaire–Adult; MFQ-C, Mood and Feelings Questionnaire–Child; MFQ-P, Mood and Feelings Questionnaire–Parent on Child; PACE+, Patient-Centered Assessment and Counseling for Exercise Plus Nutrition; PBI, Parental Bonding Instrument; PHQ-A, Patient Health Questionnaire–adolescent version; RFQ-Y, Reflective Functioning Questionnaire for Youth; SCAS-C, Spence Children's Anxiety Scale; SCAS-P, Spence Children's Anxiety Scale–Parent; SHAPS, Snaith-Hamilton Pleasure Scale; WASI, Wechsler Abbreviated Scale of Intelligence; YSI-A, Youth Strengths Inventory–Adolescent; YSI-P, Youth Strengths Inventory–Parent.*

**TABLE 3 |** IDEA-RS features in the IDEA-RiSCo sample.

| | Low risk ($n = 50$) $n$ (%)[a] | High risk ($n = 50$) $n$ (%)[a] | MDD ($n = 50$) $n$ (%)[a] | Group differences[b] |
|---|---|---|---|---|
| Sex, female | 25 (50.00) | 25 (50.00) | 25 (50.00) | LR = HR = MDD |
| Skin color, non-white | 22 (44.00) | 26 (52.00) | 26 (52.00) | LR = HR = MDD |
| Meets friends | 49 (98.00) | 40 (80.00) | 30 (60.00) | LR > HR > MDD |
| School failure | 0 (0.00) | 29 (58.00) | 25 (50.00) | LR < (HR = MDD) |
| Ran away | 1 (2.00) | 3 (6.00) | 13 (26.00) | (LR = HR) < MDD |
| Any drug use | 29 (58.00) | 44 (88.00) | 47 (94.00) | LR < (HR = MDD) |
| Fights | 0 (0.00) | 20 (40.00) | 27 (54.00) | LR < (HR = MDD) |
| Relationship with father (mean, SD) | 4.52 (0.79) | 2.48 (1.22) | 2.00 (1.18) | LR > (HR = MDD) |
| Relationship with mother (mean, SD) | 4.78 (0.54) | 3.92 (1.01) | 3.14 (1.14) | LR > HR > MDD |
| Relationship between parents (mean, SD) | 4.18 (1.08) | 2.38 (1.23) | 1.94 (1.04) | LR > (HR = MDD) |
| Childhood maltreatment | | | | |
| None | 50 (100.00) | 1 (2.00) | 0 (0.00) | LR > (HR = MDD) |
| Probable | 0 (0.00) | 12 (24.00) | 4 (8.00) | LR < (HR > MDD) |
| Severe | 0 (0.00) | 37 (74.00) | 46 (92.00) | LR < HR < MDD |

*[a] Unless noted as mean (SD). [b] For a $p < 0.05$, comparisons between low risk (LR) vs. high risk (HR), LR vs. major depressive disorder (MDD), and HR vs. MDD, as indicated. "Relationship" variables were analyzed as continuous (mean, SD), with answers ranging = considered to range from 1 (bad) to 5 (great). IDEA-RiSCo, Identifying Depression Early in Adolescence Risk-Stratified Cohort.*

irritability (ARI-P), anxiety (SCAS-P), and positive attributes (YSI-P). This was also observed for the presence of any anxiety disorder (22, 26, and 56%) and any comorbid disorder (28, 36, and 62%) for the LR, HR, and MDD groups, respectively. Further details are provided in **Table 2**, **Supplementary Material 9**.

Participants in the MDD and HR groups had an elevated load of family history of depression in comparison to the LR group (**Table 2**). There was a stepwise decrease from MDD to HR to LR in terms of reporting childhood traumatic experiences (CTQ). Adolescents in the MDD group also reported more recent negative events (LEQ) in comparison to HR and LR; no differences in regard to neutral and positive events were observed. Both MDD and HR families exhibited lower socioeconomic scores (ABEP) in comparison to those in the LR group. The three groups did not significantly differ in terms of IQ scores and body mass index.

## Qualitative Interviews

Adolescents in the MDD group included in the qualitative analysis reported their perspectives on receiving a diagnosis of depression and participating in the IDEA-RiSCo study. The last participants included in the study (2 girls, 6 boys) were interviewed from October 2019 to December 2019. Extracts of their accounts can be found in **Box 1**. Another two girls were unable to attend the second interview and therefore were not included in the current analyses.

# DISCUSSION

In this article, we described the rationale and methods for the IDEA-RiSCo study. Using a previously developed composite score (the IDEA-RS), we devised a new, risk-stratified cohort to study neurobiological correlates of risk and presence of depression among adolescents. Up to now, most studies with high-risk groups have focused on single risk factors to characterize groups. Relying on an empirically generated composite score comprising 11 sociodemographic variables allowed us to characterize groups using a definition anchored in the simultaneous occurrence of a range of risk factors and separate non-cases into those at high and low risk of future depression (rather than unhelpfully lumping them together).

Our risk score was developed using data from the Pelotas 1993 Birth Cohort study and exhibited a good discriminative capacity for the identification of adolescents at risk for depression (similar for instance to the Framingham Risk Score) (3). Although originally generated in a sample of Brazilian adolescents, the IDEA-RS has been demonstrated to predict (74) depression in other settings around the globe. Even without information on all the original 11 variables, the score was able to parse beyond chance high- and low-risk adolescents when externally assessed in samples from Nepal, New Zealand, Nigeria, and the United Kingdom (13–15). For the IDEA-RiSCo study, we collected information using the exact same questions from the Pelotas cohort, observing some differences in the prevalence of specific risk factors between the Pelotas and Porto Alegre samples, which could be at least in part understood as a consequence of differences in terms of the size of the cities (300,000 vs. 1,400,000 inhabitants), year (2008 vs. 2018–9), and setting (birth cohort vs. school-based sample) of data collection. Although the average IDEA-RS was higher in Porto Alegre in comparison to Pelotas, there was a remarkable resemblance in terms of how each factor was related to the others, as demonstrated by the similarity of the network structure in both samples.

The IDEA-RS uses sociodemographic information to stratify for the risk of developing depression. Differently from other

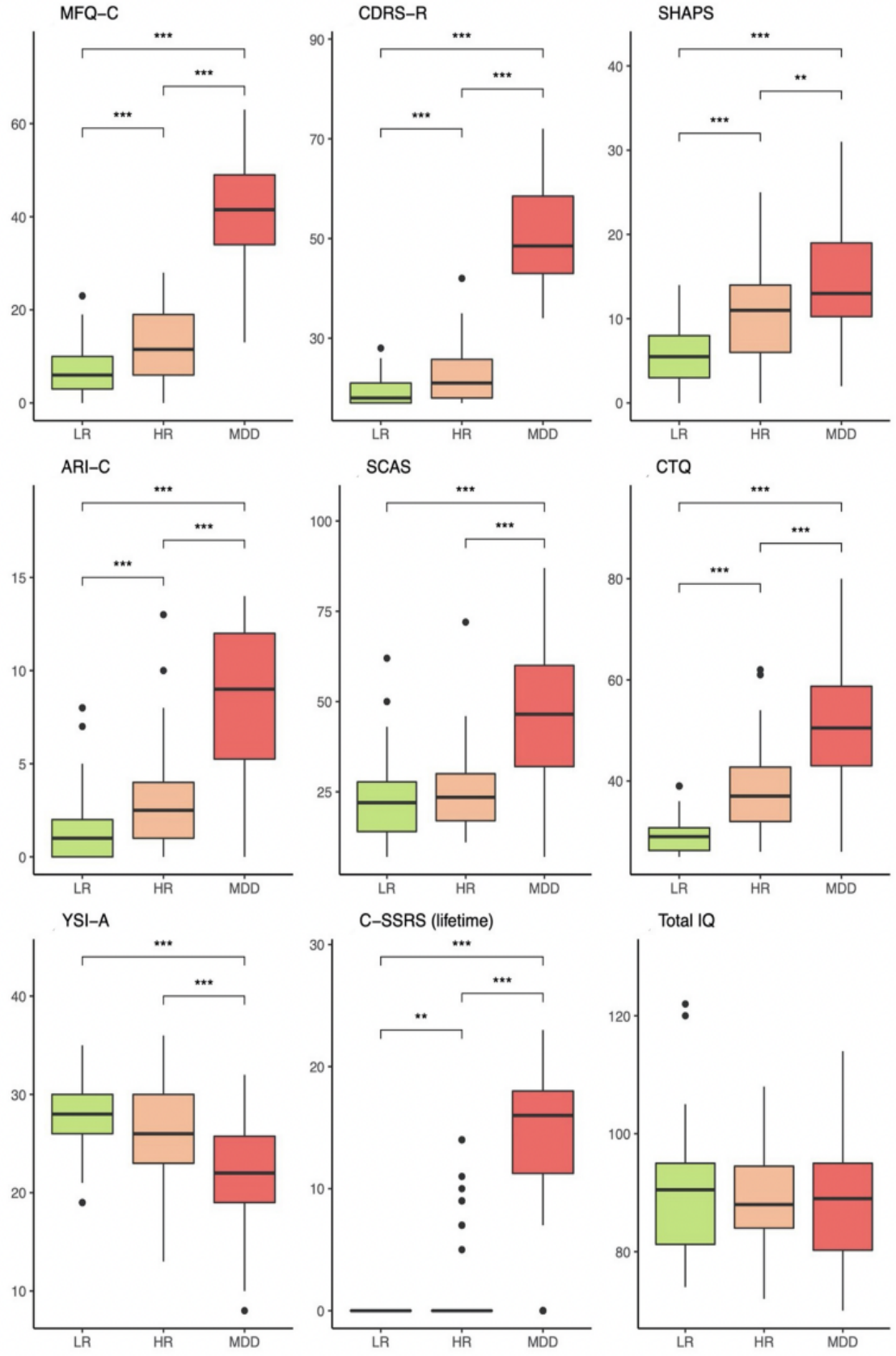


**FIGURE 8 |** Phenotypic comparisons between groups based on reports by the adolescents. LR, low-risk; HR, high-risk; MDD, major depressive disorder; MFQ-C, Mood and Feelings Questionnaire—Child; CDRS-R, Children's Depression Rating Scale Revised; SHAPS, Snaith-Hamilton Pleasure Scale; ARI-C, Affective Reactivity Index—Child; SCAS-C, Spence Children's Anxiety Scale; CTQ, Child Trauma Questionnaire; YSI-A, Youth Strengths Inventory—Adolescent; C-SSRS, Columbia-Suicide Severity Rating Scale. CDRS-R ratings were based on information from both adolescent and caregiver, with priority to the former. The non-parametric Kruskal-Wallis test was applied to compare the means. $^{**}p < 0.01$, $^{***}p < 0.001$.

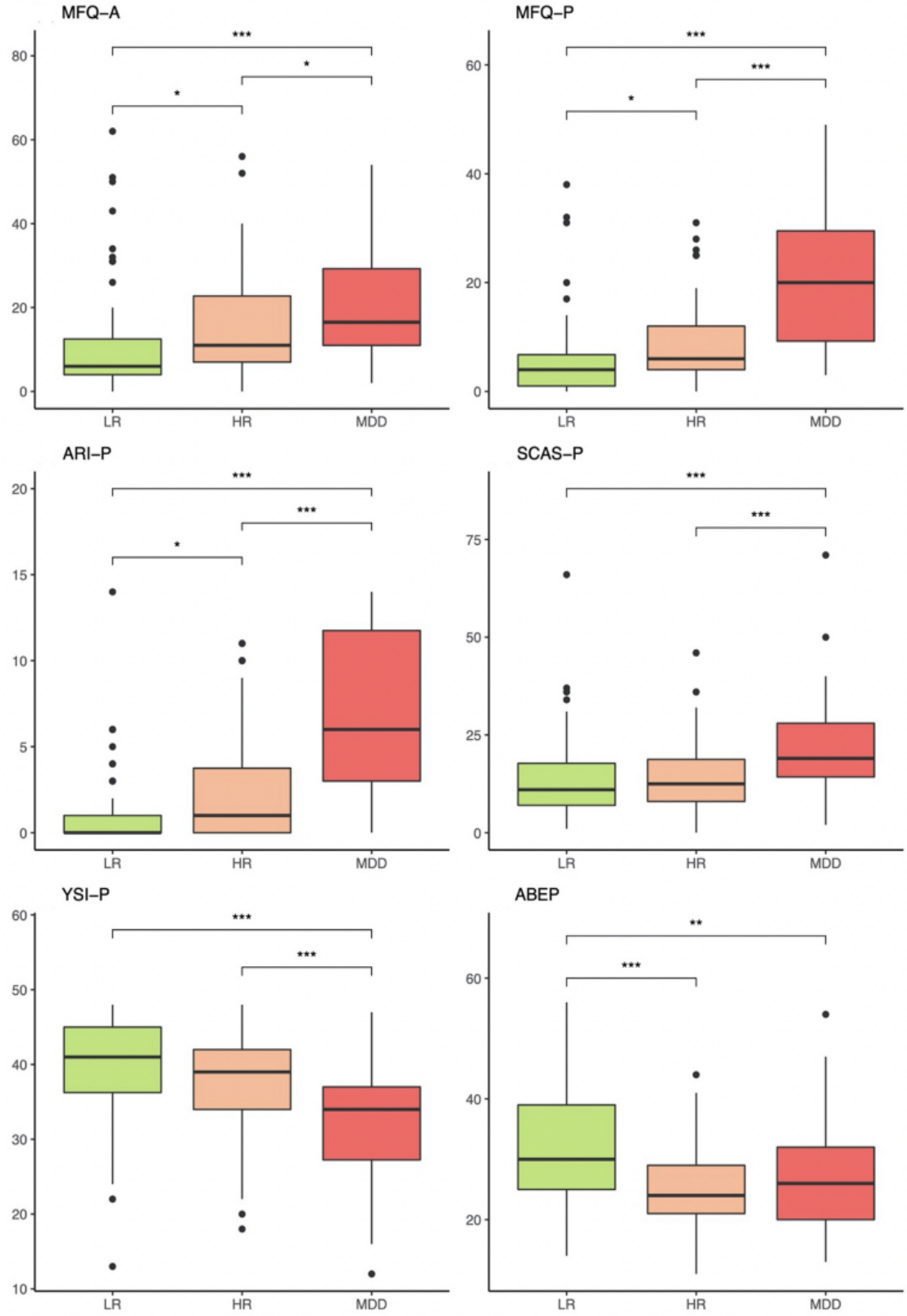


**FIGURE 9 |** Phenotypic comparisons between groups based on reports by the caregivers. LR, low-risk; HR, high-risk; MDD, major depressive disorder; MFQ-A, Mood and Feelings Questionnaire—Adult (caregiver self-report); MFQ-P, Mood and Feelings Questionnaire—Parent (caregiver report on adolescent); ARI-P, Affective Reactivity Index—Parent; SCAS-P, Spence Children's Anxiety Scale—Parent; YSI-P, Youth Strengths Inventory—Parent; ABEP, Brazil socioeconomic classification index. The non-parametric Kruskal-Wallis test was applied to compare the means. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

**BOX 1** | "Some questions we have to think a lot about": the experience of participating in the IDEA-RiSCo study.

Overall, adolescents had a limited understanding of the purposes of the research. None of them explicitly reported knowing why they underwent several steps of data collection, but rather explained the purpose of the research as being linked to the idea of finding out if they had "problems" or "something wrong with them":

*"I think [data was collected] so it can be analyzed, to look for similarities with other people who have something similar to me." (boy, age 15)*

About the initial screening phase in schools, most of the interviewed adolescents reported that they were even minded when they answered the screening questionnaire. Others, however, expressed concerns about answering the questions: they mentioned that they wondered whether they should answer truthfully. The idea of participating in the research as a way of being helped and having feelings and difficulties acknowledged was also often expressed by participants. Helping other adolescents who may be struggling with depression was also mentioned as a great motivator for participating in the research:

*"It was interesting to participate because I felt that it could help someone." (boy, age 14)*

*"In the start, I thought it was something that wasn't going anywhere, but it was something that ended up helping me a lot." (girl, age 16)*

When participating in the evaluation at the Clinical Research Center, all adolescents reported that the clinical interview was the most difficult part of the process. They expressed that it was emotional and hard to remember some past events and talk about their feelings, and answering the scales also demanded sustained attention.

*"Some questions were more emotional, about things that happened. One or two were harder, were about traumas [...] Then it gets sad having to talk again about what happened." (boy, age 16)*

However, they also added that the process was positive, even therapeutic in its own right:

*"I think it was good to at least be able to talk a little, identify with the questions and to know that I'm probably… Going through some of these problems." (boy, age 15)*

About having their blood taken, several expressed that they were nervous about it. However, the presence of the research team and the support provided to the adolescent throughout the whole process was described as a way to face the anxiety related to the procedure:

*"I liked the researchers that were in the room with me, they started to talk to me, so I felt more comfortable" (boy, age 14)*

As the last part of the clinical protocol included an MRI scan, all adolescents reported that it was the most challenging part of the protocol in the sense of procedures before and during the scan and the completion of the tasks. They also mentioned discomfort with the necessity of being still for the whole assessment and that the total length of the procedure made them tired.

*"It was… Tiresome. I almost slept. It is weird. They put you inside this machine to see your brain... [I felt] anxious." (boy, age 16)*

IDEA-RiSCo, Identifying Depression Early in Adolescence Risk-Stratified Cohort.

approaches more aligned with the concept of indicated prevention (75), our score does not rely on using subthreshold symptomatology to predict a full-blown syndrome. Using subsyndromal psychopathology to identify at-risk mental states can require training and extensive assessments (76, 77), being less suitable in general population contexts (78). Our approach also differs from many high-risk studies as the IDEA-RS does not contain information on family history of depression. Although this has been one of the most replicated risk factors in the literature (79), our score was developed to be easily collectable directly from adolescents (who are frequently unlikely to know sufficient details about family psychiatric history), without needing to engage caregivers, which can be burdensome in terms of screening procedures. Moreover, we also acknowledge that the probability of someone reporting a positive family history can be largely influenced by the probability of family members having access to services and to diagnostic assessment, something that can be highly variable, especially in low- and middle-income settings. Furthermore, we assessed the incremental value of adding information on maternal depression to the IDEA-RS in the Pelotas dataset, and no meaningful classification improvement was observed (the opposite [adding the IDEA-RS to a stratification based on history of maternal symptoms of depression], however, enhanced risk estimation) (13).

Whether and to what extent the IDEA-RS captures the liability conferred by having a positive family history of depression remains to be understood. Future analyses comparing the IDEA-RS with information from polygenic risk scores (PRS) could be one strategy to further disentangle this issue. There is some suggestion that adding PRS to traditional risk scores can improve classification, although this has not always been the case (80). Importantly, families usually share not only genetic, but also environmental backgrounds, and some of the familial influences on depression risk could have been captured by the family-related items in the IDEA-RS (e.g., relationship with and between parents).

Considering the multifactorial etiology of depression, multiple pathways to the susceptibility for developing the disorder are likely (5). Individuals with a positive family history of depression have twice as much risk of developing the disorder (81). Also, a recent PRS for depression demonstrated a 2.5-fold increase in risk when comparing the highest and lowest risk deciles (82). In the IDEA-RiSCo sample, sociodemographic information was used to stratify individuals for risk of developing depression. Taking into account the evidence on social and environmental influences on immune/inflammatory factors and brain structure and function (83–85), focusing on adolescents at low and high extremes might enhance our ability to identify neurobiological correlates of depression risk. Indeed, the magnitude of risk associated with the IDEA-RS does not appear to be inferior to what has been observed using other traditional stratification strategies. Using similar cut-offs in the Pelotas 1993 Cohort, a 15-year-old girl classified as HR (≥90th percentile), in comparison to one classified as LR (≤20th percentile), exhibited an 8.67 (95% CI 3.56–21.08) times increased odds for having depression at age 18 years. Additionally, none of the boys in the LR group had depression at age 18. Still, although efficient in terms of parsing extremes, the specific cut-offs chosen for assigning individuals to LR and HR strata are arbitrary and should be further assessed for clinical relevance in subsequent studies.

In this report, we also presented the baseline clinical characteristics of the IDEA-RiSCo sample. After an extensive school-based screening process to identify individuals at low and high risk for developing depression in adolescence, we were able to form three groups consistently distinct in a wide range

of phenotypic characteristics. Across a variety of measures of psychopathology and exposure to negative events, there was a clear pattern in which either the MDD group or both the HR and the MDD groups exhibited worse indicators in comparison to the LR group. Importantly, the differences seen between the LR and HR groups underscore the importance of not lumping them together as a homogeneous group of "non-cases."

Regarding the adolescents' perspectives on participating in the IDEA-RiSCo study, they highlighted the importance of several aspects of conducting research with adolescents. First, eliciting trust from adolescents is a crucial aspect of the process. When answering questionnaires in the school setting, adolescents reported contemplating lying on their answers. Moreover, adolescents stressed the positive role of the research team in this process of trust and self-disclosure, as well as their overall comfort during specific steps of the process. Our data suggest that it is essential for adolescent participation to ensure that the research is conducted in an adolescent-friendly manner—especially by providing comfort and trust. Understanding how to better communicate with adolescents about research purposes and design plus consulting with them in designing research studies is likely to be crucial to ensure adolescent engagement.

Among the strengths of our study is the careful phenotypic characterization of the three groups with marked differences in terms of exposure to risk factors and manifestation of symptomatology. The comprehensive clinical assessment procedures, including the use of gold-standard instruments to collect information both from the adolescent and their primary caregiver and generate best estimate diagnoses is also an asset of the IDEA-RiSCo. Given the episodic nature of depression, it is extremely relevant to ensure that individuals with past depression, but who are not in an active episode, are not wrongly classified as "at risk," as well as to require "cases" to be in a currently active depressive episode at the time of the assessment. Furthermore, we only included participants not using psychotropic medications, thereby making the sample more homogeneous. Due to possible temporal fluctuations in depressive symptomatology, performing clinical and neurobiological collections on the same day can also be seen as advantageous; unfortunately, due to logistical reasons we were not able to standardize the time of day for collection, but there were no differences in group proportions in terms of participants who were assessed in the morning or in the afternoon. The sample size can also be seen as a possible limitation of our study, which we believe can be counterbalanced by focusing on more homogeneous groups and employing comprehensive clinical assessment procedures, which is not always the case in large samples that frequently rely only on short, self-reported measures. Targeting extreme groups, although potentially advantageous for the identification of neurobiological correlates, has the intrinsic drawback of reducing the external validity of findings to individuals in the middle range. Furthermore, the requirement of a high IDEA-RS for the MDD group included in our design to allow for direct comparisons with the HR group, although focusing on adolescents with depression and high degree of vulnerability, inevitably makes the former less representative of the overall population of youths with depression. Lastly, we will be able to overcome the present cross-sectional constraint of the study with follow-up assessments that are currently underway—which will be essential, for instance, to confirm that HR adolescents are indeed at increased risk (as opposed to an alternative interpretation, according to which they could be more resilient to the emergence of depression despite high loading of risk factors).

The use of an empirically-based composite score to stratify risk for developing depression is a promising strategy to better understand the neurobiological mechanisms on the path to depression onset. The fact that nine out of ten children and adolescents in the globe live in low- and middle-income countries (LMICs) makes conducting this study in a middle-income country such as Brazil even more compelling (86, 87). Moreover, there is support for the approach adopted here among adolescent mental health experts in LMICs, including the focus on many of the IDEA-RS factors and the use of risk calculators (88). The underrepresentation of large proportions of the globe's population in the scientific literature is evident in the field of child and adolescent mental health (86, 87, 89). We hope that the IDEA-RiSCo study, by using state of the art methods to further understand the neurobiological underpinnings of risk and presence of depression among adolescents, will contribute to closing this gap.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Brazilian National Ethics in Research Commission (CAAE 50473015.9.0000.5327). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## AUTHOR CONTRIBUTIONS

CK, AC, HLF, RK, BAK, TR, LAR, JRS, and VM conceptualized the study and/or wrote the grant funding it. CK, AC, PM, AV, MA, LB, SB, HLF, BAK, RK, TM, SP, JP, TR, LS, BV, ZZ, VZ, JRS, and VM developed the study protocol. CK, CB, AC, PM, RP, AV, LB, SB, HLF, BAK, TM, SP, JP, TR, FR, LS, BV, AW, LY, ZZ, VZ, JRS, and VM contributed to data collection, analyses, and/or management. CK, CB, AC, PM, RP, AV, MA, LB, SB, HLF, RK, BAK, TM, SP, JP, TR, LAR, FR, LS, BV, AW, LY, ZZ, VZ, JRS, and VM wrote or revised sections of the manuscript. All authors approved the final version of the manuscript.

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