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Depression in Adolescents: Social Media Use and a Network Analysis of Symptom-Level Retrospective and Dynamic Assessments

Depressão em Adolescentes: Uso de Mídias Sociais e uma Análise de Rede de Avaliações Retrospectivas e Dinâmicas em Nível de Sintomas

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Dissertation presented as partial requirement for obtaining a Master Degree in Psychiatry from the Graduate Program in Psychiatry and Behavioral Sciences of the School of Medicine of the Federal University of Rio Grande do Sul.

Advisor: Prof. Dr. Christian Kieling

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To life.
To love.
To hope.

To my parents, from whom I learned how to care for people.

To my husband, Gabriel, with whom I learned what it truly means not to feel alone.

To my siblings, from whom I learned that everyone carries something special within.

To my friends, from whom I learned that life is much more than achievements.

To my colleagues at ProDia, from whom I learned that doing research can be so much fun when you are with the right people.

To my advisor, from whom I learned that it is always worth it trying my best.

ABSTRACT

Depression is a significant mental health issue during adolescence, a critical period of emotional development. Traditional assessments often rely on retrospective self-reports, which may not accurately reflect the dynamic of depressive symptoms. This dissertation explores the temporal dynamics of depression in Brazilian adolescents using both retrospective and intensive longitudinal assessments. Two empirical studies were conducted with Brazilian adolescents aged 13-19. The first study surveyed social media usage. The second study used IDEABot, a WhatsApp-based chatbot, to collect real-time data on mood fluctuations over two weeks, comparing these with retrospective self-reports. The first study found widespread daily social media use by participants. The second study revealed discrepancies between retrospective and intensive longitudinal assessments, with retrospective reports often overestimating symptom severity, with stronger associations between cognitive symptoms. Intensive longitudinal assessments, however, with somatic and affective symptoms appearing more interconnected in real-time data. Overall, the first study showed a high usage of WhatsApp, suggesting this platform could be leveraged for real-time mental health assessment. The second study revealed that retrospective assessments can be influenced by recall biases, while intensive longitudinal assessments can provide information on real-time fluctuations and interactions between depressive symptoms. Digital technologies can enhance our understanding of depression's temporal dynamics. The use of tools like IDEABot provides a detailed assessment of depressive symptoms, moving beyond the static snapshot offered by traditional methods. The study's findings have significant implications for clinical practice, particularly in developing more effective assessment and intervention strategies for adolescent depression. Future research should aim to replicate these findings across diverse cultural and socioeconomic contexts and further refine the use of digital tools for real-time mental health monitoring.

Keywords: Adolescence; depression; network analysis; psychometrics.

RESUMO

A depressão é um problema significativo de saúde mental durante a adolescência, um período crítico de desenvolvimento emocional. As avaliações tradicionais muitas vezes dependem de autorrelatos retrospectivos, que podem não refletir com precisão a dinâmica dos sintomas depressivos. Esta dissertação explora as dinâmicas temporais da depressão em adolescentes brasileiros usando tanto avaliações retrospectivas quanto longitudinais intensivas. Dois estudos empíricos foram realizados com adolescentes brasileiros com idades entre 13 e 19 anos. O primeiro estudo investigou o uso das redes sociais. O segundo estudo utilizou o IDEABot, um chatbot via WhatsApp, para coletar dados em tempo real sobre flutuações de humor ao longo de duas semanas, comparando esses dados com autorrelatos retrospectivos. O primeiro estudo encontrou um uso diário generalizado das redes sociais pelos participantes. O segundo estudo revelou discrepâncias entre as avaliações retrospectivas e as longitudinais intensivas, com os relatos retrospectivos muitas vezes superestimando a gravidade dos sintomas, com associações mais fortes entre sintomas cognitivos. As avaliações longitudinais intensivas, por outro lado, mostraram que os sintomas somáticos e afetivos apareciam mais interconectados nos dados em tempo real. O primeiro estudo mostrou um alto uso do WhatsApp, sugerindo que essa plataforma pode ser utilizada para avaliações em saúde mental. O segundo estudo revelou que as avaliações retrospectivas podem ser influenciadas por vieses de memória, enquanto as avaliações longitudinais intensivas podem fornecer informações sobre flutuações e interações entre os sintomas depressivos em tempo real. As tecnologias digitais podem ajudar nossa compreensão das dinâmicas temporais da depressão. O uso de ferramentas como o IDEABot proporciona uma avaliação detalhada dos sintomas depressivos, indo além da visão estática oferecida pelos métodos tradicionais. Os resultados do estudo têm implicações significativas para a prática clínica, particularmente no desenvolvimento de estratégias de avaliação e intervenção mais eficazes para a depressão na adolescência. Pesquisas futuras devem buscar replicar esses achados em contextos culturais e

socioeconômicos diversos e refinar ainda mais o uso de ferramentas digitais para monitoramento em tempo real da saúde mental.

Palavras-chave: Adolescência; depressão; análise de rede; psicometria.

ABBREVIATIONS

CDI	*Children's Depression Inventory*
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
EGA	*Exploratory Graph Analysis*
EMA	*Ecological Momentary Assessments*
HDRS	*Hamilton Depression Rating Scale*
IDEA	*Identifying Depression Early in Adolescence*
IRT	*Item Response Theory*
MDD	*Major Depressive Disorder*
MFQ	*Mood and Feelings Questionnaire*
sMFQ	*Short Mood and Feelings Questionnaire*
BDI	*Beck Depression Inventory*
PHQ	*Patient Health Questionnaire*
SEM	*Structural Equation Modeling*

SUMMARY

INTRODUCTION

THE PRESENT WORK

This work is part of a master's thesis titled “Depression in Adolescents: Social Media Use and a Network Analysis of Symptom-Level Retrospective and Dynamic Assessments,” submitted to the Graduate Program in Psychiatry and Behavioral Sciences.This thesis aims to explore the self-reported prevalence of social media use among Brazilian adolescents and examine the temporal dynamics of their depressive symptoms using various analytical techniques. It is structured around two distinct studies.

Using a school sample of Brazilian adolescents, the first study aimed to understand the way Brazilian youth interact with social media platforms and which platforms they use the most. The results described the self-reported prevalences and perceptions of the effects of social media use. We analyzed cross-sectional data from 7,113 adolescents aged 14 to 16 years, enrolled in 101 state public schools in Porto Alegre. The results showed that 97.7% of the adolescents reported using at least one social media platform every day, with WhatsApp being the most popular. These findings, especially regarding the high use of the WhatsApp application among adolescents, were crucial for our research group, the Child and Adolescent Depression Program (ProDIA), to initiate the creation of the Identifying Depression Early in Adolescence Chatbot (IDEABot) (Viduani et al., 2023). The IDEABot is a chatbot designed to collect data on mood via WhatsApp, and it was developed and implemented as part of the Identifying Depression Early in Adolescence Risk Stratified Cohort (IDEA-RiSCo) study (Kieling et al., 2021; Piccin et al., 2024), a larger project to which my master's studies are related (Appendices 1 and 2), where we collected intensive longitudinal data on youth's mood and enabled me to conduct the second paper.

In the second paper, I used the IDEABot previously developed by our research group to compare scores from the Mood and Feelings Questionnaire (MFQ) (Rosa et al., 2018)

retrospectively and intensive-longitudinally, to assess depressive symptoms in a group of Brazilian adolescents with a focus on symptom presentation. For this, I used network analysis to compare retrospective and intensive-longitudinal reports at the symptom level and employed the Exploratory Graph Analysis method to identify differences in the dimensions (factors) of symptoms in both reports.

CONCEPTUAL FOUNDATION

Characterization and conceptualization of depression in adolescence

Depressive disorders are recognized as one of the leading causes of health-related problems worldwide (GBD 2019 Mental Disorders Collaborators, 2022; Kieling et al., 2024). It is a common and serious medical condition that encompasses alterations in one's mood, thinking, and behavior. It is characterized by persistent feelings of sadness, loss of interest or pleasure in activities once enjoyed, changes in appetite, trouble sleeping or oversleeping, loss of energy, increased fatigue, feelings of worthlessness or guilt, difficulty thinking, concentrating or making decisions, and thoughts of death or suicide. Furthermore, the onset of depression is commonly seen in adolescents and young adults, frequently displaying a chronic and recurrent course (Davey & McGorry, 2019). Due to this, it is essential that mental health issues be monitored by precise evaluations during this stage of development, which is marked by profound biopsychosocial transformations.

During youth, individuals undergo significant physical, psychological, and social changes that can influence and exacerbate the manifestations of depression. These changes include the development of identity, increased cognitive abilities, and a greater emphasis on peer relationships (Conway et al., 2011; Morgan et al., 2013; Silk et al., 2014). Unfortunately, these transformations can also make young people particularly vulnerable to mental health disorders, including depression. During this period, depression can present differently than in adults. Youngs with depression may exhibit increased irritability, anger, or hostility rather than

sadness. They might also show changes in their eating and sleeping habits, withdraw from friends and activities, experience feelings of worthlessness or excessive guilt, have difficulty with schoolwork, and exhibit unexplained aches and pains (Mullarkey et al., 2019; Orri et al., 2018; Rice et al., 2019). These differences are partly due to the various developmental, hormonal, and social changes that adolescents go through (Pfeifer & Allen, 2021).

Exploring enhanced and more precise methods for assessing depression in young people is crucial, both for clinical practice and for research aimed at understanding the prevalence of depression during this critical developmental stage. Studies demonstrate that accurate assessment tools specifically designed for this age group can significantly improve early diagnosis and the effectiveness of interventions, thus mitigating the long-term impact of depression on individual lives (Beck et al., 2021; Uhlhaas et al., 2023). In clinical environments, refined assessment strategies allow healthcare providers to devise and implement tailored treatment plans that are more effective. From a research standpoint, these improved methods can elevate the quality of data collected, facilitating a more comprehensive understanding of the causes, progression, and treatment responses of depression.

Moreover, precise assessments are essential for epidemiological studies to accurately determine the true prevalence of depression. This, in turn, can guide policy decisions and the allocation of resources for mental health services. Specifically, longitudinal assessments of depression have proven invaluable in tracking the dynamics of depressive symptoms over time (Baltasar-Tello et al., 2018; Blain-Arcaro & Vaillancourt, 2017; Ellis et al., 2017). Such assessments help identify patterns, triggers, and the effects of environmental or personal changes on adolescents' mental health. They offer a promising approach to better understanding depression within this demographic.

Historical compilation of ways to assess depression

The assessment of depression has evolved significantly over the years, reflecting advances in psychiatric understanding, diagnostic criteria, and technology. Historically, the diagnosis of depression relied heavily on clinical judgment and observation of symptoms, without the aid of standardized tools (McPherson & Armstrong, 2022; Smith et al., 2013). In the early 20th century, psychiatric assessments were predominantly narrative descriptions of patients' behaviors and self-reported experiences (Smith et al., 2013). While this qualitative method offered rich detail, it suffered from a lack of consistency and objectivity, complicating comparisons across different patients and studies.

In the mid-20th century, a pivotal moment arrived in the field with the advent of standardized diagnostic criteria and the emergence of structured and semi-structured interviews. The American Psychiatric Association published the first edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) in 1952. This marked the beginning of efforts to establish a universal framework for diagnosing mental health conditions. This initiative gained significant momentum with the release of the third edition (DSM-III) in 1980, which included comprehensive guidelines for diagnosing conditions such as depression.. This period also saw the rise of structured questionnaires like the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), and the Beck Depression Inventory (BDI)(Beck, 1961), both introduced in the early 1960s. These tools played a foundational role, enabling clinicians to conduct more objective and quantifiable assessments of depressive symptoms. Moreover, they facilitated advancements in clinical research and fostered comparability in treatment outcomes across different studies and populations.

In response to the unique challenges of assessing depression in young people, specialized tools and approaches have been crafted to accurately reflect the distinct expressions of depression in this age group. Acknowledging that youth may exhibit depressive symptoms differently from adults, instruments such as the Children's Depression Inventory

(CDI)(Kovacs, 1985), first developed in the 1970s, have been specifically designed with age-appropriate items and terminology. These tools aimed to take into account the developmental context of adolescence, encompassing cognitive, emotional, and social stages of growth, to ensure precise and relevant assessments.

As the latter part of the 20th century transitioned into the 21st, the field witnessed the introduction of increasingly sophisticated tools and methodologies, with particular adaptations tailored for younger populations. Advances in technology facilitated the development of computerized assessments and, more recently, the adoption of digital health technologies such as mobile apps and wearable devices. These innovations enable real-time monitoring of symptoms and mood states among youth. Data collection techniques like Ecological Momentary Assessments (EMA) provide a dynamic and detailed perspective on psychiatric disorders, capturing fluctuations in symptoms over time within the individual's natural environment and daily activities (Shiffman et al., 2008). This approach is especially valuable for comprehending the rapidly changing moods that often occur during youth, offering insights that are both immediate and contextually grounded (Baltasar-Tello et al., 2018). Additionally, there has been an increasing emphasis in the field on incorporating measures of functioning and quality of life, recognizing that the impact of depression extends beyond symptomatology to affect various aspects of patients' lives, including academic performance and social interactions (Hagemann et al., 2023; Short et al., 2013; Verboom et al., 2014).

Technology and Youth Mental Health

In recent years, this digital revolution has profoundly transformed daily life, particularly for younger generations who are growing up as digital natives. Social media platforms, mobile applications, and online communities have become integral to the social and emotional development of children and adolescents. These technologies offer unprecedented opportunities for social connection, access to information, and mental health support, reflecting a shift in how youth engage with their environment and seek help. However, this

digital landscape also introduces new complexities and potential risks, including issues related to mental health that warrant careful examination.

As digital interactions become increasingly central to the lives of young people, understanding their implications for mental health is crucial. The last research made by the Pew Research Center shows that a third of teens use at least one social platform almost constantly (Pew Research Center, 2025). These results raise important questions on whether using these platforms are more beneficial or maleficial. Since its creation, social media has both facilitated new forms of social support and exposed youth to novel stressors and risks. On one hand, these platforms can provide social support, community, and access to mental health resources, fostering a sense of belonging and reducing feelings of isolation(Valkenburg et al., 2022). On the other hand, excessive use of social media has been associated with increased risks of anxiety, depression, and cyberbullying, underscoring the need for balanced and mindful usage(Twenge & Campbell, 2019).

Despite the proliferation of these digital tools, there remains a notable gap in the rigorous, long-term evidence needed to fully understand their impact on mental health. While some studies suggest that digital interventions can be effective in identifying and mitigating mental health issues in real time, the field still lacks comprehensive data on their long-term efficacy and potential unintended consequences(Hollis et al., 2017). Moreover, the rapid pace of technological advancement often outstrips the ability of researchers to conduct thorough evaluations, leading to a lag in evidence-based guidance. Consequently, there is a pressing need for continued research to establish robust frameworks and guidelines for the safe and effective integration of digital tools into child and adolescent psychiatry. This ongoing inquiry is essential to harness the potential benefits of technology while safeguarding against its risks, ensuring that interventions are both scientifically sound and practically applicable in diverse real-world settings(Rideout & Robb, 2018).

Quantitative approaches to assess depression

In this scenario, the quantitative analysis of depression, particularly through the evolution of statistical techniques, has played a relevant role in enhancing our understanding and assessment of this multifaceted disorder. Initially, depression research relied on basic statistical methods, such as calculating means and standard deviations, to quantify symptom severity and prevalence. Over time, however, the field has embraced more advanced statistical methods to explore the underlying structure and dynamics of depressive symptoms more thoroughly. Factor analysis has been a cornerstone in this methodological advancement. By exploring the correlations among various symptoms, factor analysis aids researchers and clinicians in identifying underlying dimensions or factors that clarify the patterns of symptoms observed in individuals with depression (Ballard et al., 2018; Goodmann et al., 2021). For instance, early applications of factor analysis differentiated between affective, cognitive, and somatic dimensions of depression, insights which have crucially influenced both diagnostic criteria and treatment approaches (Shafer, 2006). This detailed, nuanced understanding supports more targeted and effective therapeutic interventions, advancing the field significantly.

Factor analysis has also significantly contributed to the development and enhancement of depression assessment tools. By discerning which symptoms frequently co-occur, researchers have been able to construct more cohesive and psychometrically robust measures. This involves ensuring that scales possess both validity, and reliability, yielding consistent outcomes across various populations and over time. Furthermore, the introduction of more sophisticated statistical methodologies, such as structural equation modeling (SEM) and item response theory (IRT), has further enriched depression analysis (Embretson & Reise, 2013; MacCallum & Austin, 2000). SEM allows the examination of intricate models that delineate connections among latent variables, offering a more nuanced comprehension of how different facets of depression interrelate. On the other hand, IRT examines the properties of individual items within a scale, such as their capacity to differentiate between

various levels of depression severity. This has led to the development of more precise measurement instruments better capable of capturing the entire spectrum of depressive symptoms.

However, it is important to highlight that these techniques are based on a latent disease model (Krueger, 1999), which assumes that symptoms are manifestations of an underlying, unobservable variable—here, depression (Nuijten et al., 2016). Typically, analyses utilize questionnaires that are rated on a scale of intensity and/or frequency. The sum of the individual items in these questionnaires generates a final score. This score is then compared to a predetermined cutoff point to determine whether it falls below or above the threshold, indicating the absence or presence of the disorder. Nevertheless, criticism has been growing regarding the use of the latent model for understanding depression. In the following section, we will explore an alternative approach that has gained popularity in recent years and that differs from the latent model by prioritizing the symptoms themselves as the focal point of understanding and analysing depression.

Network analysis

The network approach to understanding psychological symptoms presents a significant shift from traditional models by focusing on the interactions among symptoms rather than on underlying latent disorders (Borsboom, 2008). This innovative framework conceptualizes symptoms as interconnected entities within a causal system, where each symptom can activate or influence others (Cramer et al., 2010). Unlike traditional views that regard symptoms as indicators of a deeper, unseen disorder, the network approach analyzes them as part of a dynamic system. In this model, symptoms are depicted as nodes—often visualized as circles—and the relationships between them are represented by edges. These edges illustrate various types of interactions, including correlations, probability ratios, or direct causal links, thus offering a more granular and interactive understanding of symptomatology. This perspective not only enhances our grasp of how symptoms develop

and sustain themselves but also opens new avenues for targeted interventions that address specific connections within the network (Blanken et al., 2019).

From the network perspective, major depressive disorder (MDD) is frequently analyzed through cross-sectional studies, which often use data from retrospective reports, in which individuals recall symptoms that they had in the past (Robinaugh et al., 2020). These studies rely on non-directional networks that map the associations between various depressive symptoms, focusing on their interconnectedness. However, such studies inherently lack the ability to delineate temporal relationships and therefore do not capture the evolution of symptoms over time. This limitation is critical when aiming to understand the full trajectory and progression of psychiatric disorders like MDD. Recognizing the temporal dynamics is essential for accurately identifying, characterizing, treating, and predicting depression outcomes, especially in youth considered at risk.

Longitudinal network analysis studies in depression emphasize how depression symptoms interact within a network. For example, it was found that central symptoms such as sadness or anhedonia often have a pivotal role, influencing other symptoms and potentially worsening the overall condition(Borsboom & Cramer, 2013). Research highlights the importance of temporal dynamics, showing that changes in the network structure can predict the course of depression and response to treatment(McElroy et al., 2019). Additionally, longitudinal studies have revealed how social and environmental factors can impact the network of depression symptoms, further complicating their evolution(Wang et al., 2023). Integrating these findings with advanced network modeling techniques promises to enhance personalized treatment approaches by targeting key symptoms and their interactions(Blanken et al., 2019; Epskamp et al., 2018).

The advancement of statistical techniques in recent years, as observed by different analytical methods created within the field of network analysis, has been pivotal in transforming the simplistic views of depression into a more comprehensive understanding of its complexities

and the variability it presents across different individuals and over time. This quantitative evolution has not only advanced scientific knowledge but has also led to the development of more sophisticated treatment strategies (Blanken et al., 2019; McElroy et al., 2019). It underscores the critical role of statistical analysis in deepening our understanding of depression and enhancing our capability to effectively address this complex disorder. This shift in methodology highlights the ongoing need for innovative approaches that can better capture the nuances of mental health conditions.

The challenge of retrospective assessment and the advances in technology

Traditionally, clinical and research understanding of how depression manifests has relied on analyzing how patients retrospectively recall the simultaneous occurrence of symptoms. Analogically, the patient's effort to evoke particular details of their past experience is similar to an artist painting a landscape from memory. This memory may highlight particular aspects while neglecting or modifying others, influenced by the artist's overarching perception or notable moments that resonated most for them. In contrast, capturing dynamic assessment of mood over time resembles a photographer taking a series of real-time snapshots of the landscape, each providing insights into photographer's perception at specific points in time. Although the landscape remains constant, the painter and photographer capture it in different ways, and therefore their different perspectives might serve for different purposes. In the psychological realm, it is equally crucial to explore if the comprehension of phenomena changes when examined through diverse methodological lenses, whether retrospectively or prospectively.

As we have discussed, traditional assessment methods for depression, either with interviews or questionnaires, often rely on static, one-time evaluations, typically inquiring about an individual's state over the previous two weeks. This approach may not adequately capture the dynamic nature of depressive symptoms, particularly in the youth population, which

experiences rapid biopsychosocial changes that might impact their symptoms recall (Van Beveren et al., 2019). A significant concern with these traditional methods is the potential for biases due to retrospective self-reporting. Individuals may find it challenging to accurately recall past feelings and behaviors, leading to recall bias (Horwitz et al., 2023). Moreover, the intensity and presentation of depressive symptoms can vary considerably, not just day-to-day but also within the same day (Crowe et al., 2019). Consequently, a one-time evaluation might not reflect these fluctuations, potentially leading to an underestimation or overestimation of the severity of depression.

The episodic nature of depression further complicates retrospective assessment. Depressive episodes can vary in duration and intensity, and individuals may experience periods of remission between episodes. When asked to reflect on their depressive symptoms over a past period, youth may focus more on their most recent state or on periods of greatest severity, overlooking fluctuations and potentially leading to biased assessments (Horwitz et al., 2023).

In recent years, various methods of longitudinal data collection related to psychiatric disorders have been explored (Hall et al., 2021). With the growing advancement of mobile technology, it is now possible to obtain repeated measures at increasingly shorter time intervals. Intensive longitudinal collections aim to measure the presence and dynamics of specific constructs over time in an individual's daily life, occurring from once to several times a day for a certain period (Shiffman et al., 2008). This type of collection is gaining popularity in youth psychiatric and psychological research, according to Russel and Gajos (Russell & Gajos, 2020), especially for: (1) reducing memory bias compared to retrospective self-reports by using a prospective assessment of symptoms and behaviors shortly after they occur; (2) providing ecological validity by administering assessments in everyday life situations, such as situations and interactions where emotions are experienced, unlike lab assessments; and (3) enabling the measurement of intrapersonal variability, allowing comparisons within an

individual over repeated measures, facilitating causal inferences as each individual serves as their own "control" over time.

Despite its significant potential, the methodology of intensive longitudinal data collection still shows considerable variability in both quantity and quality across studies (Aan Het Rot et al., 2012; Hall et al., 2021). Existing research employs diverse methods, particularly varying in the frequency of data collection and the specific questions posed each day throughout the assessment. The field has yet to establish consensus on best practices for intensive data collection tailored to different age groups. Nonetheless, the potential of this approach remains substantial. Research demonstrates that intensive longitudinal assessments can provide a comprehensive understanding of how depressive symptoms develop over time (Myin-Germeys et al., 2018). These assessments are particularly valuable for mapping the trajectory and recurrence patterns of symptoms, as they capture detailed fluctuations and contextual factors, thus offering deeper insights into the dynamics of mental health conditions (Shiffman et al., 2008; Zarate et al., 2022).

Current challenges and research gaps

The potential of technology to enhance psychiatric practices, particularly for young people, is immense. Around the globe, both clinical and academic settings are increasingly turning to mobile technology as a tool to assess and treat psychiatric disorders (Firth et al., 2017; Torous et al., 2021). Despite these advancements, the challenge of integrating technology into regular practice remains, particularly in Brazil. The absence of high-quality evidence and well-established guidelines complicates efforts to standardize and improve the assessment and treatment of depression among Brazilian youth. Addressing these gaps is crucial for leveraging technology effectively to support mental health interventions that are both efficient and accessible.

While there is significant potential for progress in the field, there is also a crucial need for data that accurately reflects the realities faced by young people in Brazil. Such data is indispensable for guiding critical clinical decisions. For instance, it involves determining which digital platforms are most popular among the youth, identifying the most effective technological tools for continuous engagement and monitoring of depressive symptoms in this demographic, and understanding how to effectively analyze and interpret digital data to provide insights pertinent to youth depression. This master's thesis addresses these needs by presenting data from two empirical studies designed to explore these questions in a focused and impactful manner.

OBJECTIVES

General objective

This study aims to characterize social media usage patterns among adolescents and investigate the temporal manifestation of depressive symptoms in Brazilian youth by leveraging commonly utilized online platforms for intensive data collection and employing advanced statistical methods to analyze depression at both dimensional and symptom-specific levels.

Specific objectives

a. Describe the prevalence of self-reported use of social media and the perceived effect of social media use in a school-based sample of adolescents from Brazil – Article #1.

b. Compare intensive-longitudinal and retrospective structures of depressive symptoms within a group of Brazilian youth, focusing on understanding how symptoms relate to each other and how these relations differ between the two assessment methods – Article #2.

HYPOTHESES

1. Most youth use one or more social media platforms at least once a day.
2. Depressive symptoms, when assessed retrospectively, are more intensely reported compared to intensive-longitudinal reporting.
3. The dimensions of depression identified from retrospective reporting differ from those found in intensive-longitudinal reporting.

ETHICAL CONSIDERATIONS

The two studies were approved prior to data collection and analysis by the National Ethics Committee on Research. Study #1 was approved under 50473015.9.0000.5327 – GPPG 2016-0131, and study #2 under CAAE 17574719.0.0000.5327 – GPPG 2019-0464, including a sample from public schools in Porto Alegre, collected between 2016 and 2019. All participants from the study #1 provided dissent terms in case of disagreement with participation. The data were de-identified, and only the raw data essential for the analyses were shared with the co-authors.

All analyses in this thesis were conducted using the free software R, version R version 4.3.1 (R Core Team, n.d.), primarily using the packages tidyverse (Wickham et al., 2019), mice (Buuren & Groothuis-Oudshoorn, 2011), EGAnet (Golino & Christensen, 2023), qgraph (Epskamp et al., 2012), bootnet (Epskamp et al., 2018). All analyses were conducted and are the responsibility of the dissertation author candidate.

FIRST STUDY, PUBLISHED IN THE TRENDS IN PSYCHIATRY AND PSYCHOTERAPY

Self-reported social media use by adolescents in Brazil: a school-based survey

Running title: Self-reported social media use by adolescents - Pereira et al.

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Abstract

Objective: Although there is a general perception that adolescent social media use is a global phenomenon, there is a scarcity of data on patterns and preferences of social media use among youth in low- and middle-income countries (LMICs). We here describe self-reported prevalence and perceived effects of social media use in a school-based sample of Brazilian adolescents.

Methods: We analyzed cross-sectional data on 7,113 adolescents aged 14 to 16 years enrolled at 101 public state schools between 2018 and 2019 in Porto Alegre, state of Rio Grande do Sul, Brazil.

Results: Of the 7,113 adolescents with complete data for analyses, 54.9% were female, and 60.6% reported their skin color as white. At least one social media platform was used by 97.7% of adolescents every day, and 64.7% reported being online “almost constantly.” YouTube and WhatsApp were the most popular platforms. Most participants perceived the effect on their lives of social media use as neutral.

Conclusion: The pattern of social media use by adolescents in Porto Alegre, Brazil, is similar to that reported for samples from high income countries. Also, we found that those who reported being constantly online were also more likely to report socializing with their friends offline.

Keywords: Adolescent, social media, internet use, prevalence.

Introduction

The current generation of teenagers and young adults is the first to be raised in highly digitized societies with access to an increasing number of activities on digital devices[1]. In this scenario, social media has become an important means of communication, entertainment, and leisure for this age group. Nonetheless, there is an ongoing debate about social media's positive or negative impacts on adolescents' lives[2-7].

Although there is a general perception that adolescent social media use is a global phenomenon, remarkably little is known about how adolescents in low and middle-income countries (LMICs) interact with social media platforms[8], which could be essential for researchers and practitioners to engage with this population and potentially create effective digital interventions. Therefore, our main objective is to describe the prevalence of self-reported use of social media and the perceived effect of social media use in a school-based sample of adolescents from Brazil, an upper-middle-income country.

Methods

Students aged 14 to 16 years, enrolled in 101 state public schools in Porto Alegre, state of Rio Grande do Sul, Brazil, were invited to participate in the study. Schools were chosen by convenience, and the questionnaires were administered by two to four researchers in a separate room designated by the school. Adolescents only took part in data collection if their parents/guardians did not disagree with their participation after reading a parent information form (PIF). Further, only adolescents who agreed to participate on the day of administration were included, after providing written informed assent prior to starting the survey. Details on the ascertainment process and data collection procedures are described elsewhere[9]. Participants answered an eight-item questionnaire regarding frequency of social media use – including Facebook, Instagram, Text/SMS, Twitter, WhatsApp, YouTube, Facebook Messenger, and other social media platforms. Following previous population-based surveys on a similar topic[10], the response options were "never," "once a week or less," "several times a week," "once a day," "several times a day," and "almost constantly." Participants

subsequently reported their perception of the effect of social media on their lives (“mostly positive,” “neither positive nor negative,” or “mostly negative”), and answered a separate yes/no question on whether they usually meet friends in person to play, chat, or do other things.

Frequency distributions were obtained. Categorical and numerical variables were compared using the chi-square and Mann-Whitney tests, respectively. All analyses were performed in R, version 3.6.1.

Ethical considerations

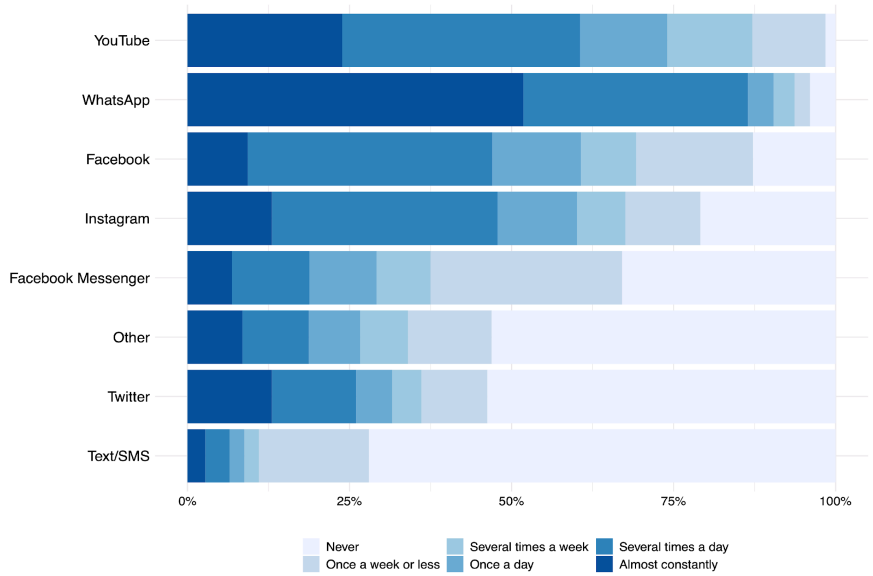
Approval for this study was obtained from the Secretaria de Educação do Rio Grande do Sul and from the ethics committee at Hospital de Clínicas de Porto Alegre (HCPA).

Results

Between July 2018 and December 2019, we assessed 7,720 adolescents, corresponding to about 70% of all students enrolled in the grades eligible for our study at state schools in Porto Alegre at the time of data collection[11]. Of the 7,113 adolescents with complete data for analyses, 54.9% were female and 60.6% reported their skin color as white. In terms of frequency of social media use, 97.7% of adolescents reported using at least one social media platform every day, and 64.7% reported being online “almost constantly,” with more girls reporting being constantly connected than boys (68.6 vs. 59.8%, respectively; $\chi^2(5) = 62.1$, $p < 0.001$).

Regarding choice of platform, 90.4% of the sample reported using WhatsApp at least once a day, followed by YouTube (74%), Facebook (60.7%), and Instagram (60.1%). Although over 86.5% of participants reported using WhatsApp “several times a day” or “almost constantly,” YouTube was the most cited platform, with 98.4% reporting some use across frequency categories. The least used platforms were Twitter and Text/SMS, with 53.8 and 72% of the sample respectively reporting they “never” use them (Figure 1A).

A)


YouTube
WhatsApp
Facebook
Instagram
Facebook Messenger
Other
Twitter
Text/SMS
0%
25%
50%
75%
100%
Never
Once a week or less
Several times a week
Once a day
Several times a day
Almost constantly

B)

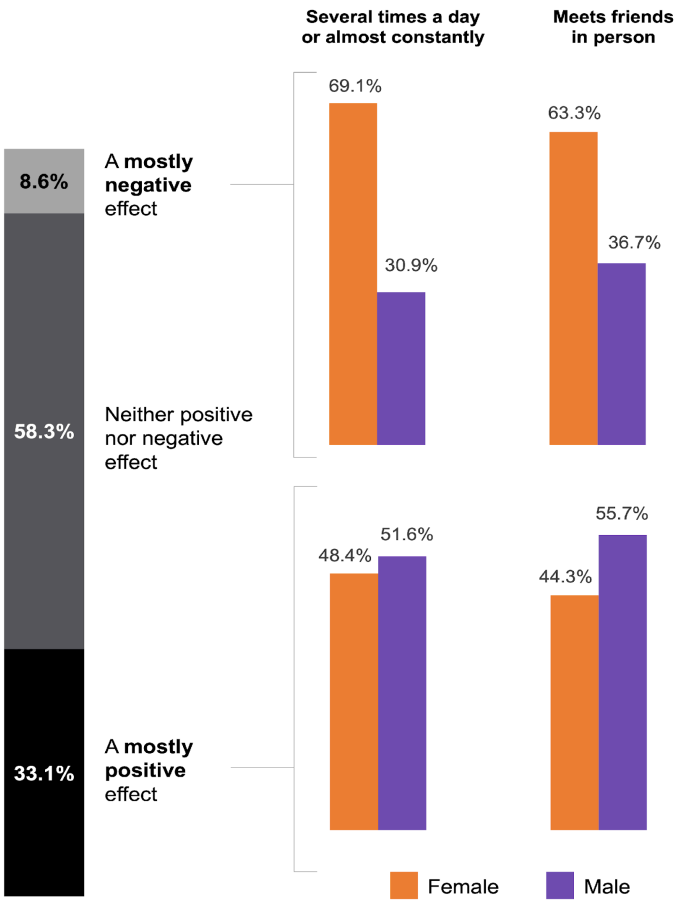

Several times a day or almost constantly
Meets friends in person
8.6%
A mostly negative effect
58.3%
Neither positive nor negative effect
33.1%
A mostly positive effect
69.1%
30.9%
63.3%
36.7%
48.4%
51.6%
44.3%
55.7%
Female
Male

Figure 1. A) Frequency of social media use by platform (n = 7,113). Percentage of social media use by platform across frequency categories. B) Perceived effect of social media use by sex (n = 7,113). “Several times a day or almost constantly” indicates the percentage of participants who reported using social media “several times a day” or “almost constantly” on any of the platforms available in the questionnaire.

When asked about the perceived effect of social media on their lives, most adolescents (58.3%) considered the impact as neutral (Figure 1B). Among those who perceived a mostly negative effect (8.6%), girls more often (10.7%) reported feeling negatively impacted by social media than boys (5.9%) ($\chi^2[2]=102.8$; $p < 0.001$). Additionally, about 75% of the sample reported usually meeting friends in person, and the frequency of social media use was associated with a higher prevalence of meeting friends in person ($U = 375,483$; $p < 0.001$).

Discussion

Our study identified that the majority of 14-16-year-old adolescents from state schools in the city of Porto Alegre, Brazil, used at least one social media platform every day and that although most of them perceived the effect of social media use on their lives as neutral, one out of nine girls and one out of 17 boys saw it as negative. These findings are in accordance with previous studies showing high use of social media by adolescents worldwide[12]. The finding of more frequent perceived negative impact of social media in girls than boys might be explained by sex differences in terms of type of online content accessed[13]. Given the increasing evidence of negative impacts of social media on mental health on some girls in high income countries, such as anxiety, depressive symptoms, and sleep disturbances[14,15], our findings suggest that similar detrimental effects may be present in middle-income countries.

Moreover, despite the considerable prevalence of social media use, three out of four adolescents in our sample reported usually meeting friends in person to chat, play games, or

do other things. Interestingly, we found that, on average, those who reported being constantly online were also more likely to report socializing with their friends offline. This is in accordance with earlier observations showing that highly connected young people are just as likely as their less-connected peers to regularly interact with friends in person[10].

These results are not without limitations. For instance, our findings are limited by the self-reported nature of the measures of social media use and the study's cross-sectional design. Moreover, although this is a large sample, it does not represent all the contexts within the country, which could be explored in future studies, both in Brazil as well as in other LMICs. Also, more recent platforms were not included in the questionnaire (e.g., Snapchat, TikTok). In spite of these limitations, however, our study adds to understanding of social media use by adolescents in an urban area from a middle-income country. Learning which platforms are mostly used by this age group can help us devise effective ways of interacting with them. For example, as the most popular social media platform in this study, WhatsApp might be a useful tool for researchers, clinicians, and policy makers to engage with adolescents, which is an aspect to be explored in future research.

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SECOND STUDY, IN SUBMISSION

CONCLUSION

This thesis, entitled "Exploring Symptom-Level Temporal Dynamics of Depression and Discrepancies between Retrospective and Momentary Assessments of Depression during Adolescence," marks a progression in our understanding of depressive symptomatology in young populations. Conducted through two comprehensive empirical studies, it utilizes digital technologies to examine how depression manifests among Brazilian youth. This research not only sheds light on the temporal dynamics of depressive symptoms but also highlights critical differences in how these symptoms are perceived retrospectively versus in real-time assessments. The findings provide important insights into the methodologies for assessing depressive symptoms, offering a deeper view of depression in this demographic.

Key Findings and Implications

The first study offers a thorough analysis of social media usage among Brazilian adolescents, revealing that messaging platforms like WhatsApp are almost universally integrated into their daily interactions. This prevalent digital engagement is especially significant, as it not only provides a context for understanding their social environments but also serves as a potential channel for mental health interventions. The strong presence of such platforms highlights a significant opportunity to integrate mental health support directly into these digital channels, thereby providing immediate and accessible care.

As a result of the study, more information was gathered on the digital behaviors of young people, supporting our hypothesis that this population uses at least one social media platform a day. This is particularly evident in the widespread use of WhatsApp, a platform that requires active interaction and was utilized many times per day by the majority of adolescents in the study. These findings not only corroborate our initial hypothesis but also highlight the importance of such platforms as potential channels for mental health interventions.

The second study uses the data from the IDEABot, an innovative tool developed by our research group, to collect real-time data on adolescents' mood variations via WhatsApp (Viduani et al., 2023). This method enabled a novel examination of momentary changes in depressive symptoms, offering an alternative to traditional retrospective assessment methods. Our findings from this dynamic data collection showed that depressive symptoms are not static; instead, they fluctuate over time.

As anticipated, our findings indicate that depressive symptoms, when assessed retrospectively, are reported more intensely compared to those reported in intensive-longitudinal assessments. This discrepancy underscores the potential biases inherent in retrospective assessments, where individuals are more likely to remember periods of significant distress rather than the nuances of their daily mood fluctuations. In contrast, the dynamic data from intensive-longitudinal assessments offer a different perspective, capturing the flow of symptoms in real-time. This approach reveals that individuals tend to report less severe symptoms when they assess their condition prospectively, suggesting that intensive-longitudinal assessments may provide a more subtle reflection of their everyday emotional experiences.

The contrast in symptom structure between retrospective and intensive-longitudinal reports also suggests that different dimensions of depression may be observed depending on the assessment method used. For instance, cognitive symptoms, such as feelings of worthlessness or excessive guilt, were more connected in retrospective assessments, potentially due to the persistent impact of negative cognitive biases that amplify such symptoms when reflecting on past feelings. Intensive longitudinal assessments, by contrast, captured the more intense interconnectedness between somatic and affective symptoms, indicating that these might be more reflective of the youth's immediate emotional states rather than their interpretative memory of those states.

The variations in symptom structure between retrospective and intensive-longitudinal assessment methods offer important insights for refining psychiatric practice, especially in diagnosing and treating depression. Retrospective assessments are relatively straightforward and cost-effective, making them accessible for widespread use. They can be particularly useful in identifying persistent cognitive patterns and long-term trends in emotional experiences. However, it is crucial for clinicians to be aware of potential biases in these assessments, as patients may inadvertently emphasize or understate certain symptoms based on negative cognitive biases when reflecting on past feelings (Myin-Germeys et al., 2018).

Alternatively, intensive-longitudinal assessments provide real-time insights into the immediate interplay between somatic and affective symptoms, offering a snapshot of the patient's emotional state that may be more reflective of current symptomatology. This immediacy can capture fluctuations in mood and symptom intensity that retrospective assessments might miss. Nevertheless, the reliability and practicality of intensive-longitudinal data are still under exploration, and it remains critical to understand how best to interpret and utilize these findings effectively in clinical settings.

Both methods contribute valuable perspectives to the understanding of depressive symptoms. Therefore, an integrative approach that leverages the strengths of both retrospective and intensive-longitudinal assessments could enhance diagnostic accuracy and treatment efficacy. However, clinicians must carefully consider the context and objectives of each assessment method to minimize biases and maximize the utility of the collected data.

Strengths, Limitations, and Future Directions

This dissertation constitutes a pioneering effort in the field of youth mental health research by examining the distinctions between retrospective and prospective reports of depressive symptoms. This comparative analysis significantly enhances our understanding of the

manifestation and fluctuation of depression over time, making an important contribution to the field.

By utilizing insights from the initial study on the most commonly used social media platforms among adolescents in Porto Alegre, we developed the IDEABot (Viduani et al., 2023), a WhatsApp chatbot designed for intensive longitudinal data collection on depressive symptoms. This tool was employed in the second study to better understand fluctuations in adolescents' self-reported depressive symptoms and the discrepancies between these momentary assessments and retrospective reports. This approach exemplifies a coherent and systematic method of building knowledge incrementally, aligning with the scientific method. It underscores the effort to enhance our understanding of depression, which is a significant strength of this dissertation. In the second study of this dissertation, by utilizing mobile technology, the study captures real-time data on the lived experiences of young individuals, thereby offering valuable insights into the temporal dynamics of depressive symptoms. This methodological approach not only provides a detailed snapshot of youth depression but also allows for a deeper comprehension of symptom evolution, filling a critical gap in existing literature.

Despite the strengths of the findings presented in this dissertation, they are primarily applicable to a specific demographic, limiting the broader generalizability of the results. To address this limitation, future studies should aim to replicate this research within diverse cultural and socioeconomic contexts. Expanding the research to different settings would help verify whether the patterns identified in this study are consistent across various environments and age groups thus broadening the applicability of the conclusions drawn.

Additionally, the use of digital tools for data collection, while innovative, poses several practical challenges. Issues such as digital literacy, access to technology, and maintaining participant engagement with tools like IDEABot require careful consideration. Moreover, there is no single established method for conducting intensive longitudinal assessments in the

existing literature. For instance, we lack knowledge about how applying different approaches using IDEABot, such as varying the frequency of symptom inquiries, might affect the outcomes. Therefore, future research should concentrate on developing user-friendly, accessible technological interventions that seamlessly integrate into adolescents' daily routines, but also that comply with previous literature suggestions. Moreover, these tools must ensure privacy, prevent user fatigue, and maintain both the effectiveness and ethical integrity of the research. Such efforts will aid in refining methodologies and enhancing our understanding of youth mental health.

Looking forward, it is essential to explore the longitudinal trajectories of depressive symptoms in youth through similar technological assessments. Understanding these long-term patterns and the potential chronic nature of depression can provide critical insights for developing preventive strategies aimed at mitigating the risk before the onset of more severe psychiatric conditions. Furthermore, the rapid advancements in technology offer new possibilities for more sophisticated data analysis through machine learning and artificial intelligence. Future studies could employ these technologies not only to monitor but also to proactively respond to early signs of depression. Predictive analytics could enable the forecasting of depressive episodes, potentially contributing to the prevention and management of depression among young populations.

Concluding Thoughts

In conclusion, this thesis represents a contribution to the field of adolescent psychiatry by showcasing how digital technologies can advance our understanding and assessment of depression. The use of intensive-longitudinal assessment tools like IDEABot provides a dynamic and nuanced view of depression in youth, moving beyond the snapshot captured by traditional assessments. With this method, it was found that retrospective self-reports differ from what intensive-longitudinal self-reports show, highlighting the importance for clinicians and researchers to take these differences into consideration when selecting a method for

better assessing depression among youth. This work lays the groundwork for future innovations in mental health diagnostics and interventions, emphasizing the importance of temporal dynamics and the potential for digital platforms to enhance our response to youth depression.

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APPENDICES

In the following pages, we present studies published during the Master's of the candidate or that are closely related to the works that compose the dissertation but were not led by the candidate.

APPENDICE #1: The Identifying Depression Early in Adolescence Risk Stratified Cohort (IDEA-RiSCo): Rationale, Methods, and Baseline Characteristics.

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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 ≤ 6 were considered for further assessment for the LR/HR groups, and those with a PHQ-A ≥ 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.

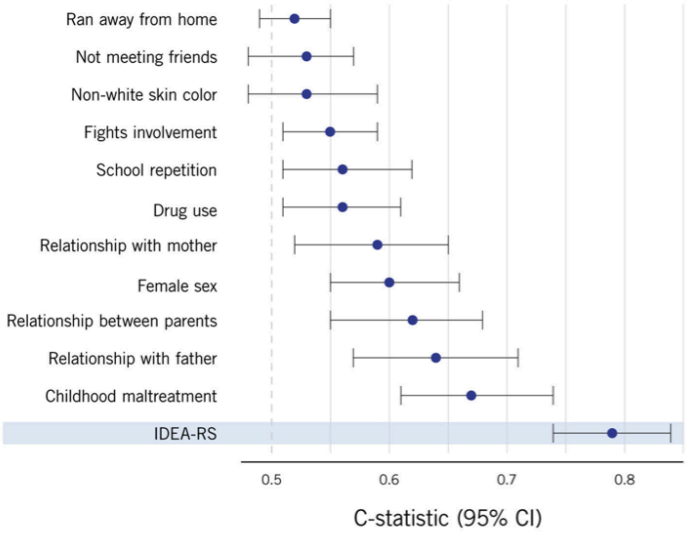

FIGURE 1 | Discriminative ability of each individual Identifying Depression Early in Adolescence Risk Score (IDEA-RS) variable, as well as the combined statistic for the IDEA-RS in the last line. Generated using data from the Pelotas 1993 Birth Cohort (13).

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

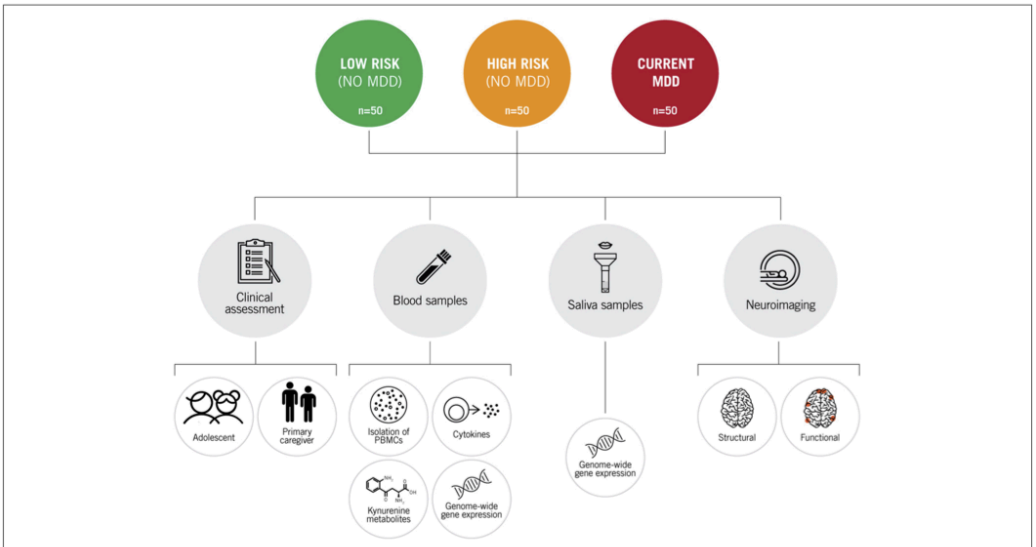

FIGURE 2 | Simplified graphic representation of the assessments and analyses performed in the IDEA-RiSCo cohort, including blood and saliva analyses such as isolation of peripheral blood mononuclear cells (PBMCs) and determination of cytokines and kynurenine metabolites and genome-wide gene expression. 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

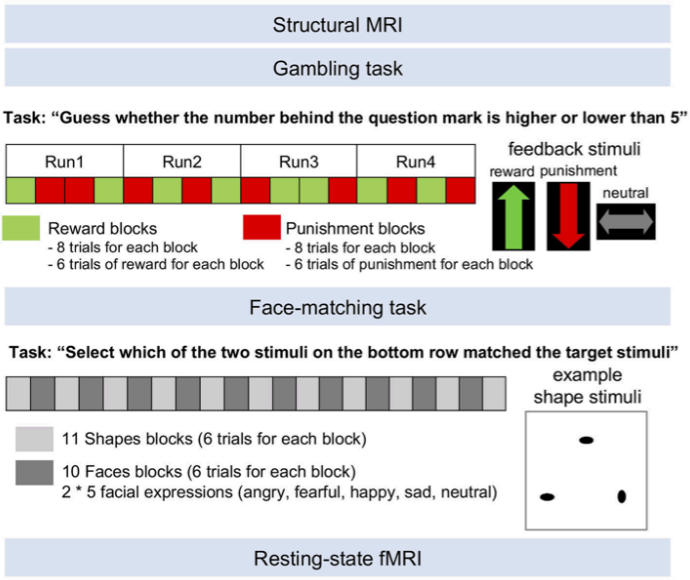

FIGURE 3 | MRI data acquisition procedure. After structural images were acquired, functional images were acquired during a gambling task, face-matching task, and resting-state. The gambling task consisted of counterbalanced presentation of reward and punishment blocks. The face-matching task consisted 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

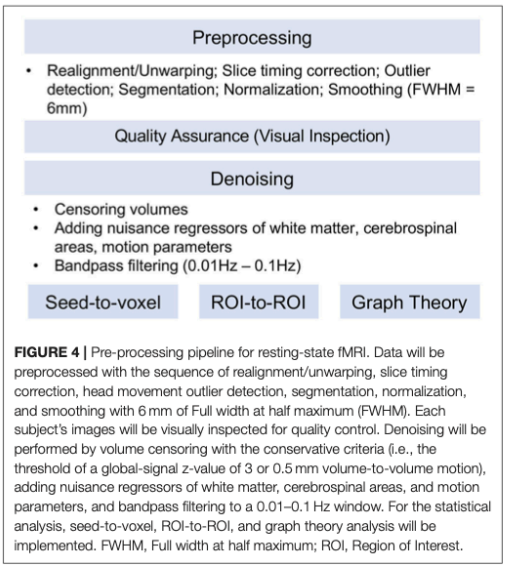

FIGURE 4 | Pre-processing pipeline for resting-state fMRI. Data will be preprocessed with the sequence of realignment/unwarping, slice timing correction, head movement outlier detection, segmentation, normalization, and smoothing with 6 mm of Full width at half maximum (FWHM). Each subject's images will 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,

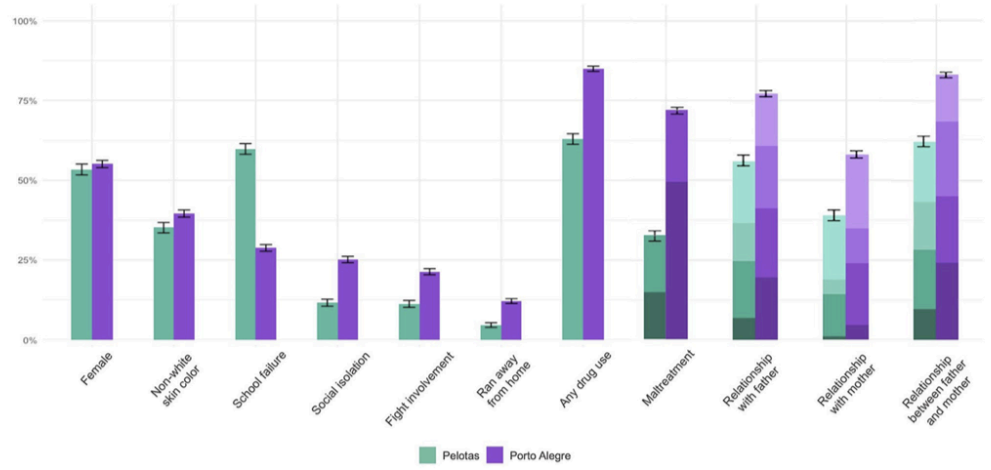

FIGURE 5 | Prevalence of risk variables in Pelotas (2008) vs. Porto Alegre (2018–9). Proportions do not reach 100% because the figure only shows responses that indicate risk for the variables (i.e., non-involvement in fights or non-use of drugs are not shown). 95% confidence intervals are shown in dichotomous 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

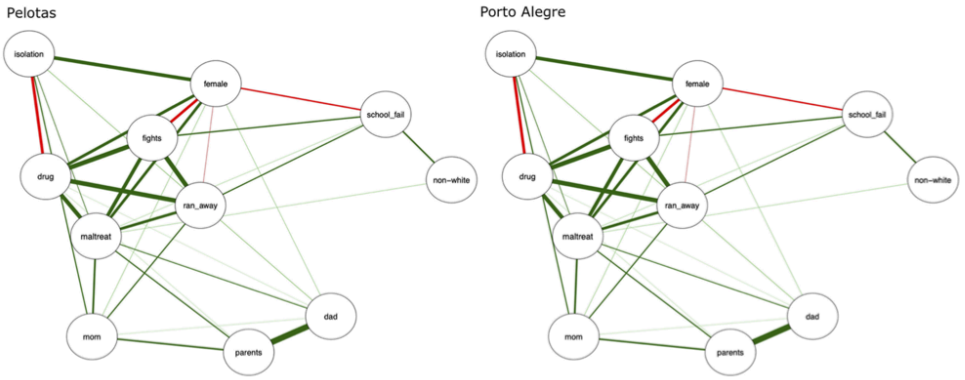

FIGURE 6 | Network analysis of variables that are part of the IDEA-RS by cohort. Structure of Pelotas and Porto Alegre Identifying Depression Early in Adolescence risk score (IDEA-RS) networks with 11 nodes, each representing one of the risk score's variables. The green linkage lines between variables 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.

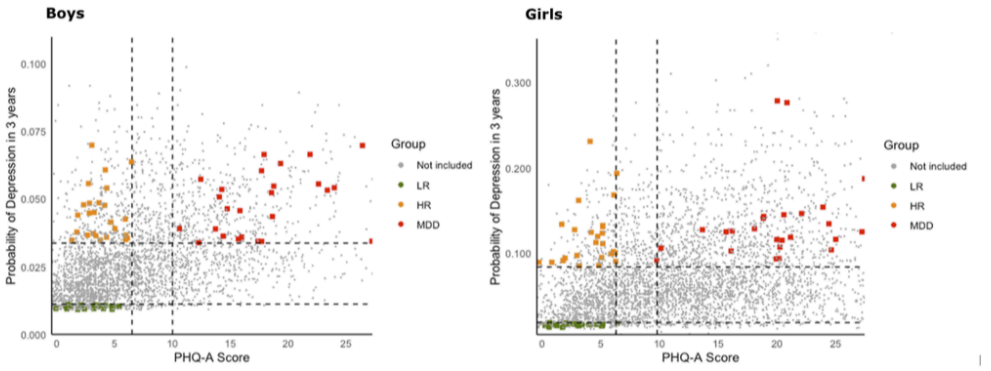

FIGURE 7 | Adolescents screened at schools and included in the Identifying Depression Early in Adolescence Risk Stratified Cohort (IDEA-RiSCo). Vertical dotted lines show the Patient Health Questionnaire—adolescent version (PHQ-A) cutoffs, and horizontal dotted lines show the Identifying Depression Early 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

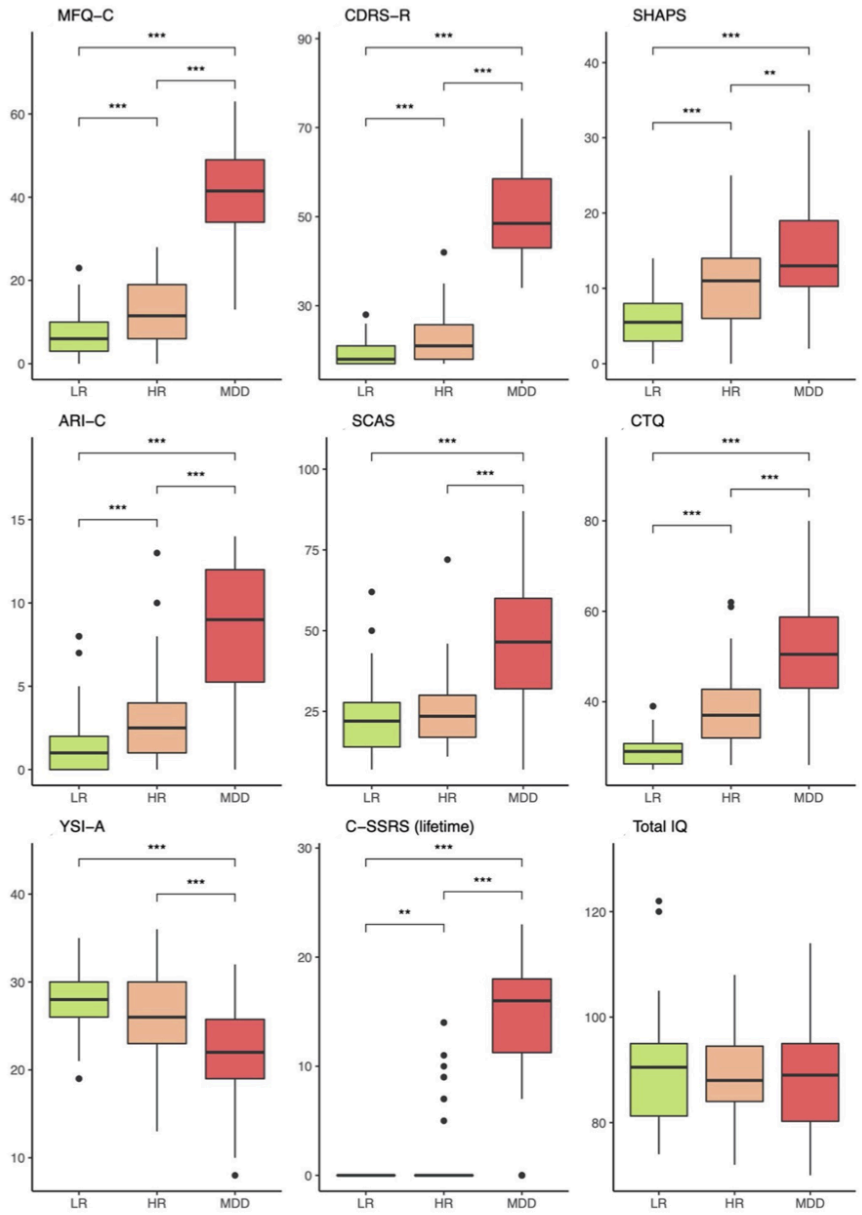

FIGURE 8 | Phenotypic comparisons between groups based on reports by the adolescents. LR, low-risk; HR, high-risk; MDD, major depressive disorder; MFQ-C, Mood and Feelings Questionnaire—Child; CDRS-R, Children's Depression Rating Scale Revised; SHAPS, Snaith-Hamilton Pleasure Scale; ARI-C, Affective 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. $^{**}p < 0.01$, $^{***}p < 0.001$.

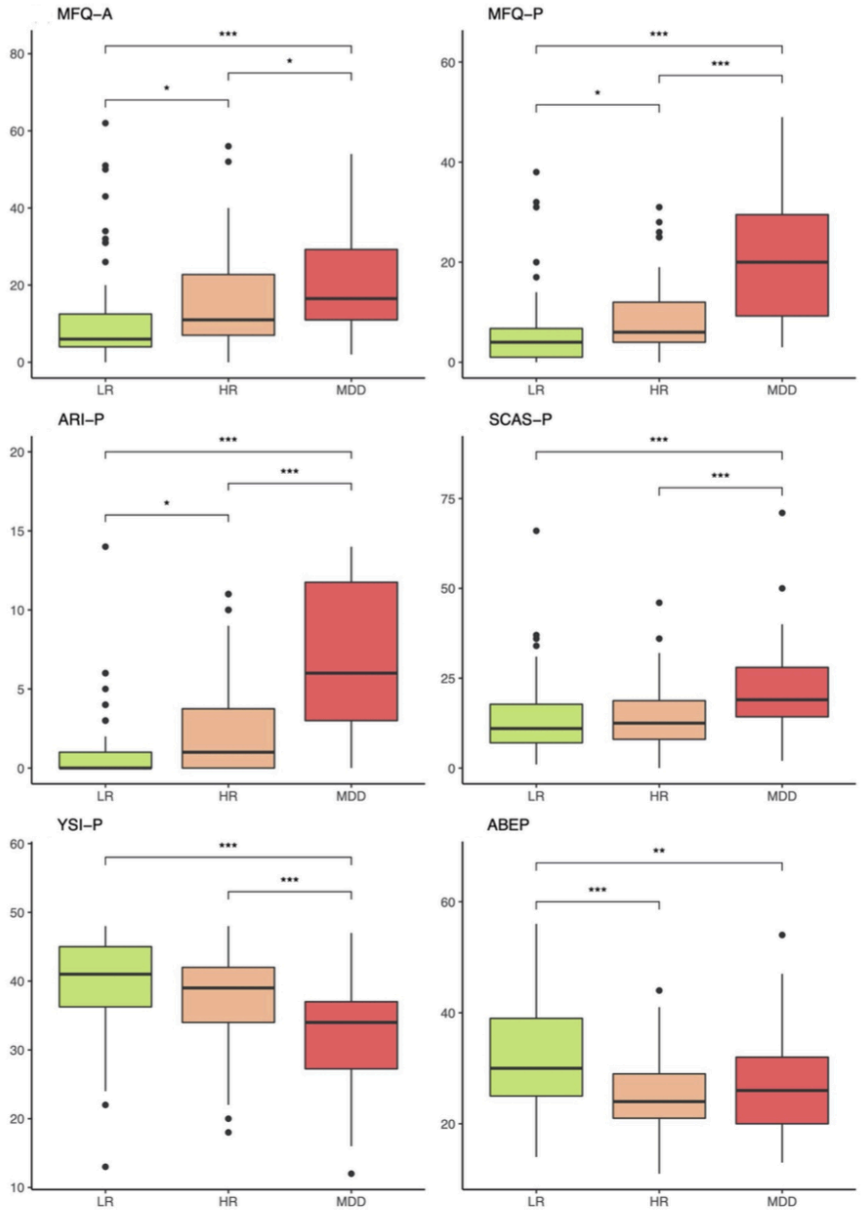

FIGURE 9 | Phenotypic comparisons between groups based on reports by the caregivers. LR, low-risk; HR, high-risk; MDD, major depressive disorder; MFQ-A, Mood and Feelings Questionnaire—Adult (caregiver self-report); MFQ-P, Mood and Feelings Questionnaire—Parent (caregiver report on adolescent); ARI-P, 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 ($\geq$90th percentile), in comparison to one classified as LR ($\leq$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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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2021.697144/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

APPENDICE #2: Prospective Follow-Up of Adolescents With and at Risk for Depression: Protocol and Methods of the Identifying Depression Early in Adolescence Risk Stratified Cohort (IDEA-RiSCo) Longitudinal Assessments.

STUDY PROTOCOL AND METHODS ADVANCEMENT

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Prospective Follow-Up of Adolescents With and at Risk for Depression: Protocol and Methods of the Identifying Depression Early in Adolescence Risk Stratified Cohort Longitudinal Assessments

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Objective: To present the protocol and methods for the prospective longitudinal assessments—including clinical and digital phenotyping approaches—of the Identifying Depression Early in Adolescence Risk Stratified Cohort (IDEA-RiSCo) study, which comprises Brazilian adolescents stratified at baseline by risk of developing depression or presence of depression.

Method: Of 7,720 screened adolescents aged 14 to 16 years, we recruited 150 participants (75 boys, 75 girls) based on a composite risk score: 50 with low risk for developing depression (LR), 50 with high risk for developing depression (HR), and 50 with an active untreated major depressive episode (MDD). Three annual follow-up assessments were conducted, involving clinical measures (parent- and adolescent-reported questionnaires and psychiatrist assessments), active and passive data sensing via smartphones, and neurobiological measures (neuroimaging and biological material samples). Retention rates were 96% (Wave 1), 94% (Wave 2), and 88% (Wave 3), with no significant differences by sex or group ($p > .05$). Participants highlighted their familiarity with the research team and assessment process as a motivator for sustained engagement.

Discussion: This protocol relied on novel aspects, such as the use of a WhatsApp bot, which is particularly pertinent for low- to-middle-income countries, and the collection of information from diverse sources in a longitudinal design, encompassing clinical data, self-reports, parental reports, Global Positioning System (GPS) data, and ecological momentary assessments. The study engaged adolescents over an extensive period and demonstrated the feasibility of conducting a prospective follow-up study with a risk-enriched cohort of adolescents in a middle-income country, integrating mobile technology with traditional methodologies to enhance longitudinal data collection.

Plain language summary: This article details the study protocol and methods used in the longitudinal assessment of 150 Brazilian teenagers with depression and at risk for depression as part of the Identifying Depression Early in Adolescence Risk Stratified Cohort (IDEA-RiSCo). Over 3 years, the authors collected clinical and digital data using innovative mobile technology, including a WhatsApp bot. Most adolescents participated in all the study phases, showing feasibility of prospective follow-up in a middle-income country. This approach allowed for a deeper understanding of depression in young populations, particularly in areas where mental health research is scarce.

Key words: depression; adolescence; risk score; cohort; digital phenotyping

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Depressive disorders constitute a leading cause of disability among youth across the globe.[1] To effectively reduce the burden associated with depression throughout the lifespan, efforts beyond treatment are needed, with prevention initiatives representing a compelling strategy, especially when targeting younger individuals.[2] However, our ability to design and to implement targeted preventive measures has been hindered by the difficulties of identifying increased risk for depression in youth. Moreover, there is still limited knowledge in terms of how the disorder develops in adolescence, and of the aspects that distinguish individuals who are at the highest or lowest

risk for depression.[3] In that sense, previous research suggests that using predictive models with multivariate scores to stratify individual-level risk constitutes a key strategy.[4,5] Although an increasing number of models to predict individualized risk of mental health outcomes is available, most prognostic studies use databases *post hoc* that were not specifically designed to test the models.[5,6] In addition, there are few prospectively designed studies using risk stratification as inclusion criteria to address trajectories of different risk groups for depression.

Two important characteristics of depression—an (often) episodic nature, with remittance and recurrence of depressive episodes across the life course,[7,8] and a heterogeneous presentation,[9] with individual variations in terms of which and how different signs and symptoms manifest—make the longitudinal approach an essential aspect for consideration by researchers in the field. Furthermore, depressive disorders frequently emerge in adolescence, in a period of intense psychosocial change[10] and neurobiological maturation,[11] with important differences in relation to adult depression, particularly in terms of clinical trajectories, treatment response, and outcomes across the life course.[12,13]

To expand the understanding regarding the phenotypic and neurobiological profiles associated with increased risk or presence of depression in adolescence, we have previously performed the Identifying Depression Early in Adolescence Risk Stratified Cohort (IDEA-RiSCo) study, an in depth study 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.[14] In that initial work, 7,720 adolescents aged 14 to 16 years were screened in 101 public schools in Porto Alegre, Brazil, using an empirically developed sociodemographic composite risk score.[14] From this sample, 150 adolescents were recruited who were also clinically assessed for current and lifetime depressive disorders.[14] Participants were stratified into 3 groups: 50 with low risk for developing depression (LR), 50 with high risk for developing depression (HR), and 50 with an active untreated major depressive episode (MDD). Detailed clinical characteristics of the IDEA-RiSCo sample (IDEA-RiSCo cohort) at baseline have been described elsewhere.[14]

Risk stratification was operationalized using the Identifying Depression Early in Adolescence Risk Score (IDEA-RS).[15] The IDEA-RS is a multivariable model developed by our group to estimate individual risk in early adolescence of developing depression at age 18 years. It was designed to be easily obtained directly from the adolescent in a brief assessment comprising 11 sociodemographic predictor variables: biological sex, skin color, drug use, school failure, social isolation, fight involvement, poor relationship with father, mother, and between parents, childhood maltreatment, and having run away from home. IDEA-RS exhibited a good discriminative performance to stratify adolescents at age 15 years in terms of individual risk for developing depression at age 18 years, as measured by a C-statistic of 0.78 (95% CI: 0.73-0.82) in the development sample.[15] IDEA-RS was subsequently evaluated across several sociocultural and economic contexts including the United Kingdom, Nigeria, New Zealand, Nepal, and North America, reaching beyond chance discriminative ability in all settings (C-statistics between 0.59 and 0.73).[15–18]

Following confirmation of this informative discriminative performance to estimate the individualized risk for depression across 5 continents, a prospective analysis of the performance of the IDEA-RS to assess the development of depression was planned for the IDEA-RiSCo cohort, a phenotypically refined sample, stratified by risk of developing depression.[14] Prospective, longitudinal assessments of the IDEA-RiSCo sample may provide insights into the trajectories of different risk groups during a crucial developmental period; evaluating the progression of adolescents in the LR and HR groups is likely to provide essential information to clarify the differences between individuals who do and do not convert to depression.

Furthermore, although 90% of the world's adolescents live in low- and middle-income countries (LMICs), most research on adolescent depression is still conducted in high-income countries (HICs), leaving a significant gap in knowledge.[19] In that sense, longitudinal studies represent important resources to capture the overall trajectories of adolescents stratified by risk of developing depression in LMICs, providing a means for generalizations, group comparisons and the monitoring of changes within a macro developmental dimension.[20] Also, most existing longitudinal datasets encompassing mood disorders in adolescence seem unable to capture granular changes or fluctuations in symptom patterns that occur over short periods of time as individuals go about their lives. Thus, leveraging the capacity of digital devices, such as smartphones and wearables, to gather repeated information in a person's natural environment while minimizing recall bias may constitute an important avenue of inquiry. The analysis of active and passive data from behavioral information obtained from mobile devices allows an ecologically valid identification of context-based digital phenotypes,[21] and novel statistical methods are capable of accounting for both individual-level differences and the behavior of a group over time.[22,23] At a global level, 1 in 3 Internet users is under 18 years of age, and smartphones are the most

popular devices used to go online.[24] This, combined with the advances in technology and integration of better, more accurate sensors in mobile phones, provides an unparalleled potential for conducting research in real-world settings in a more practical, accessible, and acceptable way. Moreover, using smartphones to collect data may also address gaps between HICs and LMICs: it enables cost-effective data collection that has the potential to improve early identification of mental health conditions.[25] Hence, to shed light on the characteristics and course of the risk and presence of depression throughout adolescence, a combination of traditional phenotypic assessment with digital phenotyping seems especially useful.[26]

Considering these aspects, we here present a detailed account of the protocol and methods designed for prospective mood assessment across time among Brazilian adolescents included in the IDEA-RiSCo cohort. In addition to the traditional phenotypic assessment focusing on clinical evaluations, the follow-up assessments also leveraged the use of innovative mobile technologies to collect intensive longitudinal information in a digital phenotyping approach.[26] Procedures for clinical and phenotypic assessments are described for 4 waves of data collection, as well as for peripheral biological sampling and neuroimaging assessments. We also present initial results in terms of feasibility and retention rates for each procedure and collection point.

METHOD

Ethics Approval

This study was approved by the Research Ethics Committee of Hospital de Clínicas de Porto Alegre and by the Brazilian National Ethics in Research Commission (CAAEs 17574719.0.0000.5327, 41801121.0.0000.5327, and 50473015.9.0000.5327). Supplemental approval was granted by the Institutional Review Board of University of California at Davis (1218177-4) and the Psychiatry, Nursing and Midwifery Research Ethics Subcommittee of King's College London (LRS-17/18-8327).

All adolescents and caregivers provided written consent in the baseline assessment and in each wave of follow-up. For adolescents under the age of 18 years, legal guardians were required to provide formal consent. If the participant reached age 18, collateral information from a parent (or another relevant adult) was collected only with the consent of the participant. In situations in which participants' scores and/or responses indicated risk, they were referred to emergency services or specialized care according to Brazilian legislation. Participants received no financial incentive for taking part in the study but were compensated for expenses related to their participation (eg, transportation to data collection site, mobile data use). Also, smartphones were lent to participants who did not own a smartphone during the study period.

Study Design and Participants

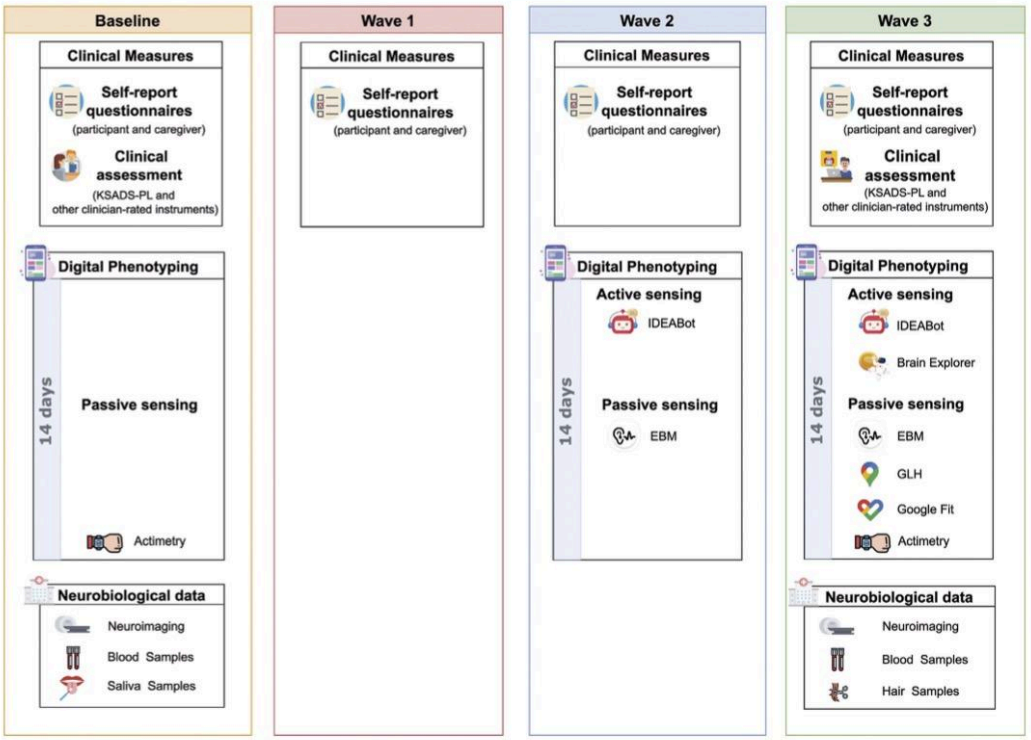
The IDEA-RiSCo sample included 150 adolescents (75 boys, 75 girls) aged 14 to 16 years (mean = 15.6 [SD = 0.82]) at baseline (Wave 0-W0). Clinical data were collected at 3 additional waves during the follow-up period lasting 3 years, to mimic the original age interval used in the development of the IDEA-RS. Recruitment for Wave 1 (W1), Wave 2 (W2), and Wave 3 (W3) occurred 12 months, 24 months, and 32 months after baseline (W0), respectively. At the last follow-up, participants were aged 17 to 19 years (mean = 18.0 [SD = 0.80])

IDEA-RiSCo participants were stratified for risk using the IDEA-RS to estimate the probability of developing depression in 3 years. Because the incidence of depression is higher in girls in comparison to boys, sex-specific IDEA-RS models were generated to avoid over-representation of female participants in the HR group and of male participants in the LR group. At baseline, participants were interviewed by a board-certified child and adolescent psychiatrist using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL)[27] and confirmed for inclusion into 1 of 3 groups: 50 low-risk participants with no current or lifetime history of depression who were at or below the 20th percentile on the IDEA-RS (LR); 50 high-risk participants with no current or lifetime history of depression who were at or above the 90th percentile on the IDEA-RS (HR); and 50 participants with current and untreated depression who were at or above the 90th percentile on the risk score (MDD). At the baseline assessment, further phenotypic, peripheral biological samples, and neuroimaging assessments were performed as described in Figure 1 and in Kieling *et al.* (2021).[14]

Follow-Up Waves and Data Collection Procedures

The 3 follow-up waves were designed for stepwise increase in the intensity of digital and mobile data collection, as described below. A timeline with details of each data collection mode across the 3 waves is presented in Figure 1. For W1 and W2, participants were recruited if they responded to the invitation within a 2-month window in relation to their expected collection date for each wave (11-13 months and 23-25 months after baseline for W1 and W2, respectively). This was done to ensure that all were followed-up at comparable intervals. Given that Wave 3 was the final data collection point, and to improve participant retention, a larger response

FIGURE 1 Timeline of Each Data Collection Mode Across the 3 Waves



Note: *EBM = electronic behavioral monitoring; GLH = Google Location History; IDEABot = The Identifying Depression Early in Adolescence Chatbot; K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime version.*

window of 6 months after the expected data collection date (30-36 months after baseline) was considered acceptable.

Wave 1 (W1). We aimed to reassess depressive symptomatology approximately 1 year after the baseline assessment. All participants and their caregivers were recruited to electronically complete self-report online questionnaires (Table 1). Participants were contacted by phone and/or text messages, and a Web link to the questionnaire was sent separately to adolescents and caregivers.

Wave 2 (W2). The aim of the second wave was to evaluate depressive symptomatology status and to collect remote data over a 14-day period. Participants and caregivers again completed self-report online questionnaires (Table 1). Moreover, a digital phenotyping component was added, including passive data sensing and active data collected via a chatbot. Passive data also included Global Positioning System (GPS), accelerometer/gyroscope and ambient audio data collected using a smartphone app, and the chatbot used for active collection of intensive longitudinal data on mood was operationalized via WhatsApp. Both passive and active data collection occurred simultaneously throughout the same 2-week period.

Wave 3 (W3). At the final wave, we aimed to perform a detailed phenotypic assessment and a new 14-day remote data collection period. Participants and caregivers were again invited to complete a set of online self-report questionnaires that consisted of measurements about depressive symptoms and other mental health domains (Table 1). Following completion of the online questionnaires, participants were invited to take part in a face-to-face assessment, including a blinded diagnostic

TABLE 1 Clinical Instruments Administered in Each Wave of the Identifying Depression Early in Adolescence Risk Stratified Cohort (IDEA-RiSCo) Study

	W0	W1	W2	W3
Adolescent self-report				
Mood and Feelings Questionnaire—Child (MFQ-C)	✓	✓	✓	✓
DSM-5 Self-rated Level 1 Cross-cutting Symptom Measure (CCSM-C)	✓	✓	✓	✓
Patient Health Questionnaire—Adolescent (PHQ-A)	✓	✓	✓	✓
Brazilian Criterion of Economic Classification (ABEP)	✓			✓
Coronavirus Health and Impact Survey (CRISIS)				✓
The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)				✓
Parental Bonding Instrument (PBI)	✓			✓
Childhood Trauma Questionnaire - Child (CTQ-C)	✓			✓
Snaith-Hamilton Pleasure Scale (SHAPS)	✓			✓
Affective Reactivity Index—Child (ARI-C)	✓			✓
Spence Children's Anxiety Scale—Child (SCAS-C)	✓			✓
Youth Strength Inventory—Adolescent Self-Report (YSI-A)	✓			✓
Adapted Resilience Scale (ARS)	✓			✓
Borderline Personality Features Scale for Children (BPFSC)				✓
The Munich ChronoType Questionnaire (MCTQ)	✓			✓
Puberty and Phase Preference Scale (PPPS)	✓			✓
Sleep Hygiene Index (SHI)	✓			✓
Athens Insomnia Scale (AIS)	✓			✓
Adolescent clinician-administered				
Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime version (K-SADS-PL)	✓			✓
Child Depression Rating Scale—Revised (CDRS-R)	✓			✓
Clinical Global Impression—Severity Scale (CGI-S)	✓			✓
Children's Global Assessment Scale (CGAS)	✓			✓
Columbia Suicide Severity Rating Scale (C-SSRS)	✓			✓
Insomnia Severity Index (ISI)	✓			✓
Caregiver-report				
Mood and Feelings Questionnaire—Parent (MFQ-P)	✓	✓	✓	✓
DSM-5 Self-rated Level 1 Cross-cutting Symptom Measure—Parent (CCSM-P)	✓	✓	✓	✓
Affective Reactivity Index—Parent (ARI-P)	✓			✓
Youth Strength Inventory—Parent (YSI-P)	✓			✓
Spence Children's Anxiety Scale—Parent (SCAS-P)	✓			✓
Mood and Feelings Questionnaire—Parent Self-report (MFQ-A)	✓			✓

interview, collection of peripheral biological samples, and neuroimaging acquisition. As in W2, participants also took part in a smartphone-based active and passive data sensing period, including assessments through the WhatsApp chatbot, as well as GPS, accelerometer/gyroscope, and ambient audio data collection, similarly to W2. In addition, cognitive data were collected from gamified tasks during the remote data collection period through the Brain Explorer application. Information on sleep and biological rhythms was also collected using self-reported and actimetry data.

Following the model proposed by Wisniewski *et al.* (2020),[28] the present protocol study included research team members who offered non-clinical support around the apps used by participants throughout the research protocol. They were able to troubleshoot simple technical app issues while guaranteeing personal, effective communication with participants. The assignment of a Digital Navigator (DN) for

each participant enabled close monitoring and quick response to problems and/or concerns that might have arisen during the participation, thereby avoiding noncompliance.

Adolescents were invited to take part in all follow-up collection waves, regardless of whether they had participated in previous ones. To improve retention, the DNs actively contacted participants and their caregivers via phone calls, text messages, e-mail, and/or social media. In each wave, DNs made at least 5 attempts to contact participants/caregivers (at various times of day, on various days) for 2 weeks. Another DN would perform the same contact procedure for another 2 weeks if previous attempts were unsuccessful. If no contact was established, the accuracy of contact information for participants was checked with their school. If contact was not possible after the contact information check, the available home address was visited.

DNs were trained with core smartphone skills and basic troubleshooting for the applications used in this study. They were also able to contact a technical support team for consultations. Because they were research team members, they were aware of the information necessary to explain to participants about the types of data being collected, as well as the study's objectives. Participants were in direct contact with DNs, notifying them of problems that might occur.

To manage participants' progress during the data collection period for W2 and W3, a Web-based dashboard was used. The DNs received training on administrator dashboard guidelines and operations to monitor the participants throughout the process. This monitoring included basic information on the completion/non-completion of digital interactions and the number of overall signals from apps. These researchers, however, intervened with data collection only when participants' signals on apps were extremely low or nonexistent for more than 48 hours. In these cases, DNs contacted participants to troubleshoot errors in the functionality of the applications and/or smartphones. Only 1 intervention during the data collection process was made, even if the problem persisted afterward. Effective monitoring and support were established in weekly staff meetings to manage any issues that could occur during the study.

Measures

Clinical Assessment. During W0 and W3, participants underwent clinical assessment of mood disorders and comorbid diagnoses using the K-SADS-PL.[27] For both data collection points, interviews were performed by board-certified psychiatrists who received prior inter-rater reliability training on the instrument and were blind to the participant's LR/HR/MDD group status (to avoid any bias during W3 interviews, different psychiatrists performed W0 and W3 assessments). For both waves, the best estimate of diagnoses for each participant was reviewed by an experienced child and adolescent psychiatrist to confirm and ensure diagnostic consistency. Whereas the W0 diagnostic interviews were conducted in person with both the participant and their primary caregiver, at W3 all diagnostic interviews were performed online via telemedicine with information obtained exclusively from the participants. To standardize the clinical assessment process, all participants were invited to conduct the psychiatric interview online at Hospital de Clínicas de Porto Alegre (HCPA) in a private room equipped with headphones and a computer to ensure consistency and privacy. For participants who were unable to come to the hospital, the option of conducting the evaluation online from home was offered to them.

Further self- and clinician-administered instruments used with the participants and their caregivers at each collection wave are summarized in Table 1.

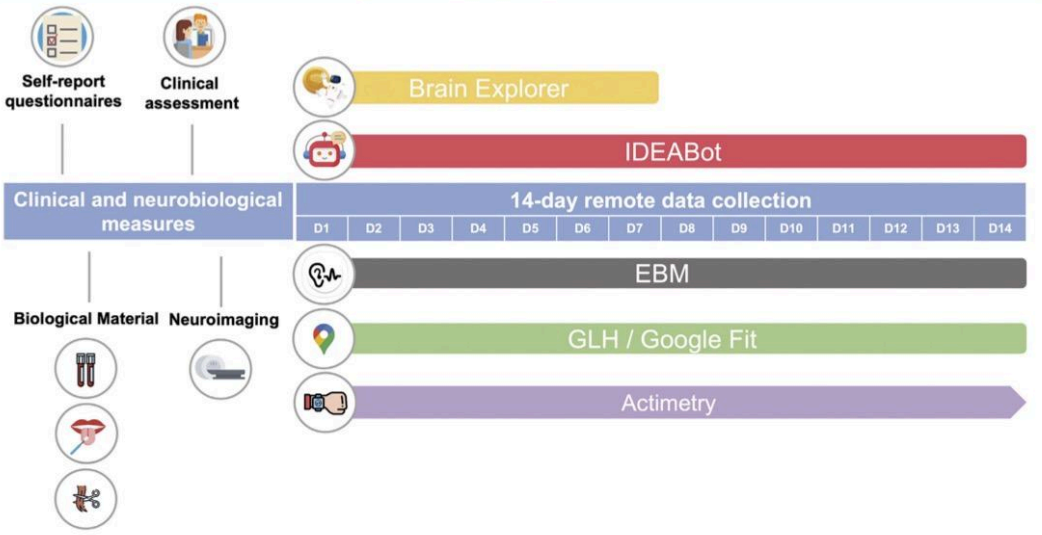
Digital Phenotyping. During W2 and W3, we conducted active and passive data sensing for digital phenotype assessment over a 14-day period. Smartphones, the most widely adopted method of digital data collection, have been used in different populations, and have had their feasibility assessed among individuals with MDD.[29] In addition, among 9- to 17-year-old Brazilians, 93% are regular Internet users, and 93% of these use mobile phones to access the Internet.[30]

In our study, the participants' own smartphones were used for remote data collection whenever possible. To explain the installation of and the features of apps used for digital data collection and digital phenotyping, animated videos were produced for participants (Supplements 1, 2, and 3, available online).

A summary of data collection procedures across the 3 waves is provided in Figure 1. Additional information about the digital phenotyping procedures is shown in Figure 2.

Active Sensing Data. IDEABot is a WhatsApp-based conversational agent designed by our team to collect active momentary assessments from adolescents through text and audio messages. In the IDEA-RiSCo study, the IDEABot was programmed to collect data over a 14-day period, coinciding with the time frame during which other active and passive detection applications were also collecting data.[31] It leverages an already-existing application—WhatsApp—and its default features to capture both

FIGURE 2 Timeline of Active and Passive Digital Phenotyping Acquisition Procedure



Note: *Self-report questionnaires were completed by participants and caregivers at all data collection waves; clinical assessments were performed in person at W0 and via telemedicine at W3 and included K-SADS-PL and other clinician-administered instruments; biological material collection included blood samples at W0 and W3, saliva samples at W0, and hair samples at W3; neuroimaging was performed at W0 and W3; IDEABot was used to collect active sensing data at W2 and W3; the EBM app was used to collect passive sensing data at W2 and W3; GLH/Google Fit were used to collect passive sensing data at W3; actimetry was used to collect rest–activity data linked to the add-on study CHRONO-IDEA during 14 days at W0 and 23 days at W3; the Brain Explorer app was used to collect remote cognitive data during W3. EBM = Electronic Behavioral Monitoring; GLH = Google Location History; IDEABot = The Identifying Depression Early in Adolescence Chatbot; K-SADS-PL = Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime version; W0 = Wave 0; W1 = Wave 1; W2 = Wave 2; W3 = Wave 3.*

real-time information on mood and to prompt audio responses from participants. The IDEABot was devised with the aim of minimizing issues regarding participant burden and to sustain engagement and retention through the use of an existing app that was already present in the daily lives of the vast majority of our target population: a recent study by our group shows that 81% of adolescents in Porto Alegre report using WhatsApp at least once every hour.[32]

The IDEABot thus constitutes a frugal innovation tool that takes advantage of human-like conversation features to assess psychological constructs in a scalable, systematic fashion.[33] Moreover, the chatbot not only collects textual data from self-reported ratings and scales, but also prompts and collects audio recordings, from which both textual (through transcription) and acoustic features can be extracted. The IDEABot performs pre-scripted interactions that follow a time-contingent sampling and require audio or text responses from participants, deciding how to respond back based on exact text matches or recording duration. The content of recordings is not analyzed by the chatbot and is stored on a secure server for subsequent use.

An initial generic message (eg, hello) sent by participants was needed to activate the chatbot (because of WhatsApp's technical requirements). To explain the bot's functioning as well as its features, an animated video was sent to the participants.[31] In addition, functioning was reviewed at the first interaction with the IDEABot. This step is critical for both standardization of instructions given to users and ensuring that participants were aware of the nature of the conversation, avoiding misconceptions (such as beliefs that the bot is a person or that the audios will be heard immediately). For more details on the development and functioning of the chatbot, see Viduani *et al.* (2023).[31]

Remote Cognitive Assessment. To collect remote cognitive data during W3, we selected the Brain Explorer application, developed by the Developmental Computational Psychiatry Group based at the Max Planck UCL Centre for Computational Psychiatry and Ageing Research.[34] The app can be used in any hand-held electronic device that runs on an Android or iOS operating system. The Brain Explorer app was created as a set of

games set in space, designed to explore cognitive mechanisms, focusing on decision making and learning. In the games, participants are space explorers who have a mission to perform outer-planet activities. Participants were asked to complete tasks over the course of 5 different games (each set in a different planet) designed to collect data on specific domains: Treasure Hunt (decision making and information gathering), Milky Way (reward learning), Pirate Market (punishment learning), Space Observer (perceptual metacognition), and Scavenger (risk-taking/gambling). These games were selected to align with the functional magnetic resonance imaging (fMRI) protocol and assessments.

Using computational models to capture behavior from these games, the app aims to trace cognitive functioning and to determine how users differ in the way they act. During W3, participants were invited to download the Brain Explorer app and to finish all of the games during the 14-day period of remote data collection. Reminders were sent every other day to participants who did not finish the games after the first 7 days of the collection period.

Passive Sensing Data. In the present protocol, we used the Electronic Behavioral Monitoring (EBM) App (version 2.0), a custom-built application that has been previously used for passive sensing of adolescent mothers with depression in Nepal.[35,36] The EBM App uses smartphone passive sensors to capture mobility patterns (both spatial, via GPS, and physical, via accelerometer/gyroscope) and ambient audio recordings (via microphone). The app was designed to capture these 3 types of smartphone data at 15-minute intervals from 6 am to 11:59 pm. Participants were instructed to download the EBM application and to log in with their phone numbers. The EBM also includes a timer that allows participants to interrupt data collection for a specified amount of time. In addition, participants were informed that no data are collected when the phone is turned off. Minimum requirements for installation are Android version 5.0 or above, a working microphone, and GPS; also, the phone must be capable of receiving a text message confirmation for logging into the application. During W2, participants who did not have a phone meeting the minimum requirements for EBM installation were offered a compatible smartphone for the 14-day period. To standardize the passive data collection using participants' own smartphones, participants without a smartphone meeting the minimum requirements were excluded from EBM data collection at W3. Participants were asked to turn on the Internet connection and GPS on their phones for the 14 days of the study, as well as to enable the application to run in the background.

To complement the information from the passive movement and location data collected from the EBM app, data from GPS, accelerometer, and gyroscope features were also collected through the Google Location History (GLH) and Google Fit app at W3. GLH is a Google Account setting that accesses the smartphone's GPS and saves the locations where the user has visited, capturing the user's location based on the smartphone's location services passively integrated into the Android operating system or with any other operating systems that have a Google application installed, such as Google Maps app. The Google Fit app is an open platform developed by Google Inc., which uses the smartphone sensors, such as accelerometer, gyroscope, and GPS system to detect changes in position (eg, moving from sitting to standing), various types of movement (walking, cycling, and others), several kinds of data (number of steps, walked distance, heart rate, and others), and different bouts of activity (time of each bout).[37]

Previous studies have used GLH services and Google Fit app to understand aspects of the health of individuals.[38–40] In the present protocol, participants who have a Google account must have their GLH and Google Fit activated in order to generate data. Those who did not have a Google account or who did not have GLH and/or activity and movement history activated were invited to create an account and/or activate GLH (Google Maps) and Google Fit. GLH and Google Fit data were collected during the same period of EBM data collection in W3. In all cases, participants shared their data through Google Takeout, a free tool developed by Google Inc. to export Google data for backup. The DNs instructed the participants to install the Google apps, activate GLH, and share their data through Google Takeout. To make comparisons between the waves, participants who already had a Google account and had already activated GLH and Google Fit were also asked to share their retrospective data for the equivalent 14-day period following the collection of W0, W1, and W2.

Sleep and Circadian Rhythms: the CHRONO-IDEA Study. The bidirectional relationship between biological rhythms and depressive symptoms has been investigated,[41–43] but is still far from being fully explored. The tools and techniques provided by chronobiology produce essential information to unveil the etiology, diagnosis, and prognosis of mental disorders.[44–46] In clinical settings, several studies have observed consistent associations between greater depressive symptoms and lower activity rhythms,[47] exposure to artificial light at night (ALAN),[48] and sleep disturbances.[49] Therefore, to investigate these features, the CHRONO-IDEA, an add-on study to IDEA-RiSCo, was designed to investigate questions related to

chronobiology in the context of risk and presence of depression in adolescence. To this end, we collected data based on self-reports of sleep–wake cycle (ie, schedules, quality, and disturbances) and circadian phenotype (ie, chronotype), but also collected actimetry data. Actimetry is a passive method to assess rest–activity profiles using a wrist accelerometer. During W0, participants were invited to collect actimetry data for 14 consecutive days, right after the clinical assessment. At W3, actimetry data were collected for 23 consecutive days, starting concurrently with the remote collection period of the other digital phenotyping applications. In the presence of a researcher, the adolescent completed the instruments and was given the actimeter. At both waves, instruments were used to collect data on sleep–wake behavior on work(school) days and work(school)-free days, schedule preferences, sleep hygiene behaviors, and sleep difficulty, respectively (Table 1). Actimeters from ActTrust Condor are equipped with a luximeter and a thermometer, enabling the assessment of environmental light exposure, and peripheral body temperature, which were used in this study.

Other Measures of Interest. All individuals who participated in the W3 data collection at the Hospital de Clínicas de Porto Alegre Clinical Research Center also took part in the same collection procedure of peripheral biological samples performed at the baseline assessment. For participants who completed the clinical interview online at HCPA, anthropometric measures were collected immediately following the interview. For those who completed the clinical interview from home, anthropometric measures were collected on the same day as the neurobiological sample collection. Height, weight, waist circumference, hip circumference, and axillary temperature were collected following the same methodology reported in Kieling *et al.* (2021).[14]

To measure a range of pro- and anti-inflammatory cytokines and other immune-related markers, serum from whole blood (4 mL of blood using Vacutainer tube without anticoagulants) and plasma samples (4 mL of blood using a K3EDTA anticoagulant tube) were collected either in the morning or in the afternoon, depending on the time of clinical assessment. To perform gene expression analyses, RNA samples were also collected (5 mL of blood using two 2.5mL PAXGene tubes, PreAnalitix, Qiagen/BD Company). Detailed immune phenotyping analytic approaches are described in the IDEA-FLAME protocol.[50]

Participants took part in MRI data acquisition on the same day as the clinical assessment, using the same protocol as in W0, including structural and functional (gambling task, face-matching task, and resting-state) imaging acquisition.[14,51–53] Throughout the study (baseline and follow-up waves), images were acquired from the same 3T Ingenia scanner (Koninklijke Phillips N.V., Netherlands), software version 5.3.1, and 16-channel head coil.

For W3, adolescents were also invited to provide hair samples for assessment of cortisol concentrations. Two hair strands were cut from the posterior vertex position of the head as close to the scalp as possible.[54]

Data Management

All clinical data were collected and managed using the Research Electronic Data Capture (REDCap) platform hosted at HCPA.[55,56] All self-report instruments were adapted to an electronic survey in REDCap; clinician-administered instruments (eg, K-SADS-PL) were also adapted, and their algorithms were fully implemented in REDCap.

The resulting database from the 14-day period of remote data collection during W2 and W3 underwent a data cleaning process to detect incomplete data or other inconsistencies. All information collected by the IDEABot was uploaded using the encrypted WhatsApp server to our own secure server. Afterward, all audio files were transcribed and subsequently stored in the cloud, encrypted and without identifying information.[31] Brain Explorer data were stored on servers at University College London (UCL).

The GPS and accelerometer/gyroscope data from the EBM app were first stored locally on the participants' smartphones as a CSV file, whereas audio files were stored in m4a format. All participant data could be accessed (and deleted) from the phone. In the presence of an Internet connection, the application automatically uploaded participant data to our private server. The passive data from the EBM app, GLH, and Google Fit were stored on a private, secure online drive using Secure Socket Layer (SSL) encrypted connection, ensuring total confidentiality, integrity, and accuracy of the data being transmitted. The processing and analysis of passive sensing data will be published in future publications.

Cohort Retention Rates

Recruitment for the last follow-up wave ended in September 2022. Data collection, cleaning, and preparation are complete, and data analysis is currently underway. Baseline characteristics of the IDEA-RiSCo sample have been presented elsewhere.[14] In each of the 3 subsequent waves, participants were considered as included if at least 1 measure of depressive symptoms (from either a participant or caregiver questionnaire) was completed.

Over the 3-year follow-up, the overall retention rates at W1, W2, and W3 were 96% (n = 144), 94% (n = 141), and 88% (n = 132). Of the participants, there were 83.3%

(n = 125) who completed at least 1 data point for each of the 4 data collection timepoints. Although loss to follow-up was higher in W3, rates were not significantly different between sexes and risk groups for all 3 waves in the follow-up ($p > .05$). Refusals were the main source of loss for all 3 waves, and only 2 participants at each wave were not found during the contact period.

A majority of the included participants, 80.8% (n = 114) at W2 and 97% (n = 128) at W3, took part in some aspect of the 14-day period of digital data collection. Of these, 70.2% and 89.1% used their own smartphone for all digital measures during W2 and W3, respectively. Preliminary results of the IDEABot have been published in a specific paper.[31]

Among the full sample, 86% (n = 129) completed the clinical assessment and underwent K-SADS-PL and other clinician-administered measures at the endpoint (W3). Of these, 93.8% (n = 121) had biological material collected (blood/hair samples), and 76.7% (n = 98) underwent MRI acquisition. Retention rates were not significantly different between study groups for both neurobiological collection data ($p > .05$). The main reason for the missing MRI data was the presence of fixed metal accessories (mostly dental braces), a contraindication to the procedure, for several participants (n = 20) at W3.

Participants' Perspectives

Eight of the 10 adolescents included at the end of the baseline assessment period who met criteria for a diagnosis of depression were invited to participate in semi-structured interviews to explore their experience as research participants.[14,57] In their accounts, adolescents reported limited understanding of the purposes of the research but stressed that the overall study process was positive; in fact, some considered that participating was even beneficial. Among the motivators for study participation, adolescents reported seeing the research as a way of being helped and of having feelings and difficulties acknowledged. Also, helping other adolescents who may be struggling with depression was mentioned as a great motivator for participating in the research.[14]

In the third wave of follow-up, we were also interested in how participants perceived the data collection process, especially the new technologies added to the research protocol. Thus, we included in the IDEABot a question regarding the participants' experiences with the tool and the completion of the research process.[31]

Overall, participants endorsed the familiarity with the research process and team (given the length of data collection over 3 years) as a motivator for sustained engagement and overall appraisal of the process:

"For me, it was very normal [to complete data collection] because I had already participated in the research, so I knew how it worked." (Girl, 19 years)

"It's always a pleasure to participate in all the surveys we do, in everything, all the stages, whether face-to-face or online." (Girl, 19 years)

The idea of helping research and other adolescents was also mentioned. At baseline, this was considered a strong motivator for study engagement. In the follow-up, adolescents also endorsed this motive; however, they also expressed doubt, revealing an overall limited understanding of the goal of data collection:

"I know that I will be helping some people, I mean, maybe not, but I think I will." (Boy, 20 years)

The study design also seems to have contributed to encouraging participants to share private aspects of their lives with the researchers. Consistent with the baseline round, participants endorsed the positive aspects of data collection as providing a space for reflection and regulation regarding their own emotions, even if the IDEABot represented a different medium for doing so.

"It was a cool, innovative experience, because I don't like showing my feelings so much, talking about things to people a lot and it ended up that I had to do this here, kind of leaving my comfort zone, you know. So I think that that was cool; it was, it made me evolve and I think I'll use that as an example. Not just talking here with the bot, but talking about something with, with people, expressing my feelings. I think this here served as a lesson." (Boy, 19 years)

Conversely, some expressed annoyance at the mode of data collection—both in and outside clinical settings, using not only questionnaires, but also audio recordings:

"Ah, it was a bit annoying having to keep talking, talking, talking, talking. Sometimes I had to give details about everything, even when I had nothing else to say, so I had to keep going on with useless and unnecessary things like I'm doing now. It was basically boring, boring, boring, boring, answering that." (Boy, 20 years)

DISCUSSION

This protocol paper describes the methods and procedures for 3 follow-up waves of a prospective study to assess the longitudinal course of depressive symptomatology among 150 adolescents stratified for risk of developing depression and presence of depression, and presents the initial results regarding feasibility of the procedures and retention. Future studies will thus focus on analyzing the wealth of data successfully captured through the application of this protocol.

The IDEA-RiSCo study is an innovative project involving deep phenotype analysis using technology-mediated data collection combined with traditional clinical assessments and neurobiological approaches. Despite the complexity of collecting longitudinal data among adolescents, the prospective follow-up achieved a low attrition rate (12%) at endpoint (W3). In contrast, similar studies with adolescents and young adults at high risk for psychosis have reported attrition rates of about 30%.[58] Therefore, the present protocol might offer insights about the feasibility of longitudinal prospective data collection in a phenotypically refined sample of adolescents.

Several studies have relied on sensing data collected from smartphones to predict mental health and well-being in adults.[59–61] It has been theorized that low-level sensor data may correlate with depression severity in young adults,[62] and behavioral data have been shown to predict symptoms of depression and post-traumatic stress disorder.[63] Little research, however, has focused on adolescent populations, even though smartphone use is widespread in this age group.[64] To address this gap, the present protocol included mobile-mediated active and passive sensing data collection at 2 of the follow-up waves. We also proposed a frugal innovation tool (IDEABot) to collect repeated measures of depressive symptomatology and brief spontaneous audio recordings.[31] The IDEABot uses WhatsApp as the interface for data collection, addressing the respondent burden, which may contribute to self-selection bias and selective nonresponse.[65] With this study, we hope to contribute to a common understanding of the applicability of data collection using smartphones in the adolescent population. This will provide interesting insights on how we can better collect, manage, and analyze robust data from smartphones to sample from adolescents' experiences.

Furthermore, the integration of digital and traditional methods presents a promising frontier in mental health, particularly given its underexplored potential within adolescent populations. Technological innovations in active and passive sensing devices have the potential to revolutionize people-centric sensing, largely due to the transformation of the near-ubiquitous mobile phone into a dynamic sensing device.[66] This evolution, coupled with the computational prowess and pervasive presence of smartphones, facilitates the collection of digital phenotypes that might echo individuals' lived experiences within their natural environments.[67] Consequently, digital phenotyping using smartphones and other digital tools can notably augment the precision of depression diagnosis.[68] Moreover, despite the challenges of a potential digital divide,[69] the use of smartphones for data collection may represent a scalable, cost-effective data gathering strategy. This potential enhancement could advance early identification of mental health conditions, as well as refine treatments by providing parameters for personalized interventions.[70]

A number of studies have been published based on IDEA-RiSCo baseline data. Findings from neuroimaging studies have demonstrated associations of reward- and threat-related neural function and frontolimbic network topology with depression and with high-risk status for developing depression.[51–53] Chronobiological findings include strategies to deal with missing data in actimetry,[71] and the relationship among different risk groups and sleep variables, motor activity rhythms, and exposure to artificial light at night.[72] Furthermore, a qualitative study was also published to explore the adolescents' initial reactions after receiving a clinical diagnosis of MDD.[57] Additional publications are currently underway, but the limitations inherent to the cross-sectional focus of the studies using only baseline data must be recognized.

Nevertheless, by setting a solid foundation for subsequent detailed analyses of the course of depressive symptomatology and neurobiological features across risk groups, the present protocol represents a significant advancement for the understanding of adolescent depression. The methodological framework that we established has enabled consistent data collection across 4 time points and opens several avenues for research. First, the predictive validity of the IDEA-RS will be assessed evaluating, in each group, the proportion of participants developing depression 3 years post-baseline. Also, it will be possible to examine whether neural function patterns, sleep, and biological rhythm variations in the LR and HR groups augment depression development prediction. In a broader context, it is essential to understand the potential for nuanced analyses in early- vs later-onset MDD. By identifying intra-individual changes in neurobiological and clinical attributes before and after the onset of depression, researchers can better pinpoint risk factors and intervention targets. Moreover, future studies should analyze whether there are any differences in earlier-onset vs later-onset MDD, identifying intraindividual changes in terms of neurobiological and clinical characteristics before and after developing depression.

Thus, this study's strengths lie not only in its potential to advance our understanding of risk profiles, symptomatic progression, and neurobiological patterns over time in Brazilian adolescents, but also in its methodological approach. The blend of active and passive sensing data collection paves the way for nested timeframe analyses. While we use a 3-year follow-up within a cohort framework, we simultaneously delve into intensive longitudinal datasets, with 28 days of repeated measures across 2 years. Such a

comprehensive approach aids in investigating intra-individual changes and variability across time.[73]

This dual approach, which allows for long-term intra-individual changes to be juxtaposed with short-term depressive symptomatology data, represents a holistic view. It not only aids in individual-focused analyses but also provides insights into group dynamics, highlighting how group and individual factors interplay.[74] Furthermore, pairing innovative collection methods with neurobiological measures will undoubtedly propel our comprehension of the neural and immune intricacies underlying adolescent depression. This strategy offers an exciting avenue for future research, facilitating data triangulation and allowing for method-wise comparison of neurobiological data. We believe that the steps that we have taken in this study will act as a cornerstone for subsequent research, elucidating the intricate web of factors contributing to adolescent depression.

However, this study is not without limitations, which are addressed below. The sample size may limit the power to compare some uncommon outcomes or parameters with higher variability between risk groups. However, we believe that we have mitigated this limitation by recruiting homogeneous groups, recognizing the heterogeneity of the group without depression, applying repeated measures, and ensuring a high level of detail in the information collected—which included in-depth clinical assessments—for each individual.

Technological limitations include that the digital data collection may be affected by limitations such as malfunction of apps, adolescents forgetting to charge their phone, or devices not retaining charge.[75,76] Moreover, concerns about privacy, interference with daily activities, and cultural issues may also influence the participants' attitudes toward the use of technology.[76] Our study has attempted to mitigate gaps in digital data collection by daily monitoring of the active and passive data acquisition with notifications to the participants if abnormalities were detected. We also included a collaborative approach in the development and implementation of all technology-mediated data collection procedures.[31]

Nonadherence is another potential shortcoming. Experimental fatigue associated with completing repeated measures might result in missing data during data collection across the waves.[77] Furthermore, longitudinal studies may also have unintended effects, such as participants engaging in healthier behaviors when tracking their own emotions and health.[78] During the 14-day remote data collection period, we conducted naturalistic data collection processes to reduce the burden on participants. We also attempted to reduce participant burden by keeping daily assessments brief and providing adaptations in the collection settings (eg, assessments from home for those who were not able to come to hospital).

The COVID-19 pandemic represents another potential limitation of this study. The coronavirus pandemic emerged during the follow-up period of this protocol. Recently, some studies have pointed out that the pandemic has influenced the mental health of young individuals.[79–81] To study the impact of the pandemic, we incorporated an adapted version of the The CoRonavIruS Health Impact Survey (CRISIS) during W3.[82] In addition, all data collection procedures during W1 and W2 and part of those conducted in W3 were performed online. In this context, the adequate retention rates achieved even in the context of the pandemic could be considered a strength of this study.

In regard to the adolescents' experience of participating in the follow-ups, some important aspects stand out. First, despite the familiarity with the research process, participants still expressed limited understanding of the research goals and objectives. This finding raises the issue of the complexification of the protocol and inclusion of innovative approaches as an additional concern regarding how to translate research into meaningful information for adolescents. Second, an interesting observation about the motivation for participating in the study was the notion that, as research participants, the adolescents would be able to help research and other adolescents. Data suggest altruism as a strong motivator for sustained engagement in research protocols, which is consistent with previous research that can be leveraged for future research.[83] In addition, meaningful rapport with the research team was an important aspect for engagement at both baseline and follow-up. Finally, participants also endorsed the use of the research process as being important for validating and reflecting upon their emotional states, which was described as therapeutic in its own right. However, we have few data on how this effect was experienced in depth by the adolescents, and thus future research is required to explore this further.

Despite the global importance of depression in adolescence, there are significant gaps in the quality and number of studies addressing the course of the disorder in this age group.[13] This is particularly meaningful in LMICs, where the majority of the world's adolescent population lives and the evidence on mental health in youth is scarce.[14] In this regard, the present protocol has shown the feasibility of conducting a prospective follow-up study with a risk-enriched cohort of adolescents in a middle-income country. Moreover, this study has contributed to knowledge regarding the integration of mobile technology with traditional methodologies to improve intensive longitudinal data collection. Furthermore, we hope to support additional studies that in the long term could increase the understanding of the clinical and neurobiological trajectories of the complex phenomenon of depression in adolescence.

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APPENDICE #3: Short Mood and Feelings Questionnaire (sMFQ).

Items
1. Eu me senti muito triste ou infeliz.
2. Eu não consegui me divertir com absolutamente nada.
3. Eu me senti tão cansado(a) que só ficava sentado(a) sem fazer nada.
4. Eu estive muito agitado(a).
5. Eu senti que eu não valia mais nada.
6. Eu chorei muito.
7. Eu achei difícil raciocinar ou me concentrar.
8. Eu me odiei.
9. Eu me senti uma pessoa ruim.
10. Eu me senti sozinho(a).
11. Eu pensei que ninguém me amava de verdade.
12. Eu pensei que eu nunca seria tão bom(boa) quanto os outros da minha idade.
13. Eu fiz tudo errado.

APPENDICE #4: Mood and Feelings Questionnaire - Child (MFQ-C).

Items
1. Eu me senti muito triste ou infeliz.
2. Eu não consegui me divertir com absolutamente nada.
3. Eu estive com menos fome do que normalmente.
4. Eu comi mais do que normalmente.
5. Eu me senti tão cansado(a) que só ficava sentado(a) sem fazer nada.
6. Eu estive me movimentando e caminhando mais devagar do que normalmente.
7. Eu estive muito agitado(a).
8. Eu senti que eu não valia mais nada.
9. Eu me culpei por coisas que não eram minha culpa.
10. Foi difícil me decidir sobre as coisas.
11. Eu fiquei emburrado(a) e de mal com meus pais.
12. Eu estive menos a fim de conversar do que normalmente.
13. Minha fala esteve mais devagar do que normalmente.
14. Eu chorei muito.
15. Eu pensei que nada de bom aconteceria comigo no futuro.
16. Eu pensei que a vida não valia a pena ser vivida.
17. Eu pensei sobre morte ou morrer.
18. Eu pensei que minha família estaria melhor sem mim.
19. Eu pensei em me matar.
20. Eu não queria ver meus amigos.
21. Eu achei difícil raciocinar ou me concentrar.
22. Eu pensei que coisas ruins aconteceriam comigo.
23. Eu me odiei.
24. Eu me senti uma pessoa ruim.
25. Eu me senti feio(a).

26. Eu me preocupei com dores no corpo.
27. Eu me senti sozinho(a).
28. Eu pensei que ninguém me amava de verdade.
29. Eu não me diverti nem um pouco nas minhas atividades.
30. Eu pensei que eu nunca seria tão bom(boa) quanto os outros da minha idade.
31. Eu fiz tudo errado.
32. Eu não dormi tão bem quanto eu normalmente durmo.
33. Eu dormi muito mais do que normalmente.