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TESE DE DOUTORADO

Transtorno depressivo maior em jovens: uma abordagem categórica, dimensional e de rede

Pedro Henrique Gaiva Manfro

Orientador: Prof. Dr. Christian Kieling

Porto Alegre, 05 de Outubro de 2021

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Tese apresentada como requisito parcial à obtenção do título de doutor em Psiquiatria pelo Programa de Pós-graduação em Psiquiatria e Ciências do Comportamento da Faculdade de Medicina da Universidade Federal do Rio Grande do Sul.

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The stigma of psychiatric illness […]

need to be addressed at both social and political levels and will not likely be solved

through the discovery of major single causes for our illnesses. The legitimacy of the

discipline of psychiatry does not rest on our ability to find single major causes of our

disorders.

(Kendler, 2019).

RESUMO

O transtorno depressivo maior (TDM) é uma das principais causas de carga de doença no mundo, com curso frequentemente recorrente e crônico, além de peso pessoal e social pela sua alta incidência na juventude. Como períodos de mudanças biopsicossociais significativas, a adolescência e a transição para a vida adulta são momentos críticos para identificar e entender o diagnóstico e os sintomas de depressão. Além disso, o TDM é um construto eminentemente heterogêneo, com apresentações clínicas e vias neurobiológicas diversas. Nessa tese, buscamos integrar a heterogeneidade fenomenológica e biológica da depressão por meio de três estudos. No estudo #1, investigamos o diagnóstico categórico, a estrutura fatorial e dimensional do TDM e de seus sintomas em jovens de 22-23 anos participantes da Coorte de Nascidos Vivos de 1993 de Pelotas. Com análises epidemiológicas, psicométricas e de rede, encontramos resultados condizentes com a literatura internacional em termos de prevalência-ponto do diagnóstico, estrutura fatorial da escala e centralidade dos sintomas depressivos. No estudo #2, ampliamos a investigação da amostra do estudo #1 ao utilizar técnicas analíticas de rede para examinar, longitudinal e transversalmente, a relação de dois marcadores inflamatórios, Proteína C Reativa (PCR) e Interleucina-6 (IL-6), com sintomas depressivos e covariáveis biopsicossociais. Apesar de não encontrarmos associações entre os marcadores inflamatórios e o diagnóstico categórico ou a soma total da escala dimensional de sintomas, encontramos relações diferenciais transversais e longitudinais de sintomas específicos com IL-6. Sendo assim, concluímos que analisar de maneira progressivamente mais detalhada a relação entre sintomas depressivos e marcadores biológicos pode ser uma avenida para melhorar o entendimento destes. No estudo #3, avaliamos duas amostras de adolescentes de escolas públicas de Porto

Alegre, recrutadas de maneira semelhante e que responderam a dois questionários de sintomas depressivos distintos, porém complementares. Na amostra que respondeu a Patient Health Questionnaire (PHQ-A; n=7,720), encontramos que os sintomas de humor triste e sentimento de culpa excessiva foram os sintomas mais centrais da rede da escala PHQ-A. Na amostra que respondeu a Mood and Feelings Questionnaire (MFQ; n=1,070), itens de ódio a si mesmo e de sentimento de solidão, ambos classificados como não explicitamente contemplados no DSM de acordo com a literatura prévia, foram os mais centrais da rede de sintomas. Encontramos que itens refletindo critérios diagnósticos do DSM e itens não explicitamente contemplados nessa classificação nosológica fazem parte de uma rede altamente interconectada de itens. Ao focarmo-nos exclusivamente nos critérios incluídos do DSM para definição nosológica, podemos estar arriscando perder informações importantes da experiência adolescente do TDM. Com os três estudos, concluímos que incorporar a heterogeneidade inerente ao transtorno depressivo maior, em oposição a buscar alternativas reducionistas, é um passo fundamental para o avanço do entendimento dos sintomas depressivos em jovens.

Palavras-chave: Depressão; adolescência; epidemiologia; psicometria; análise de rede.

ABSTRACT

Major depressive disorder (MDD) is a main cause of global burden of disease, with a recurring and chronic course, as well as elevated personal and social burden due to its high incidence during youth. As a period of profound biopsychosocial change, adolescence and the transition to emerging adulthood are critical periods for the early identification and the understanding of depressive phenomenology. Beyond that, MDD is an inherently heterogeneous construct, with multiple possible clinical presentations and diverse neurobiological pathways. On this thesis, we aimed to evaluate depression's phenomenologic and biological heterogeneity with three studies. On study #1, we investigated MDD's categorical diagnosis, as well as its factorial and dimensional structures in early adults from the 1993 Pelotas Birth Cohort. Using epidemiologic, psychometric and network analysis, our results were consistent with international literature on point-prevalence, factorial structure and symptom centrality. On study #2, we expanded study #1 by using network analytical techniques to investigate longitudinal and cross-sectional associations between depressive symptoms, C-Reactive Protein (CRP), Interleukin-6 (IL-6) and commonly studied covariates. Even though we did not find associations between inflammatory markers and either categorical diagnosis or the total sum-score on a dimensional scale, we found differential longitudinal and cross-sectional connections between specific symptoms and IL-6. As such, we came to the conclusion that employing progressively more detailed levels of analysis for the study of depressive symptoms and biomarkers may be a fruitful avenue for understanding their relations. On study #3, we evaluated two adolescent samples from public schools, similarly recruited but that answered different depression symptom assessments. In the sample that answered the Patient

Health Questionnaire – Adolescent Version (PHQ-A; n=7,720), we found that low mood and worthlessness/excessive guilt items were the most central items in the PHQ-A. In the sample that answered the Mood and Feelings Questionnaire (MFQ; n=1,070), self-hatred and feelings of loneliness, both not explicitly contemplated by the DSM according to previous literature, were the most central items. Examining two different but complementary scales in adolescents, we found that items reflecting DSM criteria and those not explicitly contemplated by the DSM criteria are part of a highly interconnect network of items. By focusing mainly on DSM criteria for defining MDD, we may risk losing important information on the adolescent experience of depressive symptoms. With these three studies, we conclude that embracing the inherent biopsychosocial heterogeneity of MDD, in opposition of searching for reductionist alternatives, is a crucial step for advancing the research of depressive symptoms during youth.

Keywords: depression; adolescence; epidemiology; psychometrics; network analysis

ABREVIATURA E SIGLAS

AU-ROC	*Area Under the Receiver-Operating Characteristic Curve*
CESD-R	*Center For Epidemiological Studies – Depression Scale – Revised*
CFA	*Confirmatory Factor Analysis*
CFI	*Comparative Fit Index*
CRP	*C-Reactive Protein*
DSM	*Diagnostic And Statistical Manual of Mental Disorders*
EDM	*Episódio Depressivo Maior*
HIC	*High Income Countries*
IDEA	*Identifying Depression Early in Adolescence*
IL-6	*Interleukin-6*
LMIC	*Low and Middle Income Countries*
MDD	*Major Depressive Disorder*
MDE	*Major Depression Episode*
MINI	*Mini International Neuropsychiatric Interview*
NIMH	*National Institutes of Mental Health*
NPV	*Negative Predictive Value*
PHQ-A	*Patient Health Questionnaire – Adolescent Version*
PPV	*Positive Predictive Value*
RDoC	*Research Domain Criteria*
RMSEA	*Root Mean Square Error of Approximation*
TDM	*Transtorno Depressivo Maior*
TLI	*Tucker–Lewis Index*

Sumário

RESUMO

O transtorno depressivo maior (TDM) é uma das principais causas de carga de doença no mundo, com curso frequentemente recorrente e crônico, além de peso pessoal e social pela sua alta incidência na juventude. Como períodos de mudanças biopsicossociais significativas, a adolescência e a transição para a vida adulta são momentos críticos para identificar e entender o diagnóstico e os sintomas de depressão. Além disso, o TDM é um construto eminentemente heterogêneo, com apresentações clínicas e vias neurobiológicas diversas. Nessa tese, buscamos integrar a heterogeneidade fenomenológica e biológica da depressão por meio de três estudos. No estudo #1, investigamos o diagnóstico categórico, a estrutura fatorial e dimensional do TDM e de seus sintomas em jovens de 22-23 anos participantes da Coorte de Nascidos Vivos de 1993 de Pelotas. Com análises epidemiológicas, psicométricas e de rede, encontramos resultados condizentes com a literatura internacional em termos de prevalência-ponto do diagnóstico, estrutura fatorial da escala e centralidade dos sintomas depressivos. No estudo #2, ampliamos a investigação da amostra do estudo #1 ao utilizar técnicas analíticas de rede para examinar, longitudinal e transversalmente, a relação de dois marcadores inflamatórios, Proteína C Reativa (PCR) e Interleucina-6 (IL-6), com sintomas depressivos e covariáveis biopsicossociais. Apesar de não encontrarmos associações entre os marcadores inflamatórios e o diagnóstico categórico ou a soma total da escala dimensional de sintomas, encontramos relações diferenciais transversais e longitudinais de sintomas específicos com IL-6. Sendo assim, a análise progressivamente mais detalhada a relação entre sintomas depressivos e marcadores biológicos pode ser uma avenida para melhorar o entendimento destes. No estudo #3, avaliamos duas amostras de adolescentes de escolas públicas de Porto Alegre, recrutadas de maneira semelhante e que responderam a dois

questionários de sintomas depressivos distintos, porém complementares. Na amostra que respondeu a Patient Health Questionnaire (PHQ-A; n=7.720), encontramos que os sintomas de humor triste e sentimento de culpa excessiva foram os sintomas mais centrais da rede da escala PHQ-A. Na amostra que respondeu a Mood and Feelings Questionnaire (MFQ; n=1.070), itens de ódio a si mesmo e de sentimento de solidão, ambos classificados como não explicitamente contemplados no DSM de acordo com a literatura prévia, foram os mais centrais da rede de sintomas. Encontramos que itens refletindo critérios diagnósticos do Diagnostic and Statistical Manual of Mental Disorders (5th edition) e itens não explicitamente contemplados nessa classificação nosológica fazem parte de uma rede altamente interconectada de sintomas. Ao focarmo-nos exclusivamente nos critérios incluídos do DSM para definição nosológica, podemos estar arriscando perder informações importantes da experiência adolescente do TDM. Com os três estudos, concluímos que incorporar a heterogeneidade inerente ao transtorno depressivo maior, em oposição a buscar alternativas reducionistas, é um passo fundamental para o avanço do entendimento dos sintomas depressivos em jovens.

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ABSTRACT/RESUMEN/RÉSUMÉ

Major depressive disorder (MDD) is a leading cause of disease-related burden globally, with an often recurring and chronic course, as well as elevated personal and social burden due to its high incidence among youth. As a period of profound biopsychosocial change, adolescence and the transition to emerging adulthood are critical periods for the early identification and the understanding of depressive phenomenology. Beyond that, MDD is an inherently heterogeneous construct, with multiple possible clinical presentations and diverse neurobiological pathways. On this dissertation, we aimed to evaluate depression's phenomenologic and biological heterogeneity with three studies. On study #1, we investigated MDD's categorical diagnosis, as well as its factorial and dimensional structures in early adults from the 1993 Pelotas Birth Cohort. Using epidemiologic, psychometric and network analysis, our results were consistent with international literature on point-prevalence, factorial structure and symptom centrality. On study #2, we expanded study #1 by using network analytical techniques to investigate longitudinal and cross-sectional associations between depressive symptoms, C-Reactive Protein (CRP), Interleukin-6 (IL-6) and commonly studied covariates. Even though we did not find associations between inflammatory markers and either categorical diagnosis or the total sum-score on a dimensional scale, we found differential longitudinal and cross-sectional connections between specific symptoms and IL-6. As such, the use of progressively more detailed levels of analysis for the study of depressive symptoms and biomarkers may be a fruitful avenue for understanding their relations. On study #3, we evaluated two adolescent samples from public schools, similarly recruited but that answered different depression assessment instruments. In the sample that answered the Patient

Health Questionnaire – Adolescent Version (PHQ-A; n=7,720), we found that low mood and worthlessness/excessive guilt items were the most central items in the PHQ-A. In the sample that answered the Mood and Feelings Questionnaire (MFQ; n=1,070), self-hatred and feelings of loneliness, both not explicitly contemplated by the Diagnostic and Statistical Manual of Mental Disorders (5th edition) according to previous literature, were the most central items. Examining two different but complementary scales in adolescents, we found that items reflecting DSM criteria and those not explicitly contemplated by the DSM criteria are part of a highly interconnect network of items. By focusing mainly on DSM criteria for defining MDD, we may risk losing important information on the adolescent experience of depressive symptoms. With these three studies, we conclude that embracing the inherent biopsychosocial heterogeneity of MDD, in opposition of searching for reductionist alternatives, is a crucial step for advancing the research of depressive symptoms during youth.

Keywords: depression; adolescence; epidemiology; psychometrics; network analysis

1. APRESENTAÇÃO

Esse trabalho consiste na tese de doutorado intitulada "Transtorno depressivo maior em jovens: uma abordagem categórica, dimensional e de rede", apresentada ao Programa de Pós-Graduação em Psiquiatria e Ciências do Comportamento. Essa tese tem como objetivo avaliar a complexidade e heterogeneidade fenomenológica do transtorno depressivo maior e seus sintomas em jovens por meio de múltiplas técnicas de análise. A tese é composta de três estudos.

O primeiro estudo avaliou, com dados oriundos da Coorte de Nascidos Vivos de 1993 de Pelotas, a prevalência-ponto do diagnóstico categórico do transtorno depressivo maior, usando entrevista estruturada e escala dimensional paralelamente para a avaliação epidemiológica e sintomática de sintomas depressivos. Esse artigo incluiu análises tradicionais da epidemiologia, como prevalência-ponto, valor preditivo positivo e área sob a curva ROC; além de análises da psicometria clássica, como análise fatorial confirmatória e suas métricas; e análises de rede, técnica recentemente implementada na literatura em psicopatologia.

No segundo artigo, ampliamos a investigação da fenotipagem de sintomas depressivos reportados por jovens ao avaliar transversal e longitudinalmente a relação entre marcadores inflamatórios (IL-6 e PCR), covariáveis biopsicossociais e diagnóstico categórico de depressão, soma de uma escala dimensional e itens específicos desse instrumento.

No terceiro artigo, estudamos duas amostras de adolescentes de escolas públicas de Porto Alegre, recrutadas com protocolos semelhantes. Com esse estudo, buscamos ampliar o conhecimento da estrutura fenomenológica do TDM ao avaliar escalas complementares em adolescentes. Objetivamos avaliar a frequência e

estrutura latente e de rede de itens considerados como critérios diagnósticos pelo DSM e critérios não explicitamente contemplados nessa classificação nosológica.

2. BASE CONCEITUAL

2.1 A relevância da epidemiologia da depressão na adolescência

O TDM é uma das principais causas de carga de doença em adolescentes e jovens (Ferrari et al., 2013) com importante pico de incidência na adolescência e na transição para a vida adulta (Avenevoli et al., 2015). Como um período de amadurecimento psicossocial e neurobiológico intenso (Giedd et al., 2008; Marsh et al., 2008; Thapar et al., 2012), o entendimento de processos psicopatológicos específicos da juventude é fundamental para a mitigação das repercussões clínicas e funcionais da depressão, que podem ser cumulativas ao longo da vida (Davey & McGorry, 2019).

É crucial o entendimento dos sintomas depressivos em contextos variados, tendo em vista o desequilíbrio entre densidade populacional de jovens em países de baixa e média renda e disponibilidade de dados de larga escala com amostras destes países (Kieling et al., 2011). Estudos como o National Comorbidity Survey – Adolescent Supplement (Avenevoli et al., 2015; Kessler et al., 2005) e o World Mental Health Survey International College Student (Auerbach et al., 2018) muito acrescentaram ao entendimento da prevalência-ponto do TDM na adolescência e no início da vida adulta. Ainda assim, há escassez de dados transculturais sobre a epidemiologia e a caracterização dos sintomas depressivos em amostras populacionais, não-clínicas e da faixa etária da adolescência e da transição para a vida adulta em países de baixa e média renda.

Apesar da importância dos transtornos mentais na carga global de doenças não-comunicantes, nossa compreensão ao redor de aspectos cruciais da sua identificação e entendimento nosológico ainda é pauta de inúmeros debates. Para os fins dessa tese, dividirei a revisão teórica dessas questões em três pontos: revisão

histórica sobre a nosologia do TDM e suas consequências; análise da heterogeneidade do conceito atual de TDM; e revisão filosófica sobre a relação entre critérios diagnósticos e componentes da doença depressão.

2.2 Revisão histórica do conceito de TDM

Inicialmente com o conceito de melancolia como desregulações na "bile negra" descrito por Hipócrates (Berrios, 1988), a história da depressão é longa, detalhada e repleta de descrições e teorias discordantes. No século XVII, o médico inglês Thomas Sydenham propôs que as doenças da mente poderiam ter apresentações uniformes em diferentes indivíduos (DeRubeis & Strunk, 2017). Emil Kraepelin descreveu a melancolia como parte da síndrome maníaco-depressiva – no entanto, Kraepelin considerou que ambos os polos do que é hoje o transtorno bipolar teriam origens patofisiológicas comuns (Horwitz et al., 2017). Entretanto, mesmo Kraepelin e posteriormente o psicanalista Sigmund Freud teriam enfatizado a importância da multiplicidade de origens e causas da síndrome melancólica e adotado conceitos distintos para diferentes apresentações da doença (Freud, 1917). Freud segmentou o conceito de melancolia em depressão melancólica, típica de pacientes hospitalizados e causada por alguma disfunção cerebral, e depressão neurótica, mais típica de amostras comunitárias e uma das psiconeuroses oriundas de adversidades psicossociais. Com a inclusão de melancolia como um dos três principais transtornos psicóticos nas primeiras duas versões do DSM (Horwitz et al., 2017), a influência desses dois médicos na construção das duas primeiras versões do DSM é notável.

Entretanto, a baixíssima concordância dos diagnósticos psiquiátricos, até então de pouco interesse para a tradição psicanalista vigente (Beck, 1962), muito dificultava o estudo da psiquiatria em diferentes partes do mundo. Sendo assim, no

período dos anos 1950 até 1980, Eli Robins e Samuel Guze conduziram a força-tarefa que culminou na publicação do DSM-III (Kendler et al., 2010). Hoje, a base do que consideramos Transtorno Depressivo Maior vem deste texto, estando o conceito de cinco sintomas sendo no mínimo um deles humor triste ou anedonia virtualmente intacto desde então. O conceito de TDM segundo o DSM-III foi, por sua vez, altamente influenciado pelos critérios sugeridos por John Feighner (Feighner, 1972), que, por sua vez, foi influenciado pela publicação de Walter Cassidy em 1957 "Clinical Observations In Manic-Depressive Disease: A Quantitative Study Of One Hundred Manic-Depressive Patients And Fifty Medically Sick Controls" (Cassidy, 1957). Mesmo com a adoção dos seus critérios de maneira quase *ipsis literis* pelo DSM-III, o próprio grupo de Feighner reconheceu os critérios como longe de uma definição conclusiva para qualquer doença (Horwitz et al., 2017). Interessantemente, apesar de presente na descrição de TDM do DSM-III, alterações nosológicas características da infância e adolescência não estão contempladas entre os critérios diagnósticos (American Psychiatric Association, 1980). No capítulo 3, seção "*Disorders Usually First Evident in Infancy, Childhood or Adolescence*", é feita a observação de que "componentes essenciais dos transtornos do humor são os mesmos em crianças e adultos". Comentário semelhante é feito no DSM-IV, apesar da ressalva de que sintomas proeminentes podem mudar conforme a idade e da aparição de irritabilidade como critério cardinal alternativo a humor deprimido (American Psychiatric Association, 1994).

Apesar da inegável contribuição do DSM-III e suas subsequentes iterações para a pesquisa e prática da psiquiatria globalmente, os estudos conduzidos pelos próprios *Working Groups* do DSM questionam a confiabilidade do diagnóstico de depressão. *Field Trials* conduzidos nos Estados Unidos e no Canadá com o intuito de

investigar métricas de confiabilidade teste-reteste de diferentes categorias diagnósticas sugerem ser "questionável" a confiabilidade do conceito de depressão, com um Kappa de Cohen de 0.28 (Regier et al., 2013). Para fins de comparação, o diagnóstico de Transtorno de Personalidade Borderline, notadamente divergente na prática clínica, teve um Kappa de 0.34. Além disso, são raras as publicações referentes ao desenvolvimento do conceito do TDM na infância e adolescência e como foi definida a expansão do conceito de adultos para adolescentes. Limitações significativas desses aspectos fundamentais trazem questões sobre a suficiência da definição baseada em consenso do DSM para o entendimento do fenômeno da depressão ao redor do mundo (Haroz et al., 2017; Kendler & Solomon, 2016).

2.3 A heterogeneidade do conceito de depressão

O Transtorno Depressivo Maior (TDM) na infância e adolescência é definido pelo DSM-5 como uma síndrome contendo no mínimo cinco de nove sintomas possíveis, sendo que deve estar presente pelo menos um dos dois sintomas cardinais de humor deprimido/irritável ou anedonia (American Psychiatric Association, 2013). Essa definição é uma extensão do conceito de depressão na vida adulta, que contempla os mesmos sintomas mas não considera a possibilidade de humor irritável como sintoma cardinal. Essa definição, todavia, é de natureza heterogênea – 227 diferentes combinações de sintomas que preenchem os critérios acima podem estar presentes em adultos (Zimmerman et al., 2015).

Apesar de amplamente utilizada na literatura acadêmica, tal definição de TDM vem há décadas sofrendo críticas. É importante ressaltar que essa classificação é uma operacionalização baseada em consenso e não em dados (Kendler, 2016). Já em 1988, 8 anos após o lançamento do DSM-III, Angold já salientava a potencial

perda de informações particulares à experiência da adolescência ao se considerar depressão na adolescência como mera expansão do conceito da vida adulta (Angold, 1988). Esse pesquisador ressaltava a importância de operacionalizações criadas e avaliadas especificamente para a adolescência como forma de melhor entender o fenômeno nessa faixa etária. Isso se torna ainda mais relevante quando consideramos a dificuldade em estabelecer evidências de grande tamanho de efeito para tratamentos psicoterápicos ou farmacológicos para o tratamento do TDM na adolescência (Cipriani et al., 2016; Cuijpers et al., 2020). Sendo assim, é plausível hipotetizar que os critérios sugeridos pelo DSM deixem de capturar elementos importantes da experiência de sintomas depressivos durante a vida jovem.

Apesar disso, alternativas acadêmicas que visam a contemplar a dimensionalidade do construto "depressão" sofrem também de heterogeneidade considerável e de definições arbitrárias. Por exemplo, há 52 diferentes sintomas de depressão em sete escalas rotineiramente utilizadas na literatura sobre TDM na vida adulta (Fried, 2017). Frequentemente, as escalas refletem a importância dada por diferentes autores a aspectos da síndrome depressiva, como o foco cognitivo da escala de Beck e sua versão para a infância e adolescência na Children's Depression Inventory (Kovacs, 1985) ou a valorização de sintomas psicomotores da escala de Hamilton e a sua adaptação para adolescentes na Children Depression Rating Scale (Poznanski & Mokros, 1996). Além disso, instrumentos autoaplicáveis comumente não provêm avaliações de prejuízo funcional como exigido pelo DSM-5 e potencialmente superestimam a prevalência da doença em relações a avaliações clínicas estruturadas (Martin et al., 2017).

A história da definição baseada em consenso do conceito de TDM somada à heterogeneidade expressiva e a possível consequência de limitação do entendimento

sobre identificação e tratamento da depressão na adolescência nos levanta uma questão ainda posterior a esse conceito. Qual a concepção filosófica da operacionalização do TDM segundo o DSM-5? E é ela condizente com o entendimento moderno da complexidade do fenômeno da depressão maior?

2.4 Critérios diagnósticos e suas associações com componentes dos transtornos mentais

Tomemos, por exemplo, o diagnóstico de infarto agudo do miocárdio (IAM). Apesar de exames complementares amplamente disponíveis (eletrocardiograma, troponina, creatinina-quinase, etc.), um IAM não se define como alterações sugestivas no eletrocardiograma. Isso porque conhecemos parte considerável da fisiopatologia do IAM – sabemos que um IAM é a morte tecidual decorrente da oclusão progressiva de uma artéria coronária. Portanto, é possível que um paciente tenha um eletrocardiograma sugestivo e não tenha IAM – ou o contrário: que tenha um eletrocardiograma normal, mas esteja sofrendo um IAM. Os testes diagnósticos são, portanto, índices falíveis de um construto diagnóstico: isso configura uma relação indexical.

Por outro lado, um paciente com depressão geralmente só pode ser assim diagnosticado se preencher os critérios diagnósticos conforme descritos no DSM-5: cinco critérios positivos, sendo no mínimo um deles a presença de humor triste (e/ou irritável para crianças e adolescentes) e/ou anedonia. Formalmente, não podemos diagnosticar uma pessoa com depressão se ela possuir apenas humor triste, aumento de apetite e insônia, mesmo que esses três sintomas sejam altamente prejudiciais à paciente. Tal definição se torna especialmente precária por não conhecermos a fisiopatologia da depressão: sendo assim, o TDM é definido pelos critérios

diagnósticos do DSM-5 tanto quanto os critérios diagnósticos do DSM-5 definem a doença. Isso configura uma relação constitutiva entre critérios diagnósticos e transtorno, argumentada como sendo problemática tanto pela história da seleção dos sintomas que fariam parte do TDM quanto pelo pouco entendimento atual sobre a etiopatologia do TDM. Uma relação indexical, como descrita acima, é mais coerente com a nossa limitação de conhecimento sobre a fisiopatologia do TDM e contempla a possibilidade de o DSM não estar incluir aspectos importantes da experiência do TDM na juventude. Além disso, as mudanças de critérios diagnósticos para diversas categorias nosológicas ao longo das diversas iterações do DSM sugere uma postura implicitamente indexical (Kendler, 2017).

2.5. O problema da validade

As questões filosóficas e históricas referentes à nosologia do TDM se estendem para a operacionalização do conceito. O DSM-III foi desenvolvido com a ideia de aumentar a confiabilidade das categorias diagnósticas em diferentes ambientes de clínica e pesquisa psiquiátrica. Porém, conforme revisto acima, são questionáveis as evidências para o sucesso desse objetivo. Parte do insucesso em se atingir confiabilidade no diagnóstico de TDM pode ser relacionado à questão da validade. Validade é o termo empregado para expressar o quão adequada é uma definição empírica para um conceito "real" (Kendler et al., 2012). Em termos mais práticos, validade é a característica de uma inferência que deve ser verdade se todas as suas premissas são verdadeiras (Kendell & Jablensky, 2003). Por exemplo: um paciente com humor deprimido, anedonia, diminuição do apetite, diminuição da concentração e fadiga, há mais de 15 dias e com prejuízo funcional significativo decorrente desses sintomas, tem TDM. Segundo Robins e Guze (Robins & Guze,

1970), um diagnóstico é válido quando ele preenche cinco critérios: descrição clínica; estudos laboratoriais, psicológicos e/ou radiológicos; delimitação de outros transtornos (i.e., critérios de exclusão); estabilidade de diagnóstico por meio de estudos longitudinais (i.e., continuidade homotípica); e estudos familiares. Apesar de não diretamente dependentes (Kendell, 1989), problemas de confiabilidade são estreitamente relacionados a problemas de validade – se a métrica que estamos utilizando não mede o construto que estamos nos propondo a medir, é pouco provável que ela seja confiável em medir sempre o mesmo atributo. Para a determinação da confiabilidade de um diagnóstico, são utilizados testes ou escalas que têm pressupostos filosóficos do que está sendo medido. Para a determinação do diagnóstico de depressão, parte-se, portanto, do pressuposto que sabemos o que é e/ou que o TDM se limita aos nove sintomas presentes no DSM. Na raiz do nosso entendimento atual sobre o transtorno depressivo está a ideia de que o TDM existe como uma entidade distinta com uma ou algumas causas específicas que é responsável principal pela origem e variação dos sintomas depressivos. Essa é uma ideia que pode ser encarada como ambiciosa (Borsboom et al., 2018; Kendler et al., 2011). A validade do construto TDM imagina que o transtorno se comporta como "latente", sendo ele o responsável principal pela variação dos sintomas.

2.6. Modelos psicométricos dos transtornos mentais

2.6.1 Modelo latente

As doenças psiquiátricas são tipicamente consideradas como causadas por um fator ou entidade latente que causa os sintomas de determinada doença, tal qual a bactéria *Pneumococcus pneumoniae* causa os sintomas de uma pneumonia bacteriana. No modelo latente, os sintomas (medidas observáveis) são indicadores

que se correlacionam por compartilharem uma causa comum: o construto latente, variável não-observável que causa e é responsável pela variação dos sintomas (Brown, 2015). Ou seja, os sintomas de humor triste, anedonia, dificuldade de concentração e fadiga co-ocorrem por serem causadas pelo mesmo construto latente subjacente, a variável latente "depressão". Se a variável latente "depressão" for extinta, os sintomas deixarão de se correlacionar.

Figura 1: Modelo latente do transtorno depressivo maior.
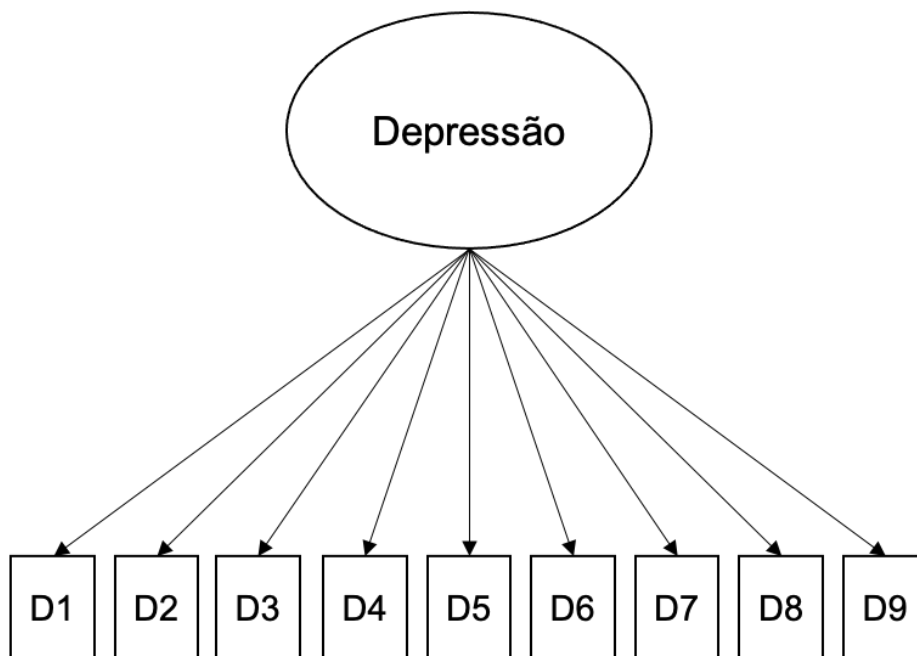
Formatos ovais representam variáveis latentes, enquanto quadrados representam variáveis observáveis. D1 a D9: sintomas de depressão.

Análises fatoriais são os modelos estatísticos mais comuns para a avaliação de variáveis latentes. Estas análises dividem a variância de cada indicador em variância comum, explicada pela variável latente; e variância individual, um misto de variâncias única ao indicador e aleatória. As *análises fatoriais confirmatórias* (CFA) são modelos estatísticos que, baseados em consolidação teórica prévia, soluções fatoriais que avaliam o quão bem uma (ou mais) variável latente explica a variância

de dado conjunto de itens em determinada amostra. Uma CFA é, portanto, uma forma usual de avaliar a validade interna de um construto – por exemplo, se hipotetizamos 20 itens de uma escala de sintomas depressivos de fato avaliam o construto latente "depressão", conduz-se uma CFA para avaliar a quão apropriada é essa hipótese. Dois aspectos definem a adequação de uma CFA à amostra: as *cargas fatoriais*, o quanto a variância de cada indicador é explicada pela variação do construto latente; e os *índices de ajuste*, valores matemáticos com limites que indicam essa adequação. Os índices de ajuste mais comuns são o *root mean square error of approximation* (RMSEA)*,* o *comparative fit index* (CFI)*,* e o *Tucker–Lewis index* (TLI) (Xia & Yang, 2019). Pontos de corte tradicionais da literatura psicométrica são de RMSEA ≤0.06; CFI ≥ 0.95; e TLI ≥ 0.95 (Hu & Bentler, 1998). Uma propriedade importante dos modelos de CFA é que os indicadores são tipicamente fixados; ou seja, um indicador não pode formar dois fatores concomitantemente.

Tipicamente, as CFA buscam avaliar a dimensionalidade de determinado construto – se o construto latente "depressão", por exemplo, é unidimensional ou multidimensional. Portanto, se uma escala de sintomas depressivos tiver índices de ajustes sugestivos de unidimensionalidade, diz-se que a escala reflete apenas um construto, o construto "sintomas depressivos". Por outro lado, se ela for multidimensional, diz-se que a escala reflete múltiplos construtos – sintomas somáticos, sintomas cognitivos, sintomas de suicidalidade, etc. Muito usados no campo dos estudos de inteligência, modelos chamados de bifatoriais (Reise, 2012) contemplam ambas as possibilidades ao sugerir que uma avaliação de sintomas depressivos pode medir um fator latente geral ("depressão") e outros sub-fatores que explicariam a variância não explicada pelo fator geral. Além da dimensionalidade, avalia-se o conceito de invariância de medida da escala – como a escala se comporta

em diferentes grupos populacionais. Avaliações típicas de invariância de medida envolvem sexo (diferença de ajuste da escala para meninos e meninas) e temporalidade (adequação de como a escala é respondida ao longo do tempo). Há grande divergência na literatura psicométrica sobre a adequação das escalas dimensionais de sintomas depressivos visto que múltiplas avaliações questionam tanto a presença de unidimensionalidade, sugerindo uma potencial falha conceitual na construção das escalas e/ou na nossa interpretação dos seus resultados (Fried, van Borkulo, et al., 2016; Reise et al., 2013; Shafer, 2006).

Figura 2: Modelo latente bifatorial hipotético do transtorno depressivo maior.
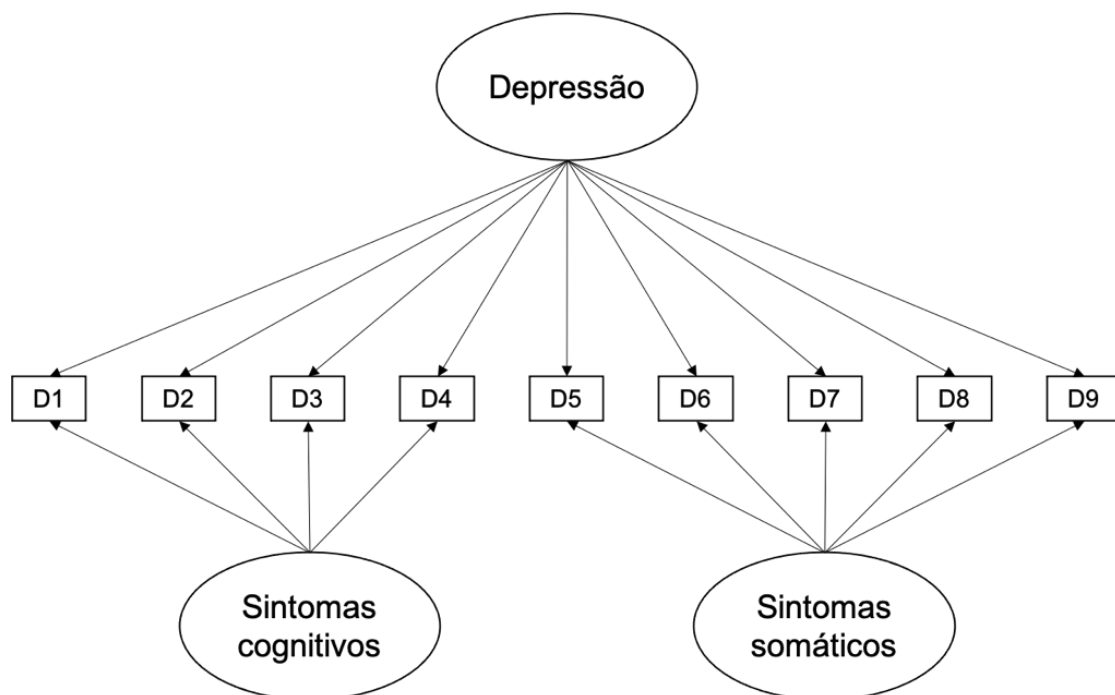
Formatos ovais representam variáveis latentes, enquanto quadrados representam variáveis observáveis. D1 a D9: sintomas de depressão.

Sendo assim, o modelo latente considera sintomas de depressão como indicadores passivos de um construto subjacente "depressão". Essa perspectiva considera que os sintomas não serão correlacionados quando a variável latente for

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estatisticamente controlada. Fundamental para a discussão proposta nesta tese, o modelo latente considera sintomas como medidas observáveis permutáveis – a presença de um ou outro sintoma é igualmente importante para a definição clínica categórica do TDM (Fried & Nesse, 2015). Isso é conhecido como o pressuposto da equivalência dos sintomas. Da mesma maneira, somas totais de instrumentos para a avaliação dimensional de sintomas depressivos como a Patient Health Questionnaire – Adolescent Version (PHQ-A) ou a Center for Epidemiological Studies – Depression Scale – Revised (CESD-R) priorizam o número e não a qualidade dos sintomas para a estimação de gravidade do transtorno – se um sintoma inespecífico como fadiga for presente, ele tem o mesmo valor de um mais preditivo de desfechos negativos como ideação suicida.

2.6.2 Modelos de rede

Como exposto nos parágrafos anteriores, o modelo médico aplicado à saúde mental postula que há uma causa para os sintomas de determinada doença – se um paciente tem humor triste, anedonia, dificuldade de concentração, fadiga e lentificação psicomotora, ele tem então o diagnóstico de depressão. Sendo assim, uma porção considerável de recursos humanos e financeiros das últimas décadas tem sido dedicada à busca de "marcadores biológicos" que indiquem tal origem. No entanto, a procura por alterações que comprovem bases biológicas da depressão tem se confrontado com tamanhos de efeito pequenos (Borsboom et al., 2018; Howard et al., 2019; Paulus & Thompson, 2019), que pouco explicariam um fenômeno de tal magnitude e complexidade psicossocial como o da depressão maior. Além disso, estudos de vias genéticas, cerebrais e inflamatórias do transtorno depressivo maior pouco encontram marcadores específicos da doença, mas sim evidências mais

robustas de achados transdiagnósticos entre diversas categorias nosológicas (Gillan & Seow, 2020). Ainda, o modelo latente pode ser visto como, em certo grau, tautológico – sabemos que um paciente tem TDM por apresentar sintomas de depressão, ao mesmo tempo que sabemos que ele tem sintomas de depressão por ter TDM. Portanto, pesquisadores têm questionado o paradigma central do modelo médico – o de que *um fator causal* é determinante para o desenvolvimento da doença psiquiátrica.

Apesar de o pressuposto da equivalência de sintomas ser fundamental para a construção teórica dos modelos latentes, a experiência clínica com pacientes vai contra tal pressuposto – na visão clínica, parece óbvio que um sintoma como suicidalidade seja mais importante para a avaliação da gravidade do fenômeno da depressão do que outro como dificuldade de concentração; igualmente, parece fazer sentido um paciente apresentar fadiga e dificuldade de concentração caso apresente problemas de sono. No entanto, tanto o DSM-5 quanto a maioria das escalas dimensionais de avaliação de sintomas, como a PHQ-9 ou a CESD-R, avaliam que a presença e não a qualidade dos sintomas é primordial para a definição da presença ou ausência do diagnóstico de depressão.

Os modelos de rede são habitualmente usados no campo das ciências sociais como uma série de técnicas que compartilham uma perspectiva metodológica comum: a de que os fenômenos sociais podem ser interpretados como redes altamente interligadas e podem, assim, sugerir que as estruturas sociais são diretamente derivadas das variadas relações entre as entidades que compõe a rede (Chiesi, 2015). No campo da psicopatologia, o modelo de redes vem crescendo rapidamente de popularidade a partir dos estudos do psicometrista Denny Borsboom (Borsboom et al., 2016; Borsboom & Cramer, 2013). A perspectiva de rede pressupõe

que sintomas de um transtorno e seus correlatos (fatores sociais, ambientais e biológicos) constroem redes interconectadas em que cada elemento influencia direta e individualmente no próximo (Borsboom & Cramer, 2013). Ao contrário do modelo latente, no modelo de rede os sintomas são ingredientes ativos da psicopatologia em questão. Essa mudança de paradigma se torna fundamental se hipotetizarmos que, quando olhamos para os sintomas como alvos principais de investigação científica, abre-se a possibilidade de diferentes intervenções terapêuticas: em vez de uma intervenção psicofarmacológica ou psicoterápica com ênfase em "depressão", a intervenção passa a ser voltada para o sintoma de dificuldade de sono ou anedonia (Blanken et al., 2019). De fato, algo semelhante já é realizado na prática clínica, como as intervenções de ativação comportamental (McCauley et al., 2016).

Fundamental para o modelo de rede e suas potenciais aplicações práticas é o conceito de centralidade *(centrality),* que diz respeito ao quão inter-correlacionado cada item de uma rede é. Em aplicações clássicas sociológicas dos modelos de rede, usa-se os conceitos de *strength centrality (*a soma total das correlações de um item da rede)*, betweenness centrality (*o quanto um nó está no caminho entre outros nós) e *closeness centrality (*o quão perto um nó está dos outros nós da rede). No estudo de redes de psicopatologia, no entanto, são utilizados principalmente a *strength centrality* e a *expected influence centrality* (a soma total em módulo de todas as correlações de um item da rede) devido a estabilidade estatística dessas medidas (Robinaugh et al., 2016). É possível que sintomas mais centrais para a estruturação da rede de determinada doença sejam sintomas-alvo para a determinação. Dessa maneira, cada elemento da rede reforçaria o elemento seguinte: se um paciente tem insônia, é possível que ele tenha fadiga; tendo fadiga, é possível que tenha dificuldade

de concentração; e tendo dificuldade de concentração, é possível que falhe em uma tarefa importante e tenha humor deprimido.

Mesmo que aplicações clínicas do modelo de rede ainda estejam algo distantes do seu uso na prática psiquiátrica (David et al., 2018; Epskamp, van Borkulo, et al., 2018), os modelos de rede trazem a oportunidade de examinar relações únicas entre sintomas. Dois estudos recentes ilustram a utilidade das análises de rede para a compreensão da fenomenologia da depressão. Fried e colegas mostraram em análise secundária de dados de 3,463 adultos com diagnóstico de depressão avaliadas no Sequenced Treatment Alternatives to Relieve Depression (STAR*D), um dos maiores ensaios clínicos sobre a eficácia dos tratamentos para depressão, que, na escala de 30 itens Inventário de Sintomas Depressivos (IDS), sintomas contemplados explicitamente pelo DSM não foram mais graves, variáveis ou centrais na rede de sintomas depressivos do que sintomas não explicitamente contemplados pelo DSM (Fried, Epskamp, et al., 2016). Em estudo de metodologia semelhante, Kendler e colegas apresentaram uma análise de rede dos sintomas de 5,952 mulheres chinesas com o diagnóstico de depressão por meio de entrevista aplicada por psiquiatras do Composite International Diagnostic Interview (CIDI). Nesse estudo, os dois sintomas mais interconectados da rede foram alterações de sono, classificado como "sintoma DSM"; e desesperança, classificado como "sintoma não-DSM" (Kendler et al., 2018). Assim, os autores de ambos os estudos concluíram que os sintomas contemplados e não contemplados pelo DSM fazem parte de uma rede altamente interconectada de sintomas, sem segregação explícita entre os sintomas incluídos ou não no DSM como critérios diagnósticos para TDM.

Figura 3: Modelo de rede hipotético do transtorno depressivo maior.
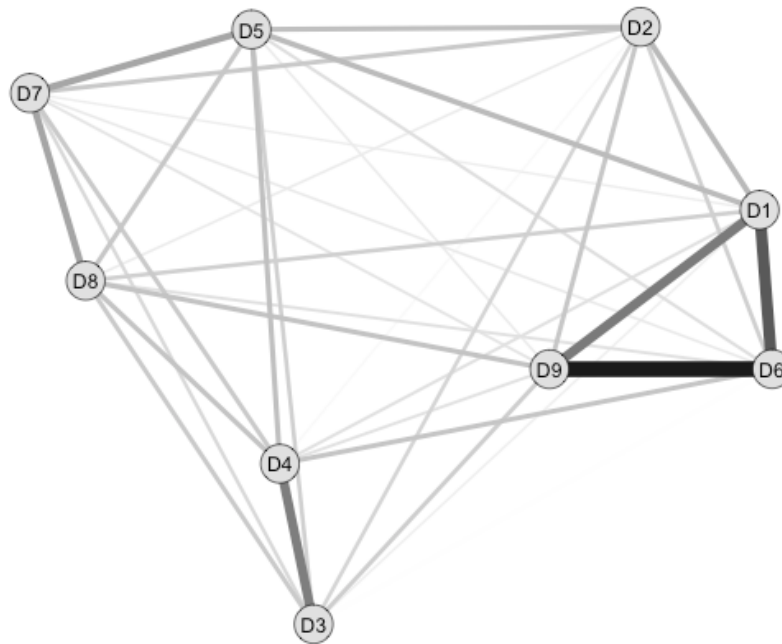
D1 a D9: sintomas de depressão. A espessura da linha e a proximidade entre círculos representa a força da associação entre sintomas.

2.6.3 Conceptualização estatística dos modelos de rede

Ao usar a linguagem matemática da teoria de gráficos e pressupostos da álgebra de matrizes (Epskamp, Borsboom, et al., 2018), a avaliação dos modelos de redes pode ser feita pela chamada análise de redes (*network analysis*). As redes são formadas por nós (*nodes*; variáveis) que são conectados por meio de arestas (*edges*). As arestas correspondem a correlações parciais em uma matriz de correlações em que todos as variáveis são correlacionadas entre si, ajustando para o efeito de todas as outras (por exemplo: item A correlacionado ao item B, ajustando para a influência do item C nesta correlação). Para evitar efeitos de testagem múltipla, uma taxa L1 (ou *lasso*; *least absolute shrinkage and selection operator*) pode ser imposta aos coeficientes de correlação. Com essa taxa, arestas com pequenas correlações são definidas como zero, encontrando assim a rede mais parcimoniosa e ajustada para testagem múltipla (Epskamp & Fried, 2016). A taxa L1 é influenciada pelo pesquisador

ao definir um parâmetro *lambda* de ajuste – quanto mais alto o lambda, mais rigorosa será a taxa L1 sobre as correlações parciais. Apesar disso, mais recentemente ter a necessidade da aplicação da taxa L1 em análises de rede com variáveis de diferente natureza (sintomas, fatores de risco e variáveis biológicas) vem sendo questionada (Moriarity et al., 2021; Williams et al., 2019).

As análises de rede são altamente influenciadas pelo número de variáveis em cada rede e pelo tamanho amostral disponível. Sendo assim, torna-se fundamental estudar a estabilidade dos parâmetros calculados nas redes. Conforme recomendado na literatura, são realizadas análises de *bootstrap* para calcular intervalos de confiança ao redor das estimativas de correlação encontradas (Epskamp, Borsboom, et al., 2018). Para as análises de centralidade, usa-se um procedimento de *bootstrap case-drop,* que realiza redução progressiva do tamanho amostral até a obtenção de intervalo de confiança de 95% de uma correlação de pelo menos 0.7 com os coeficientes de centralidade originais (Epskamp, Borsboom, et al., 2018). Avalia-se então o coeficiente de estabilidade (CS (cor=0.7)), que deve ser ao redor de 0.5.

Além disso, existe a possibilidade de sobreposição topológica de variáveis da rede que possam ser altamente correlacionadas – por exemplo, um item questionando sobre "humor triste" e outro sobre "humor deprimido". Sendo assim, usamos o procedimento *goldbricker* para avaliar a redundância de nós e a possibilidade de redução de nós (Jones, 2020). Para encontrarmos nós que possam ser altamente correlacionados mas não redundantes, procuramos grupos (*clusters*) de itens usando o algoritmo *walktrap* (Golino & Epskamp, 2017).

2.7. Os modelos de rede como alternativa baseada no pluralismo

Como descrito anteriormente, a adoção do modelo médico de doença levou a intensa procura por explicações mono/oligocausais para os transtornos psiquiátricos

(Kendler, 2019). No entanto, mesmo doenças clínicas com fisiopatologia mais bem esclarecida como o infarto agudo do miocárdio são modernamente entendidas como multifatoriais – a oclusão coronariana decorre de aterosclerose, aumento de níveis pressóricos, atividade inflamatória aumentada, etc. Isso sugere que mesmo linhas de pesquisa fundamentalmente biológicas dentro da psiquiatria potencialmente se beneficiariam de perspectivas plurais ao buscar explicações multifatoriais para os transtornos mentais (Smoller et al., 2019). Em artigo de 2019, Isvoranu e colegas exemplificaram as análises de rede como possível avenida de integração dessa multifatorialidade ao avaliar a relação de sintomas psicóticos e depressivos com escore de risco poligênico (PRS) (Isvoranu et al., 2019). Hilland e colegas mostraram a possibilidade da aplicação da perspectiva de rede no estudo de associações de estruturas cerebrais com sintomas específicos de depressão, usando a ativação de determinadas estruturas anatômicas como nós na rede (Hilland et al., 2020).

2.7.1. Aplicando análises de rede à hipótese inflamatória do TDM

A imunologia dos transtornos mentais, em específico vias inflamatórias periféricas, é uma das principais linhas de pesquisa que busca esclarecer as alterações neurobiológicas do TDM (Dooley et al., 2018; Enache et al., 2019; Osimo et al., 2020). Existe evidência meta-analítica mostrando elevação de marcadores inflamatórios periféricos, sobretudo interleucina-6 (IL-6) e proteína C-reativa (PCR), em pessoas com depressão em comparação a controles (Dowlati et al., 2010; Mitchell & Goldstein, 2014; Osimo et al., 2020). O TDM é hipotetizado como um estado de inflamação crônica e de baixa intensidade, com impacto dos marcadores periféricos por meio de efeitos no sistema nervosa central, além de alterações endocrinológicas (Hodes et al., 2016; Pace & Miller, 2009). Esse estado pró-inflamatório teoricamente

deriva de exposição a situações psicossociais estressantes como bullying, maus tratos, dificuldades socioeconômicas ou hiper-reatividade a estímulos ambientais percebidos como ameaçadores (Berk et al., 2013). A responsa inflamatória de baixa intensidade induz ao chamado comportamento de doença, síndrome que corresponde a mudanças comportamentais, físicas e motivacionais que acompanham estados inflamatórios e/ou infecciosos (van Eeden et al., 2020). Os sintomas da síndrome de comportamento de doença têm sobreposição importante com alguns sintomas depressivos como anedonia, anorexia, diminuição da energia e lentificação psicomotora (Haroon et al., 2012). No entanto, a IL-6 e a PCR são marcadores não-específicos de inflamação aguda – a PCR é um marcador genérico da fase inflamatória mais aguda que tem sua produção estimulada por uma molécula específica de IL-6 (Hodes et al., 2015).

Mesmo assim, a ligação entre inflamação periférica e depressão também está sujeita a heterogeneidade. Estudos meta-analíticos de estudos caso-controle em crianças e adolescentes falharam em identificar diferenças significativas de níveis periféricos dos dois marcadores inflamatórios supracitados (D'Acunto et al., 2019). Em adultos, a aplicação de análises focadas em sintomas específicos mostrou que existe associação diferencial de marcadores inflamatórios com alguns sintomas de depressão (Duivis et al., 2013; Fried et al., 2019; Jokela et al., 2016; Moriarity et al., 2020). Nesses estudos, há uma tendência de que sintomas somáticos (fadiga, alterações de sono e apetite, etc.) estejam mais conectados a marcadores de inflamação periférica. É importante considerar também que parte dessas relações diferenciais pode ser influenciada por confundidores como índice de massa corporal, uso de substâncias e tabaco, nível socioeconômico e comorbidades psiquiátricas (Horn et al., 2018). De fato, um estudo recente mostrou que há atenuação importante

das relações entre soma total de uma escala dimensional de escore depressivo e marcadores inflamatórios quando se considera o papel de covariáveis como as acima descritas (Fried et al., 2019). Consequentemente, é fundamental aplicar técnicas múltiplas de análise de dados que considerem simultaneamente sintomas e covariáveis biopsicossociais para avaliar a qualidade dessas associações e evitar mascarar informações potencialmente importantes (Fried & Nesse, 2015; Moriarity & Alloy, 2020).

2.7.2. Otimizando o entendimento do TDM em jovens ao integrar complexidade

Considerar as limitações inerentes ao atual estado-da-arte da pesquisa em psicopatologia é fundamental para avançar nosso entendimento de doenças que causam tamanho prejuízo funcional a quem delas sofre. Em artigo de 2020, Chevance e colegas mostraram o descompasso entre as prioridades de pacientes com TDM e profissionais da saúde, com diferentes níveis de importância para diferentes aspectos da psicopatologia (Chevance et al., 2020). Em termos de transculturalidade, Haroz e colegas mostraram, em revisão sistemática incluindo 138 estudos qualitativos de 76 diferentes nacionalidades/etnias, que apenas 7 dos 15 sintomas depressivos mais mencionados estão incluídos nos critérios diagnósticos do DSM-5 para TDM (Haroz et al., 2017), com variações expressivas em diferentes países. Em comentário recente, Paulus e Thompson alertaram para o "novo normal" da pesquisa em psiquiatria biológica – os desafios e oportunidades de pequenos tamanhos de efeito (Paulus & Thompson, 2019). Os autores concluem que, assim como a evidência de outros campos da medicina indica, explicações mono ou oligocausais para os transtornos psiquiátricos são pouco prováveis de serem encontradas. Como exemplo, um estudo recente na revista *Nature Neuroscience* mostrou, em meta-análise do

genoma da depressão com dados de mais de 800.000 indivíduos (246,363 casos), que escores de risco poligênicos explicam até 3.2% da variância na biologia do fenótipo depressivo (Howard et al., 2019). O entendimento dos transtornos psiquiátricos, em especial o TDM, de maneira complexa, com múltiplos fatores de risco biológicos, psicológicos e sociais influenciando e sendo pelos sintomas depressivos (Kendler et al., 2011), pode ser uma alternativa realista, apesar de ambiciosa, para aumentar o entendimento da depressão em jovens.

Figura 4: Modelo hipotético de relações diferenciais entre sintomas depressivos e covariáveis biopsicossociais
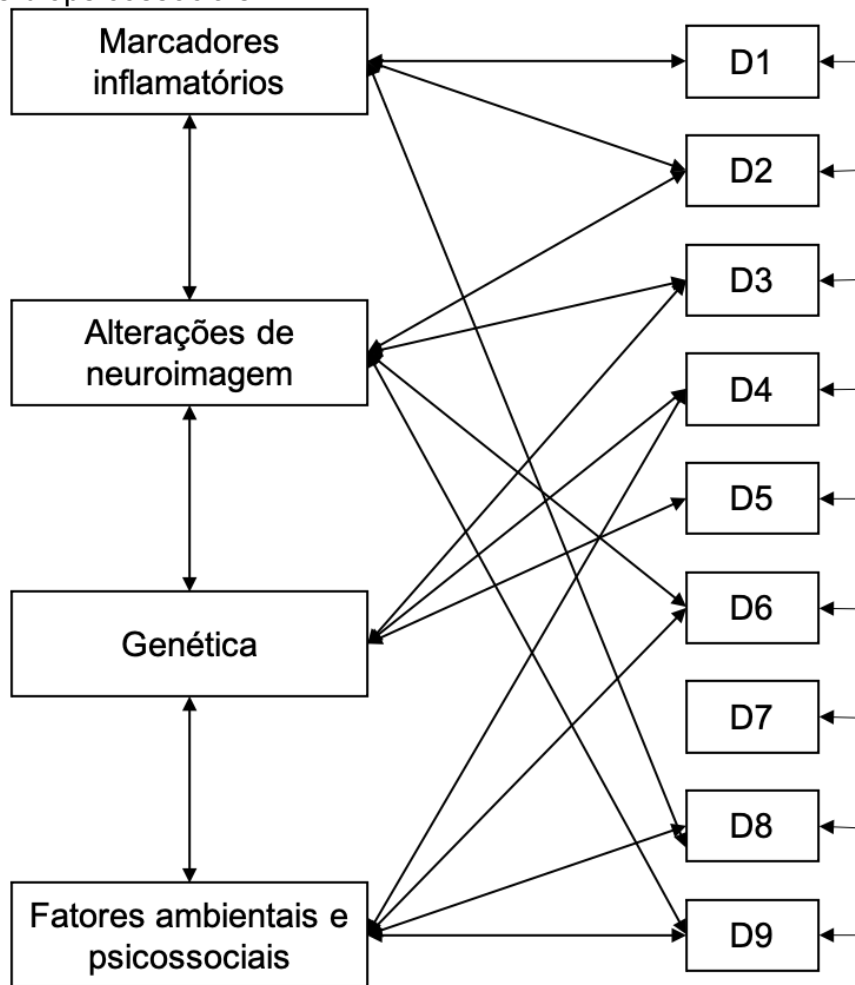
D1 a D9: sintomas de depressão. Setas bidirecionais representam relação de mutualidade. Retângulos representam variáveis observáveis.

3. OBJETIVOS

Objetivo geral

Este trabalho tem como objetivo avaliar a apresentação do transtorno depressivo maior na adolescência e na transição para a vida adulta usando medidas categóricas, dimensionais e a nível de sintomas. Para isso, implementamos métodos estatísticos do campo da epidemiologia clássica, modelos psicométricos latentes e análises de rede para avaliação de relações específicas dos sintomas depressivos entre si e com variáveis biopsicossociais.

Objetivos específicos

1. Estudar a apresentação clínica do TDM na transição adolescência-vida adulta numa coorte populacional de um país de média renda.

2. Avaliar associações longitudinais e transversais de sintomas depressivos com marcadores inflamatórios periféricos.

    2.1. Avaliar a influência de covariáveis psicossociais na associação entre sintomas depressivos e marcadores inflamatórios periféricos pela perspectiva das análises de rede.

3. Estudar a apresentação do TDM na adolescência em duas amostras recrutadas em ambiente escolar.

    3.1. Avaliar a importância de itens representando critérios contemplados e não contemplados no DSM.

4. HIPÓTESES

- A epidemiologia do TDM avaliada aos 22-23 anos em uma coorte populacional em país de média renda será semelhante a da literatura de países de alta renda.

- Sintomas depressivos serão longitudinal e transversalmente associados a marcadores inflamatórios periféricos.

- Covariáveis psicossociais terão influência importante na associação entre sintomas depressivos e marcadores inflamatórios periféricos.

- Avaliar as associações entre sintomas específicos do TDM revelará correlações significativas para o entendimento nosológico da depressão na adolescência.

- Itens representando critérios do DSM e itens não contemplados no DSM serão igualmente importantes em uma rede de sintomas depressivos.

5. CONSIDERAÇÕES ÉTICAS

Todos os estudos incluídos nesta tese foram aprovados pelos respectivos Comitês de Ética em Pesquisa antes da coleta e análise de dados. Os estudos #1 e #2 incluíram amostras da Coorte de Nascidos Vivos de Pelotas de 1993. Todos os participantes da Coorte de Nascidos Vivos de Pelotas de 1993 forneceram consentimento informado por escrito antes da inclusão no estudo. O estudo #3 foi aprovado pelo Comitê Nacional de Ética em Pesquisa (CONEP; CAAE 50473015.9.0000.5327) e incluiu amostras de escolas públicas de Porto Alegre, coletadas entre 2016 e 2019. Todos os participantes das amostras do estudo #3 forneceram termos de dissentimento no caso de não concordância com a participação. Os dados foram desidentificados e apenas os dados brutos essenciais para as análises foram compartilhados com os coautores.

Todas as análises dessa tese foram conduzidas no software livre *R*, versão 3.6.1 (R Core Team, 2019), usando principalmente os pacotes *psych*, *mice, lavaan, qgraph*, *bootnet*, *igraph*, e *networktools* (Buuren & Groothuis-Oudshoorn, 2011; Epskamp, Borsboom, et al., 2018; Epskamp et al., 2012; Jones, 2020; Rosseel, 2012). O código para todas as análises e a geração das figuras correspondentes está em anexo ao final do documento. Todas as análises foram conduzidas e são de responsabilidade do candidato autor da tese.

6. Article #1

DEPRESSION IN A YOUTH POPULATION-BASED SAMPLE FROM BRAZIL: PREVALENCE AND SYMPTOM STRUCTURE

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ABSTRACT

Background: We aimed to examine the occurrence of major depressive disorder (MDD) in a population-based youth sample, assessing both categorical and dimensional presentations of the disorder and its clinical and sociodemographic correlates.

Methods: We analyzed cross-sectional data from the latest assessment of the 1993 Pelotas Birth Cohort (n = 3,780), a population-based study from Brazil that followed individuals up to age 22 years. We estimated point-prevalence for categorical diagnosis of MDD and comorbid diagnoses using DSM criteria in a structured interview by trained psychologists. Dimensional symptomatology was assessed with the Brazilian Portuguese version of the Center for Epidemiological Studies–Depression Scale–Revised (CES-D-R).

Results: Point-prevalence of a current unipolar major depressive episode was 2.85% (95%CI 2.37-3.43%). The CES-D-R showed a mean of 9.20 (SD=9.72), with an area under the curve of 0.93 (95%CI 0.91 to 0.95) for the categorical diagnosis of MDD using a cutoff point of 16. Sad mood and somatic symptoms were the most frequent, and also had lower levels of latent values required for endorsement. Sad mood and anhedonia items were the most central items in the network structure.

Conclusions: In a population-based sample of youths from a middle-income country, MDD prevalence estimates and comorbidity profile were consistent with previous global literature. A focus on symptoms might advance our understanding about MDD among youths by disentangling the heterogeneity of the disorder.

Keywords: depression; prevalence; symptom-level analysis; youth; epidemiology.

INTRODUCTION

Major depressive disorder (MDD) is a leading cause of burden of disease among youth (Ferrari et al., 2013), with high incidence in adolescence and early adulthood (Avenevoli et al., 2015). As a period of intense psychosocial (Sussman and Arnett, 2014) and neurobiological maturation (Giedd et al., 2008; Marsh et al., 2008; Thapar et al., 2012), the adolescence-early adulthood transition is a sensitive period that has attracted increased research interest (Cuijpers et al., 2020). Early identification of MDD during this period is crucial for alleviating the clinical and functional repercussions of depression, which may be cumulative over time (Davey and McGorry, 2019). Although a proportion of individuals will have only one or two depressive episodes in life, for a significant proportion MDD will manifest as a chronic and recurrent condition, with cumulative prevalence estimates reaching up to one in four individuals over their lifetime (Kessler et al., 2001; Lewinsohn et al., 1998).

The identification of MDD in youth is, however, complicated by the disorder's highly heterogeneous symptomatology, with up to 52 different symptoms in commonly used scales (Fried, 2017a) and up to 227 possible symptom combinations to meet the current DSM-5 criteria for diagnosis (Zimmerman et al., 2015). Such heterogeneity is also found in the neurobiological characteristics, risk factors, clinical presentation, and prognosis of MDD. Accordingly, a characterization of MDD as a combination of particular symptom patterns (Fried, 2017b, 2015; Fried and Nesse, 2015) has been proposed as a better paradigm than that of MDD as a single, binary condition. Despite the DSM's binary approach to mental illness being arguably relevant for decision-making in clinical practice (Ruscio, 2019), the call for a better understanding of psychiatric symptomatology beyond categorical criteria has gained momentum in recent years (Patel, 2017).

The use of sum-scores to diagnose MDD, as often done in clinical studies, is limited by the fact that a large percent of patients does not share specific symptomatology (Fried and Nesse, 2015). Using sum-scores of depression scales entails assigning similar weights to all symptoms – for example, fatigue, a non-specific symptom, would contribute as much as anhedonia, recognized as a major risk factor for treatment non-response and negative outcomes (McMakin et al., 2012), which may lead to less useful assessments. Beyond the deleterious impacts of full-blown depressive episodes, the presence of symptoms without a full diagnosis has also been associated with impaired functioning and suicide risk (Balázs et al., 2013), as well as increased risk of a depressive episode later in life (Bertha and Balázs, 2013). This suggests the need for a dimensional (Davey and McGorry, 2019) approach to depression – with possible implications for prevalence estimates.

Studies such as the National Comorbidity Survey – Adolescent Supplement (11% lifetime prevalence in late adolescence) (Avenevoli et al., 2015), the National Comorbidity Survey – Replication (15.4% lifetime prevalence in the 18-29 age range) (Kessler et al., 2005) and the World Mental Health Survey International College Student initiative (4.5-7.7% 12-month prevalence in the 18-22 age range) (Auerbach et al., 2018) have provided important information on depression's lifetime- and point-prevalence in adolescence and early adulthood. However, less is known about characteristics of depressive symptomatology on this transition age range on population-based samples from low- and middle-income countries (LMICs) (Asselmann et al., 2018; Kieling et al., 2011; Mall et al., 2018). LMICs comprise the majority of the global youth population – even so, most of the literature on youth depressive disorders is based on high-income countries samples, with less coverage and information available on the characterization of MDD prevalence and

symptomatology from LMIC populations (Erskine et al., 2017). Therefore, with the current literature emphasizing the importance of transculturality (Guinart et al., 2019) and issues with the generalizability of psychological findings (Yarkoni, 2019), the study of MDD's prevalence in different contexts and cultures is an important step towards better understanding the condition's global impact. We studied a population-based youth sample from a middle-income country to determine the point-prevalence of MDD, as well as the prevalence, psychometric characteristics, and association among symptoms according to a dimensional measure.

METHODS

Sample description

In the present study we analyzed cross-sectional data from the 22 year-old follow-up assessment of the 1993 Pelotas Birth Cohort, an ongoing longitudinal study in which all children born in the city of Pelotas during the year of 1993 (5,249 individuals) were assessed at multiple timepoints until 22 years old. Our final sample size was 3,780 (76.26% retention rate from birth to 22 years old, Gonçalves et al., 2018). Further details on the cohort's design and methodology can be found elsewhere (Gonçalves et al., 2018; Victora et al., 2006) (Supplementary Materials, Figure S1). All participants provided written informed consent, and data was properly coded to ensure anonymity in database handling. The study had approval from the Ethics Committee of the Universidade Federal de Pelotas. The questionnaires used in this report are available at http://www.epidemio-ufpel.org.br/site/content/coorte_1993-en/questionnaires.php.

Measures

Psychiatric diagnoses

The Mini International Neuropsychiatric Interview (MINI) is a short structured diagnostic interview that explores major psychiatric disorders according to DSM-IV criteria. The validated Brazilian Portuguese version of the MINI (Amorim, 2000) was adapted to be aligned with DSM criteria (American Psychiatric Association, 2013) and administered to participants by trained clinical psychologists. Of note, in our adapted version of the MINI, we initially asked about the presence/absence of each cardinal symptom – sad mood or anhedonia – and subsequentially about the frequency of it. In accordance with DSM criteria, participants were only asked about accessory symptoms if at least one of the cardinal symptoms was reported as being present "most of the time." Because the DSM lists irritability as a possible cardinal symptom of depression in adolescents, participants were also asked about the presence and frequency of it, without, however, including it in the diagnostic algorithm. Moreover, to reflect DSM criterion B, we also included an additional question on impairment, inquiring participants on how much impairment the reported depressive symptoms caused in their life. The options for answer were none, mild, moderate, or severe. Following previous analyses (Matte et al., 2015), the presence of clinical impairment was operationally defined as having a score of moderate or severe. In the present study, we focused on the prevalence of current (i.e., in the past 15 days) unipolar major depressive episode (MDE). Participants were also assessed for comorbid diagnoses: antisocial personality disorder (APD); attention-deficit/hyperactivity disorder (ADHD); generalized anxiety disorder (GAD); post-traumatic stress disorder (PTSD); and social anxiety disorder (SAD). In alignment with DSM criterion E, all participants who had a lifetime episode of mania – meeting therefore criteria for bipolar disorder (BD) diagnosis – were not considered as unipolar MDE in our analyses.

Dimensional measure of depressive symptomatology

The Center for Epidemiological Studies – Depression Scale – Revised (CES-D-R, Eaton et al., 2004) is a revised version of the CES-D (Radloff, 1977) consisting of 20 items on the symptomatology of MDD. The CES-D-R has five Likert-style response options: "not at all or less than 1 day"; "1–2 days"; "3–4 days"; "5–7 days"; and "nearly every day for 2 weeks". The CES-D-R is a freely available (CESD-R: Center for Epidemiologic Studies Depression Scale Revised Online Depression Assessment), commonly used self-reported depression measure with good indices of validity and reliability in clinical and population-based samples (Van Dam and Earleywine, 2011). We performed the process of translation and cultural adaptation of the scale following procedures recommended by the Translation and Cultural Adaptation Group of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (see Supplementary Material S2 for further details on the process). In the present sample, 4.7% of participants had missing values on the CES-D-R; therefore, we conducted multiple imputation with the *mice* (Buuren and Groothuis-Oudshoorn, 2011) R package. There were no significant differences in the imputed sample and the whole sample regarding sociodemographic or general medical variables.

Sociodemographic and general medical variables

Socioeconomic status was assessed using the wealth index, a measure of a household's cumulative living standard (Howe, 2009). Education was measured as the number of complete years of formal schooling. Current smoking was defined as a positive answer to the questions "Have you ever had the habit of smoking?" and to

"Do you still smoke every day?". Alcohol consumption was assessed through the AUDIT questionnaire (Williams, 2014), a 10-item screening tool developed by the World Health Organization (WHO) to assess alcohol consumption, drinking behaviors, and alcohol-related problems (National Institute on Drug Abuse, 2018). Body mass index (BMI) was measured as weight mass divided by the square of height and is presented as kg/m^2. Participants were also asked if they had ever received a diagnosis of hypertension, asthma, and/or diabetes. Participants were excluded if they were unable to answer the questionnaires due to low IQ (n=19), muteness/deafness (n=5) or illiteracy (n=6).

Statistical analysis

We calculated mean and standard deviations for continuous variables, as well as frequencies and percentages for categorical variables. We conducted Mann-Whitney U and χ^2 tests to compare people diagnosed with current MDD vs. those without MDD on continuous and categorical variables respectively. We calculated the area under the receiver-operating characteristic (AU-ROC) curve for evaluation of CES-D-R cut-off values based on the MINI diagnosis of MDD, as well as positive predictive value (PPV) and negative predictive value (NPV) derived from the AU-ROC cutoff.

Confirmatory factor analysis

For the CES-D-R factor structure analysis, we performed Confirmatory Factor Analysis (CFA) using a unidimensional structure as well as a previously suggested two-factor structures (Van Dam and Earleywine, 2011) that separated symptoms into two factors, finding both solutions to be similarly robust. We considered a factor

loading of an absolute value >0.3 to be meaningful (Brown, 2015). In order to encompass the unidimensional and multidimensional solutions, we also conducted bifactor model analysis to ensure validity and reliability of the correlated model subscales, as it can suggest unidimensionality even in the presence of multidimensionality (Reise et al., 2013). The best-fitting solution was then used to extract item thresholds – analogous to item response theory's item difficulty, item thresholds are a measure of necessary latent trait to endorse one option over another (e.g., once or twice a week over none or once in the last 15 days).

For reliability analysis, we calculated McDonald's omega (ω) (Revelle and Zinbarg, 2009), an estimate based on CFA and used to estimate the proportion of variance in the total scores attributable to all sources of common variance. Omega can be subdivided into omega hierarchical (ω_h), a measure of common variance explained by the general factor, and omega group (ω_g), a measure of reliability of each subscale. For fit indices, we followed the Hu and Bentler (Hu and Bentler, 1998) suggested cut-offs of the Comparative Fit Index (CFI) equal or greater than 0.95, and Root Mean Square Error of Approximation (RMSEA) equal to or smaller than 0.06. To measure invariance (how differently the scale behaves across groups and/or time) between sex, a delta CFI criterion of -0.01 (Cheung and Rensvold, 2002) was used.

Network analysis

We used the network analysis framework to study relationships between specific symptoms of depression. The network approach to psychopathology can be viewed as a complement to the traditional common cause model of depression (Borsboom and Cramer, 2013). However, despite promising advances in the use of longitudinal and intensive data, most studies (like our own) use cross-sectional data

to derive non-directed network structure and centrality estimates. Thus, the current network literature emphasizes element relations rather than causality (Fried and Cramer, 2017; Ryan et al., 2019).

We used network analysis as a descriptive tool. Connections between symptoms (edges) are estimated using L1-regularized partial correlation, in which all symptoms are regressed on each other controlling for the effect of all other symptoms. To control for multitesting, an L1-penalty is imposed on regression coefficients to balance goodness of fit and parsimony (also called the least absolute shrinkage and selection operator - *lasso*). Therefore, small edges are set to zero, which enables finding the sparsest (most parsimonious) network. Network estimation also allows for the study of symptom centrality – a measure of the associations each node exhibits with all other nodes. We focused our analysis on expected influence centrality, the sum of all (positive and negative) edge weights connected to a given node. A high expected influence means a node is highly connected to other nodes. As suggested in the network literature, we analyzed the correlation of node variance and expected influence centrality (the sum of absolute edge weights connected to a given node), given that a positive correlation may bias centrality estimates (Wasil et al., 2020) and conducted the *goldbricker* procedure to check for node redundancy (Jones et al., 2018). Because edge-weights and centrality estimates are inferred from multiple correlations and depend on sample size and number of nodes, we analyzed network accuracy by estimating confidence intervals around edge-weights with a bootstrapping procedure. Furthermore, we estimated centrality stability from a case-drop procedure by reducing sample size and re-estimating network centrality – if estimates remain similar after a 50% decrease in sample size, centrality is deemed stable (Epskamp et al., 2018).

All analyses were done in R with the *tidyverse*, *lavaan*, *qgraph*, and *bootnet* (Epskamp et al., 2018, 2012; Rosseel, 2012; Wickham et al., 2019) packages and are available on the Supplementary Materials.

RESULTS

Descriptive statistics

Our final sample included 3,780 participants (53.46% females). Sociodemographic, clinical and psychiatric comorbidities are presented in Table 1. The prevalence of a current unipolar major depressive episode (MDE) was 2.85% (95%CI 2.37% to 3.43%) – among females the prevalence was 4.16% (95%CI 3.37% to 5.12%); for males, 1.36% (95%CI 0.90% to 2.02%). The mean CES-D-R total score was 9.20 (SD=9.72) for the overall sample, and 31.96 (SD=13.29) for unipolar MDE current cases. Table 1 also shows descriptive averages and diagnostic frequencies for the overall sample, for participants without and for those with a current unipolar MDE. Comorbidity with other psychiatric diagnoses was high, especially for GAD (54.63%) and PTSD (27.78%).

----- INSERT TABLE 1 HERE ------

Categorical symptom prevalence

In the overall sample, among the three symptoms assessed using the adapted version of the MINI in all participants, irritability had the highest occurrence (51.37%), followed by sadness (38.67%) and anhedonia (11.19%). In terms of frequency, irritability was present "most of the time" in only 15% of those who endorsed the item – the same frequency was reported by 13% of individuals for sad mood and 23%, for

anhedonia. A total of 425 participants endorsed sad mood and/or anhedonia as being present "most of the time". The most commonly reported accessory symptom was fatigue (76%), while the least endorsed was morbid ideation (34%; see Supplementary Materials Table S3). Among the sub-sample of participants who met criteria for current unipolar MDE, however, sadness (99%) was virtually ubiquitous, followed by irritability (84%) and anhedonia (73%). In terms of frequency, amongst those with a current MDE, 85% reported sadness "most of the time", while 66% reported anhedonia and 49% reported irritability with the same frequency.

CES-D-R descriptive statistics

Figure 1 shows the prevalence and distribution of CES-D-R items (numeric values can be found on Supplementary Materials Table S4). As a result of the nature of the sample (population-based) and the timeframe investigated by the scale (past 15 days), CES-D-R total sum score and item distribution were right-skewed toward absence of symptoms (Supplementary Materials Figure S5). CES-D-R mean value was higher in females (mean=10.65; SD=10.71) than in males (mean=7.52; SD=8.11; t=9.95; p<0.001). "Trouble focusing on activities," "felt sad," and "slept more" were the most commonly endorsed items. This result was not changed when only participants without current MDD were considered (18.45% endorsing symptoms once or twice per week). "Slept more" (5.95%), "trouble focusing on activities" (5.69%), and "difficulty getting to sleep" (5.61%). "Trouble focusing on activities" (5.53%), "tired all the time" (5.29%), and "nothing made me happy" (5.21%) were the most common items reported as occurring "almost every day," while "wanted to hurt myself" and "felt a bad person" were the least common. ROC analysis revealed an area under the curve (AUC) of 92.8% (95%CI 90.5% to 95.1%) for an optimal total CES-D-R sum score cut-

off from the categorical diagnosis of current MDD of 16 with a sensitivity of 89.5% (95%CI 83.7% to 95.4%) and a specificity of 84.3% (95%CI 83.1% to 85.5%), as well as a PPV of 15% (95%CI 11.9% to 17.3%) and a NPV of 99.6% (95%CI 99.4% to 99.8%; see Supplementary Materials Figure S6 and Table S7).

----- INSERT FIGURE 1 HERE ------

Confirmatory factor analysis

The unidimensional solution had suboptimal fit indices (CFI=0.911, TLI=0.900, RMSEA=0.09), while the two-factor correlated model fitted the model better (CFI=0.946, TLI=0.940, RMSEA=0.07). Overall, the bifactor model with two subfactors had the best fit (CFI=0.970, TLI=0.962, RMSEA=0.050; see Supplementary Materials Table S8 for further details in all models) and was mostly structurally invariant across sex (delta CFI=0.001). McDonald's omega for reliability was also highest on the bifactor model (ω_h=0.96, ω_g=0.68 and 0.93 for subfactors). Therefore, we used the bifactor model solution to extract latent thresholds for CES-D-R items, as presented in Table 2. **"**I felt like a bad person", "I lost weight", "I wished I were dead" and "I wanted to hurt myself" had the highest initial thresholds (i.e., required higher depression severity in order to endorse the item "1-2 days a week" over "not at all or less than 1 day"). "I had trouble keeping my mind on activities" and "I felt sad" had the lowest initial thresholds, although the item "I felt sad" had a major increase in necessary latent value from "None" to "1-2 days a week" to "1-2 a week" to "3-4 days a week".

----- INSERT TABLE 2 HERE ------

Network analysis

Figure 2 presents the whole sample network structure. There were 94 non-zero edges out of 190 possible edges, with a mean weight of 0.04. As expected, CFA based subfactors grouped together well on graphical analysis, with strong partial correlations. The items with highest expected influence centrality were items 4 ("I felt depressed"), 10 ("I lost interest in my usual activities) and 20 ("I could not focus on important things") (Supplementary Materials Figure S9). Network structure accuracy was adequate, with lower confidence intervals showing higher accuracy. Centrality estimates for expected influence had optimal level of stability (CS-coefficient = 0.75) and were not biased by node variance (r=0.15). There was no suggestion of node redundancy from the *goldbricker* procedure.

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DISCUSSION

This study aimed to investigate how depression presents among youth using a large population-based sample from a middle-income country by assessing the occurrence and structure of depressive symptomatology. At age 22, the prevalence of a current unipolar MDE was 2.85%. This point-prevalence estimate is consistent with the HIC literature – for instance, the prevalence of early adulthood depression in the National Comorbidity Survey – Replication (Kessler et al., 2005) (2.59% specifically among those aged 22 years (Alegria et al., 2016).

There is a scarcity of literature from LMICs on the prevalence of depression in early adulthood, a crucial transitional life period that may have distinguishing

characteristics from both adolescence and adulthood. Although not representative of the entire population, recent meta-analytical evidence on the prevalence of depression among university students in LMICs may be as high as 24% (Akhtar et al., 2020; Auerbach et al., 2016). Methodological discrepancies may explain, to a large extent, the variation between the aforementioned studies and the current report: our sample underwent face-to-face interviewing with a trained psychologist, which usually produces more conservative prevalence estimates (Martin et al., 2017; Stuart et al., 2014).

Prevalence estimates of depression are often based on depression scales designed for screening, rather than validated diagnostic interviews, leading to a potential prevalence overestimation of up to 2.5 times (Levis et al., 2020). Furthermore, the evidence for the equivalence of scale cutoffs from self-report questionnaires and clinical impairment is inconsistent (Thombs et al., 2018). The aforementioned meta-analysis calculated prevalence estimates based mostly on self-report scales such as the Beck Depression Inventory (BDI), the Center for Epidemiological Studies – Depression Scale (CES-D) and the Patient Health Questionnaire (PHQ-9), while only one study based prevalence rates on a structured interview (Akhtar et al., 2020). If we had calculated MDD's prevalence from the CES-D-R cutoff of 16, it would yield an estimate of 19.17% (95%CI 17.95 to 20.04%); by following the suggested CES-D-R algorithm for meeting MDD criteria (CESD-R: Center for Epidemiologic Studies Depression Scale Revised Online Depression Assessment), prevalence would have been 6.79% (95%CI 6.03% to 7.64%).

Additionally, our study's diagnostic criteria using the adapted version of the MINI were aligned with the DSM's in demanding both presence and frequency for cardinal symptoms to be considered positive for the investigation to continue, as well

as requiring recognition of impairment and excluding all participants with a current or previous manic episode. Interestingly, if we follow current conceptualizations of adolescence as continuing up to age 24 years (Sawyer et al., 2018) and follow DSM criteria for adolescent depression and consider irritability as a possible cardinal symptom in our sample, the prevalence estimate would be 3.57% (95%CI 3.02% to 4.21%). This estimate is similar to the prevalence of the disorder assessed in the same population at age 18 years (when irritability was considered one of the possible cardinal symptoms): 4.02% (95%CI 3.45% to 4.67%). Similarly, ignoring the impairment requirement would inflate the prevalence estimate to 11.1% (95%CI 10.10% to 12.23%). Future comparisons to our study should take into account, however, that we used an adapted version of the MINI that required cardinal symptoms to be present "most of the time" and be considered impairing, following DSM-5 criteria for MDE. Although we recognize advantages in using self-report instruments for the assessment of depressive symptomatology, the importance of an external validation with an accurate clinical interview conducted by a trained researcher cannot be understated.

In line with the literature (Auerbach et al., 2018; Avenevoli et al., 2015; Blay et al., 2018), current depression diagnosis in our sample had high comorbidity with other psychiatric disorders, especially GAD and PTSD. The association of MDD and GAD is well-established and likely bidirectional (Jacobson and Newman, 2017), with shared causal pathways as a potential reason for this link (Kessler et al., 2011). A recent meta-analysis suggested that comorbidity presents as a different predictor of future outcomes than either condition alone (Melton et al., 2016). Symptom-based analysis studies showed that specific symptoms may bridge the two conditions (Borsboom and Cramer, 2013). High comorbidity with PTSD is also expected as some diagnostic

criteria overlap and risk factors can be common to both disorders, especially sexual and physical abuse (Spinhoven et al., 2014). Also consistent with the literature, there was a higher prevalence of depressive episodes and CES-D-R total score in females than in males. Gender differences in depression prevalence are one of the most well-established findings in the literature (Salk et al., 2017) and are hypothesized to arise from the interaction of social and neurobiological characteristics.

Depression is widely acknowledged to be a dimensional construct and previous studies show subsyndromal symptoms having a life-long impact (Balázs et al., 2013; Pietrzak et al., 2013). Major depressive episode burden throughout the lifespan partially result from a peak incidence early in life, as early years of illness coincide with major biopsychosocial changes (Davey and McGorry, 2019; Giedd et al., 2008; Sussman and Arnett, 2014). In the present study, a substantial percentage of the sample endorsed depressive symptomatology present on "not at all or less than 1 day", "1–2 days" or "3–4 days" (Supplementary Material, Table S3) and could thus be considered "subsyndromal". Even though the definition of subsyndromal depression is not consistent throughout the literature (Carrellas et al., 2017), symptom presence is associated with functional impairment and is a risk factor for the development of MDD in both adolescents and adults (Pietrzak et al., 2013; Uchida et al., 2018). In our sample, concentration issues, sad mood, and excessive sleep were the most commonly endorsed symptoms. Factor analysis showed these symptoms to have low initial thresholds, i.e., to be relatively "easy" to endorse, although "I felt sad" had an important increase in necessary latent value to go from "1-2 days a week" to "3-4 days a week." However, symptoms suggestive of greater depression severity such as "I wanted to hurt myself" had lower frequencies and higher initial thresholds (i.e., they were "harder" to endorse). This finding is consistent with the conceptualization of

depression as an inherently dimensional construct, with some individual symptoms present as non-specific, normative and non-impairing experiences and others as more psychologically and/or functionally impairing (Patel, 2017; Ruscio, 2019). Previous item response theory analyses in a college-based sample also showed items on the Beck Depression Inventory to vary significantly in difficulty, with "changes in sleep" as the easiest and feelings of worthlessness as the hardest symptom to endorse (de Sá Junior et al., 2018).

We used a network analytic approach to study specific MDD symptoms and their connections. As this is a relatively new method of analysis, the existing literature has focused mostly on depressive symptoms in either younger adolescents (McElroy et al., 2018) or older adults (Fried and Nesse, 2015). Partially in line with a previous report from a community sample of adolescents (Mullarkey et al., 2018), we found sad mood ("felt depressed" and "felt sad") and anhedonia ("lost interest in activities"), the two cardinal symptoms of major depression, to be the most central (interconnected) symptoms. This finding is not explained by CES-D-R requirements as, in opposition to the MINI, it does not require participants to endorse either cardinal symptom for full investigation. This is also in accordance with a recent study from India (Wasil et al., 2020). Using a large clinical adult sample, one study (Borkulo et al., 2015) identified depressed mood to be a marker of persistence after MDD treatment, while another (McElroy and Patalay, 2019) found worthlessness to be a highly central symptom in adolescents.

Rapidly growing in popularity, the network approach to psychopathology is considered a promising method of symptom-level analysis, suggesting central symptoms as potential intervention targets (Borsboom and Cramer, 2013). However, it should be noted that the network approach has been mainly used as a descriptive

tool for cross-sectional studies (Ryan et al., 2019), has relied heavily on clinical samples (Fried and Cramer, 2017; Robinaugh et al., 2019) and had been used mainly in high-income country samples. To the best of our knowledge, our paper is only the second study applying the network framework to depression's symptom structure in a youth sample from a low- or middle-income country (LMICs; Wasil et al., 2020) and the first one to examine the late adolescence to emerging adulthood transition. Because LMICs comprise the majority of the global youth population, providing detailed data and analysis from such samples is consistent with the current literature focus on transculturality and generalizability (Guinart et al., 2019; Yarkoni, 2019) and is paramount for understanding MDD's presentation in diverse settings. Gradually incorporating state-of-the-art network analysis in population-based samples may represent a rich opportunity studying the course of depression from an epidemiological perspective and complement more traditional analyses of categorical diagnosis and sum-scores.

A number of limitations have to be acknowledged: we did not have lifetime-prevalence estimates, which may limit our ability to capture all aspects of a disorder that can be chronic, even though retrospective assessments of lifetime psychopathology are known to undercount prevalence estimates in prospective studies (Moffitt et al., 2010); the use of a population-based sample from a middle-income country precludes generalization of the findings to other populations, even to other regions of Brazil, or to clinical samples; the CES-D-R, as a self-report item constructed for epidemiological purposes, may lead to biases in terms of symptom reporting in comparison to clinician-rated scales or structured interviews (Martin et al., 2017); and by focusing on quantitative assessments of DSM-5 criteria and pre-selected scales, one may risk losing different cultural-based expressions of

depression (Haroz et al., 2017). Lastly, using the CES-D-R with the suggested cutoff point of 16 derived from ROC analysis showed a low positive predictive value (15%) – however, this is somewhat expected given the population-based nature of our sample and the similarity of the derived prevalence value using a cutoff point of 16 (around 19%).

Nonetheless, our study had several strengths. A large population-based sample, unbiased by clinical referrals or in-hospital settings, allows for the study of depression's presentation in a setting that is closer to the real-world's and may enhance our comprehension of the clinical presentation of depressive symptomatology. Additionally, we adapted the MINI questionnaire to more accurately reflect DSM criteria, requiring participants to report cardinal symptom presence, frequency, and impairment for the diagnostic algorithm. The diverse analytical techniques used to investigate depression, including the point-prevalence estimates of diagnosis and symptomatology, allow for a better understanding of depression phenomenology by evaluating the condition as both a categorical diagnosis and dimensional construct. Even further, such in-depth analyses was conducted in a large middle-income country sample, therefore covering an important gap in the existing literature (Kieling et al., 2011). Also, categorical diagnoses were derived from a structured clinical interview conducted by a trained psychologist, which allowed for the calibration of the optimal cut-off for the dimensional measure.

In summary, the present study sought to investigate the point-prevalence of depression diagnosis and symptomatology in a population-based sample of youths. We used various analytical approaches to examine depression symptoms, thereby embracing the disorder's inherent complexity. Point-prevalence estimates were similar to other findings of the literature on this age group. In dimensional analysis, we found

symptoms to differ in item response distribution and difficulty thresholds, with more frequent symptoms requiring lower latent value to be endorsed. Using a network analytic approach, sad mood and anhedonia were the most central items in the network structure. Focusing on the transitional period from late adolescence to emerging adulthood – a fundamental moment of change from biological, psychological and social perspectives – is critical for the determination of early interventive measures that can mitigate depression's lifelong burden. Considering that most young people in the planet currently live in LMICs, enhancing the understanding of depression in resource-limited contexts may be a unique opportunity to reduce the global burden of depression.

DECLARATIONS

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TABLES

Table 1. Descriptive statistics for the whole sample, as well as for those without and with a current MDE.

	Whole Sample (n=3,780)	No current MDE (n=3,672)	Current MDE (n=108)
Females (%)	2,021 (53.46%)	1,937 (52.75%)	84 (77.77%)*
Mean Years of Education (SD)	9.83 (2.35)	9.83 (2.35)	9.61 (2.43)
Mean CES-D-R (SD)	9.20 (9.72)	8.52 (8.72)	31.96 (13.29)*
Wealth Index z-score	0.01 (2.17)	0.01(2.17)	-0.34(2.04)*
APD (%)	40 (1.05%)	39 (1.06%)	1 (0.92%)*
ADHD (%)	168 (4.44%)	151 (4.11%)	17 (15.74%)*
BD (%)	61 (1.61%)	61 (1.66%)	-
GAD (%)	395 (10.44%)	336 (9.15%)	59 (54.62%)*
PTSD (%)	168 (4.44%)	138 (3.75%)	30 (27.77%)*
SAD (%)	187 (4.94%)	167 (4.54%)	20 (18.51%)*
Mean AUDIT (SD)	4.31 (4.92)	4.27 (4.86)	5.92 (6.61)*
Current smokers (%)	635 (16.79%)	604 (16.44%)	31 (28.70%)*
Mean BMI (SD)	25.23 (5.30)	25.23 (5.27)	25.51 (6.35)
Asthma, diabetes or hypertension (%)	1,202 (31.79%)	1,160 (31.59%)	41 (37.96%)

* Independent sample test as significant with No MDE as reference, considering alpha=.05. SD, standard deviation; MDE, major depressive episode. CES-D-R, Center for Epidemiological Studies–Depression Scale–Revised; ADHD, attention deficit and hyperactivity disorder; APD, antisocial personality disorder; BD, bipolar disorder; GAD, generalized anxiety disorder; PTSD, post-traumatic stress disorder (PTSD); SAD, social anxiety disorder.; AUDIT, Alcohol Use Disorders Identification Test; BMI, body mass index, measured in kg/m^2.

Table 2. Confirmatory factor analysis (CFA) thresholds from the bifactor model of the CES-D-R; thresholds are presented as standardized latent values (LV); with columns presenting the required values for endorsing one option over another (i.e., how much depression one has to have to endorse a harder option over an easier one).

CESD-R items	Thresholds (ƛ)			
	1-2 days a week	**3-4 days a week**	**5-7 days a week**	**Almost every day**
2. I could not shake off the blues	0.695	1.285	1.528	1.684
4. I felt depressed	0.444	1.236	1.560	1.738
6. I felt sad	0.053	1.094	1.464	1.684
8. Nothing made me happy	0.285	1.082	1.409	1.621
9. I felt like a bad person	1.231	1.893	2.128	2.287
14. I wished I were dead	1.591	1.924	2.115	2.268
15. I wanted to hurt myself	1.893	2.217	2.359	2.506
17. I did not like myself	1.024	1.530	1.781	1.970
1. My appetite was poor	0.407	1.274	1.642	1.809
3. I had trouble keeping my mind on what I was doing	-0.109	0.951	1.381	1.591
5. My sleep was restless	0.166	0.987	1.420	1.624
7. I could not get going	0.587	1.344	1.705	1.881
10. I lost interest in my usual activities	0.627	1.346	1.684	1.842
11. I slept much more than usual	0.126	0.978	1.369	1.567
12. I felt like I was moving too slowly	0.816	1.442	1.741	1.932
13. I felt fidgety	0.225	1.042	1.506	1.757
16. I was tired all the time	0.255	1.007	1.398	1.619
18. I lost a lot of weight without trying to	1.355	1.735	1.873	2.032
19. I had a lot of trouble getting to asleep	0.249	0.986	1.360	1.591
20. I could not focus on important things	0.366	1.164	1.539	1.751

FIGURES

Figure 1. Center for Epidemiological Studies–Depression Scale–Revised (CES-D-R) item response distribution for the whole sample.
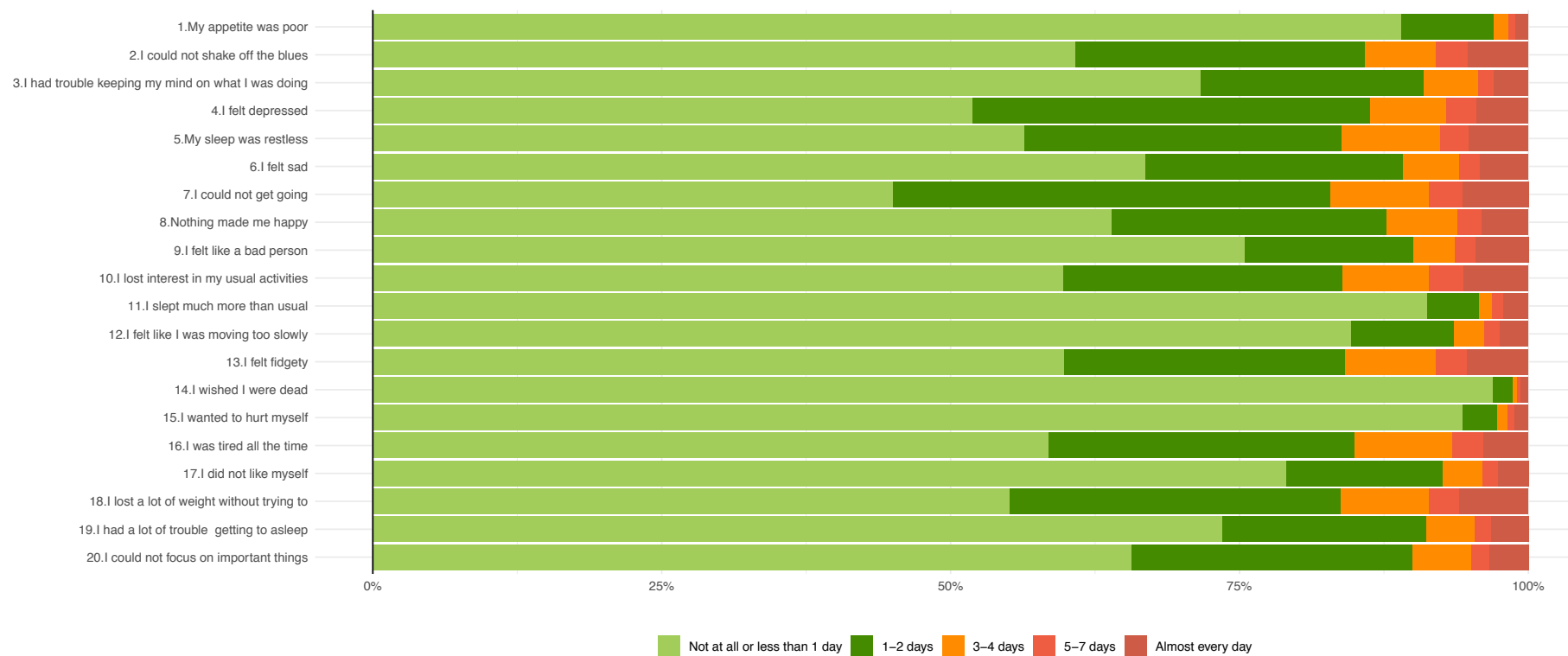
Figure 2. Network structure of the Center for Epidemiological Studies–Depression Scale–Revised (CES-D-R) symptoms.

Factor 1
- 2: I could not shake off the blues
- 4: I felt depressed
- 6: I felt sad
- 8: Nothing made me happy
- 9: I felt like a bad person
- 14: I wished I were dead
- 15: I wanted to hurt myself
- 17: I did not like myself

Factor 2
- 1: My appetite was poor
- 3: I had trouble keeping my mind on what I was doing
- 5: My sleep was restless
- 7: I could not get going
- 10: I lost interest in my usual activities
- 11: I slept much more than usual
- 12: I felt like I was moving too slowly
- 13: I felt fidgety
- 16: I was tired all the time
- 18: I lost a lot of weight without trying to
- 19: I had a lot of trouble getting to asleep
- 20: I could not focus on important things

SUPPLEMENTARY MATERIALS

Supplementary Material Figure S1. Pelotas birth cohort follow-up flowchart; for more details, see [1]. The Pelotas birth cohort is an ongoing longitudinal study in which all children born in the city of Pelotas, in the south of Brazil, in the year of 1993 (5,249 individuals) were assessed at multiple timepoints until 22 years old (2015). There were 3,810 interviews at the 22-year-old follow up, added to 193 participants known to have died, which results in a 76.26% retention rate. Further details can be found at [1].
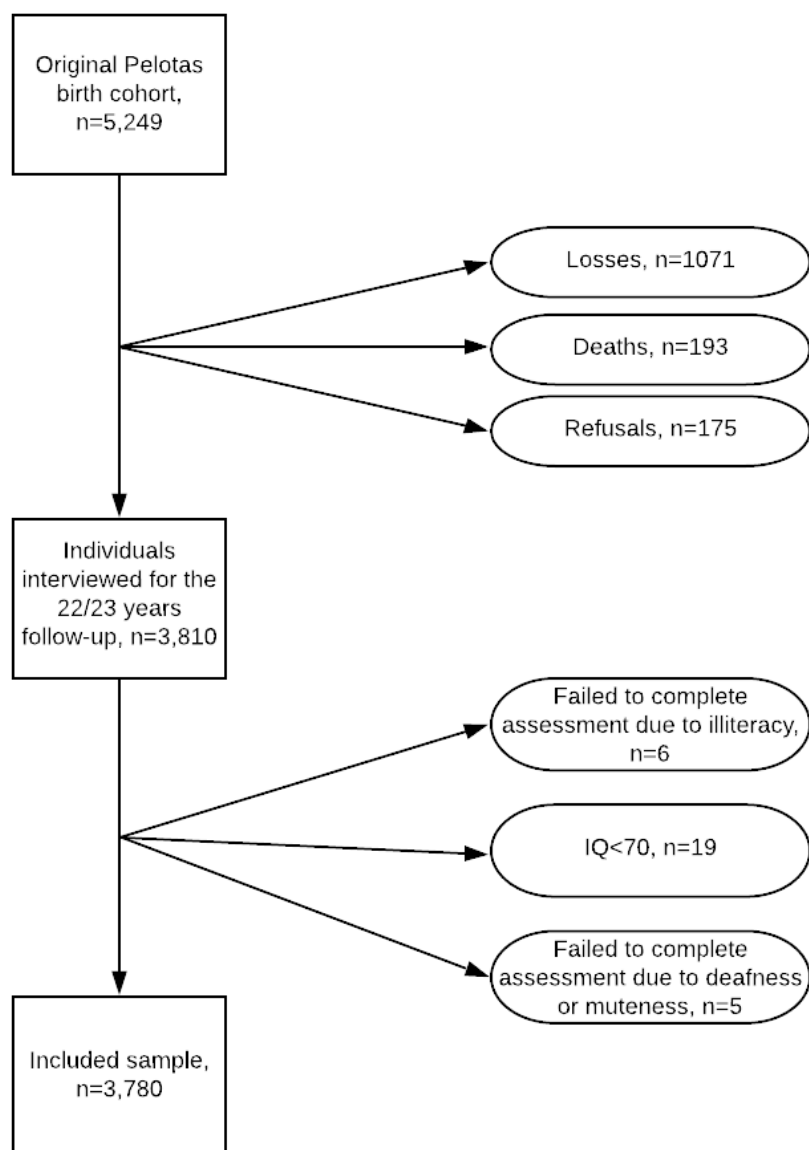
Supplementary Material S2: Translation and cross-cultural adaptation into Brazilian Portuguese of the CESD-R. The Center for Epidemiological Studies – Depression Scale – Revised (CES-D-R) is a freely available [3] dimensional measure comprising 20 items on the symptomatology of MDD. For the translation of CESD-R, we followed the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines for translation and cultural adaptation, including the steps of preparation, forward translation, reconciliation, back-translation, back-translation review, harmonization, cognitive debriefing, review of cognitive debriefing results and finalization, proofreading and final report [2]. In the first step (preparation), we asked for the author's (W.E.) permission to use the instrument, invited him to be involved in the process, and recruited translators. In the second step (forward translation), two independent translations were performed (by C.K and R.K. – the latter is listed in the Acknowledgments). In the third step (reconciliation), the forward translations were reconciled into a single forward translation (any discrepancies were discussed between C.K. and R.K.). In step four, a native speaker of English (J.M.) performed a back-translation of the instrument into the original language. In step five, the back-translation was reviewed and discussed with the original author of the instrument (W.E.) to ensure the conceptual equivalence of the translation with the original instrument. The sixth step consisted of harmonization across different translations. In step seven (cognitive debriefing), the level of comprehensibility of the translation was assessed in a sample of 11 young people (63% female; mean age = 25.81, SD = 11.26), who took an average of 6.31 minutes (range from 2 minutes to 13 minutes) to complete the scale and they did not report significant difficulties understanding and answering it.

Supplementary Material Table S3. MINI categorical symptom prevalence on the whole sample. The Mini International Neuropsychiatric Interview (MINI) is a short structured diagnostic interview that explores major psychiatric disorders according to DSM-IV criteria. For the present study, we analyzed data on the prevalence and current (i.e. in the last 15 days) major depressive episode and symptomatology. Following DSM criteria, we only advanced on the depression module from the MINI interview if participants endorsed sadness and/or anhedonia symptoms (depression's cardinal symptoms) as "most of the time". Furthermore, we required participants to report symptoms as "somewhat" or "very" impairing for the diagnosis of an MDE. The Supplementary Material 2 shows cardinal symptom distribution for the whole sample (n=3,780) and, for those who endorsed sadness and/or anhedonia symptoms as "most of the time" (n=425), accessory symptoms.

MINI symptoms	Total %
Sadness*	39%
Irritability	51%
Anhedonia*	11%
Weigth/appetite changes**	65%
Fatigue**	76%
Sleep problems**	71%
Psychomotor agitation**	61%
Feeling worthless/did not like oneself**	40%
Concentration difficulty**	72%
Morbid ideation**	34%

*cardinal symptoms, asked for the 3,780 cohort members; ** accessory symptoms, asked to the 425 participants that had at least one of the cardinal symptoms reported as most of the time.

Supplementary Material Table S4. CES-D-R Item distribution across the whole

sample. It is a numerical presentation of Figure 1 from the full text article.

| Item response frequency to the question: How often, in the past one or two weeks, did you feel any of the following?					
	Not at all or less than 1 day	**1-2 days**	**3-4 days**	**5-7 days**	**Almost every day**
1. My appetite was poor	65.61%	24.05%	5.26%	1.48%	3.60%
2. I could not shake off the blues	75.61%	14.55%	3.57%	1.72%	4.55%
3. I had trouble keeping my mind on what I was doing	45.45%	37.43%	8.76%	2.83%	5.53%
4. I felt depressed	66.96%	22.14%	4.95%	1.83%	4.13%
5. My sleep was restless	56.72%	27.17%	8.41%	2.49%	5.21%
6. I felt sad	51.96%	34.47%	6.48%	2.54%	4.55%
7. I could not get going	71.61%	19.23%	4.71%	1.46%	2.99%
8. Nothing made me happy	60.85%	24.95%	6.11%	2.83%	5.26%
9. I felt like a bad person	88.89%	8.12%	1.27%	0.58%	1.14%
10. I lost interest in my usual activities	73.28%	17.72%	4.47%	1.32%	3.20%
11. I slept much more than usual	54.42%	29.13%	7.91%	2.70%	5.85%
12. I felt like I was moving too slowly	79.05%	13.54%	3.31%	1.40%	2.70%
13. I felt fidgety	58.41%	26.77%	8.39%	2.62%	3.81%
14. I wished I were dead	94.34%	2.86%	1.01%	0.61%	1.19%
15. I wanted to hurt myself	97.06%	1.61%	0.40%	0.29%	0.63%
16. I was tired all the time	59.95%	24.29%	7.62%	2.86%	5.29%
17. I did not like myself	84.60%	9.05%	2.62%	1.32%	2.41%
18. I lost a lot of weight without trying to	91.08%	4.68%	1.11%	0.98%	2.14%
19. I had a lot of trouble getting to asleep	59.50%	24.15%	7.57%	3.25%	5.53%
20. I could not focus on important things	64.07%	23.84%	6.01%	2.14%	3.94%

Supplementary Material Figure S5. CES-D-R Total Sum Scores distribution; the dotted blue, black, and red lines represent the mean CES-D-R total sum score for the sample without a current MDE, for the whole sample, and for the sample with a current MDE, respectively.

CES-D-R Total Sum Score Histogram
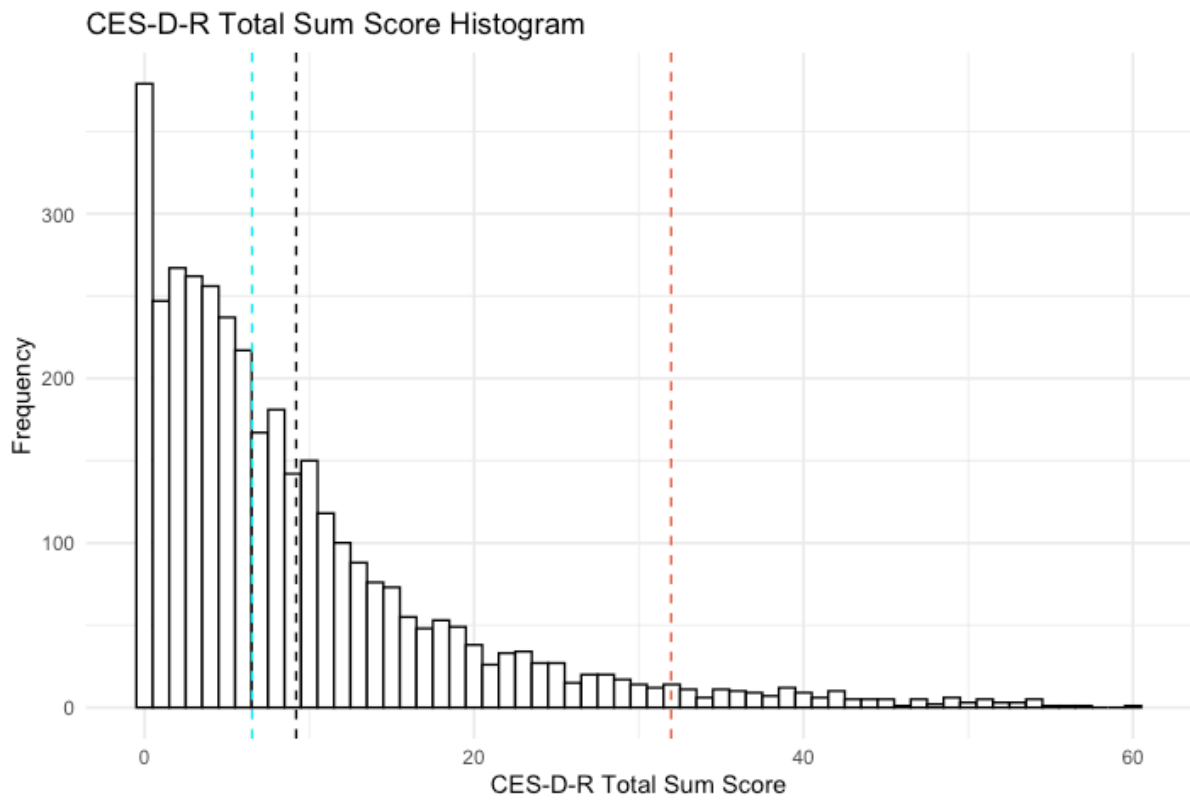
Supplementary Material Figure S6. AU-ROC Curve and derived statistics. We calculated the area under the receiver-operating characteristic (AU-ROC) curve. The AU-ROC curve indicates the probability that a participant with a current diagnosis of unipolar MDE according to the MINI to have a higher CES-D-R score than one that does not have a diagnosis (perfect discrimination=1, no discrimination=0.5).
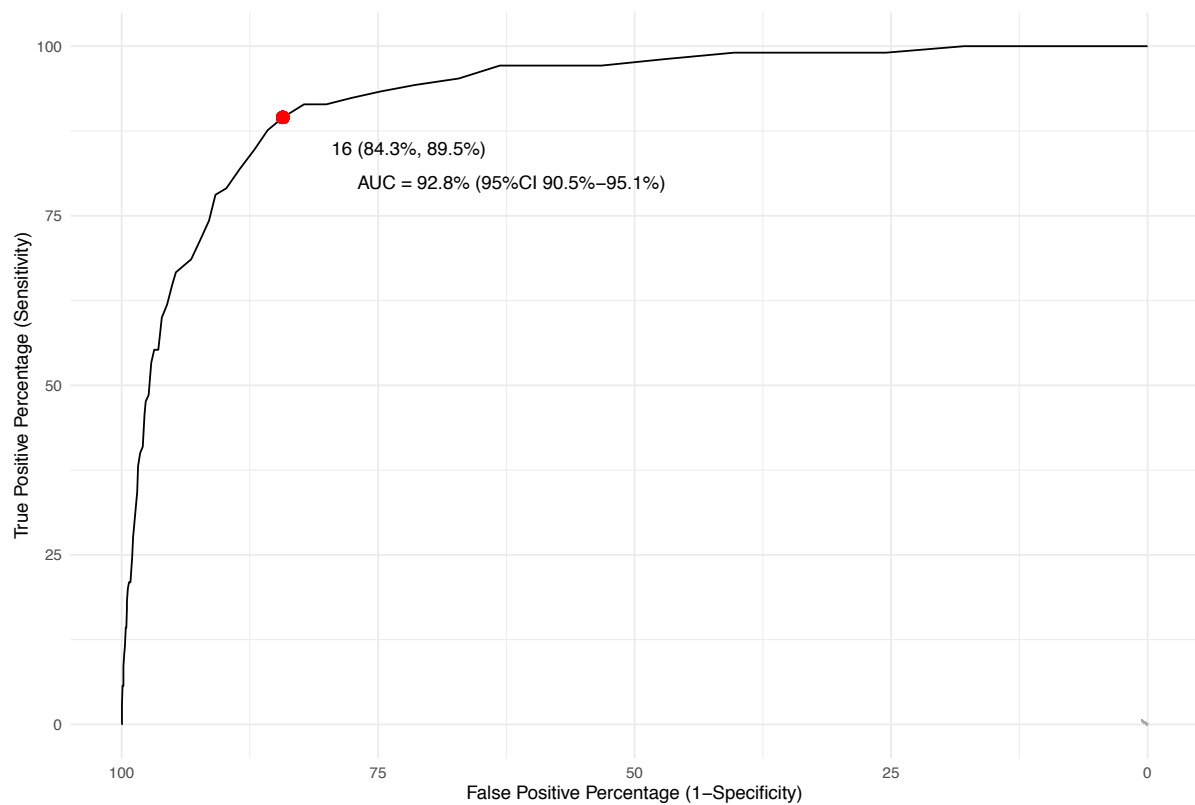
Supplementary Material Table S7. Sensitivity, specificity, positive and negative predictive values derived from the proposed CES-D-R categories [3] compared with the adapted MINI diagnosis.

	Meets criteria	Probable MDE	Possible MDE	Subthreshold Depression Symptoms
Sensitivity	39%	56%	64%	24%
Specificity	98%	95%	94%	89%
Positive Predictive Value	33%	26%	23%	6%
Negative Predictive Value	98%	99%	99%	98%

MDE = Major depressive episode; Definition for every column, according to [3]: Meets criteria for MDE = Anhedonia or dysphoria nearly every day for the past two weeks, plus symptoms in an additional 4 DSM symptom groups noted as occurring nearly every day for the past two weeks; Probable MDE = Anhedonia or dysphoria nearly every day for the past two weeks, plus symptoms in an additional 3 DSM symptom groups reported as occurring either nearly every day for the past two weeks, or 5-7 days in the past week; Possible MDE = Anhedonia or dysphoria nearly every day for the past two weeks, plus symptoms in an additional 2 other DSM symptom groups reported as occurring either nearly every day for the past two weeks, or 5-7 days in the past week; Subthreshold depression symptoms = People who have a CES-D-R score of at least 16 but do not meet above criteria.

Supplementary Material Table S8. Unidimensional, Correlated two-factor and bifactor with two subfactors solutions factor

loadings, reliability and fit indices.

CESD-R items	Unidimensional (ƛ)	Two Factors (ƛ)		Bifactor with two subfactors (ƛ)		
		Factor 1	Factor 2	g	Factor 1	Factor 2
2. I could not shake off the blues	0.828	0.839		0.824	0.473	
4. I felt depressed	0.885	0.899		0.597	0.540	
6. I felt sad	0.668	0.678		0.881	0.580	
8. Nothing made me happy	0.737	0.747		0.751	0.436	
9. I felt like a bad person	0.667	0.676		0.739	0.186	
14. I wished I were dead	0.820	0.829		0.677	0.502	
15. I wanted to hurt myself	0.775	0.783		0.790	0.442	
17. I did not like myself	0.769	0.779		0.773	0.308	
1. My appetite was poor	0.497		0.500	0.735		0.144
3. I had trouble keeping my mind on what I was doing	0.716		0.720	0.508		-0.154
5. My sleep was restless	0.862		0.875	0.906		0.498
7. I could not get going	0.719		0.724	0.643		-0.205
10. I lost interest in my usual activities	0.783		0.789	0.752		-0.099
11. I slept much more than usual	0.454		0.458	0.419		0.025
12. I felt like I was moving too slowly	0.697		0.701	0.650		-0.067
13. I felt fidgety	0.536		0.539	0.509		0.188
16. I was tired all the time	0.725		0.730	0.679		-0.083
18. I lost a lot of weight without trying to	0.597		0.601	0.612		0.134
19. I had a lot of trouble getting to asleep	0.669		0.673	0.668		0.539
20. I could not focus on important things	0.802		0.807	0.665		-0.179
McDonald's Omega	0.930	0.951	0.497	0.960	0.680	0.930
CFI	0.911	0.946		0.970		
TLI	0.900	0.940		0.962		
RMSEA	0.090	0.070		0.050		

Supplementary Material Figure S9. Expected Influence Centrality of the Center for Epidemiological Studies–Depression Scale–Revised (CES-D-R) symptoms derived from network analysis. The graph displays the sample's CES-D-R expected centrality, the sum of all edge weights connected to a node. A high expected influence means a node is highly connected to other nodes, which makes them theoretically more important in the network structure and a good candidate for possible interventions.

Expected Influence Centrality
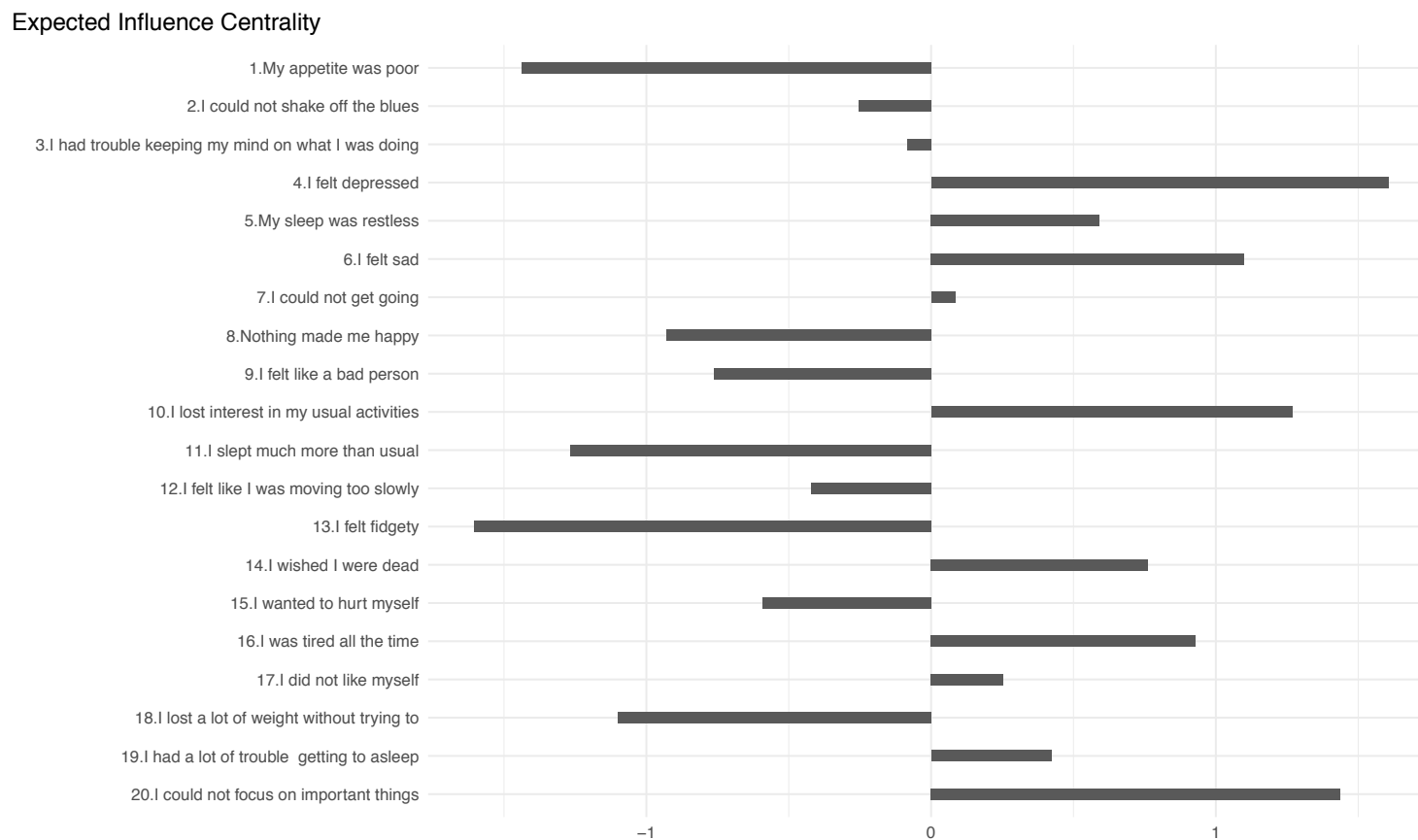
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2.   Wild D, Grove A, Martin M, et al (2005) Principles of Good Practice for the Translation and Cultural Adaptation Process for

      Patient-Reported Outcomes (PRO) Measures: Report of the ISPOR Task Force for Translation and Cultural Adaptation.

      Value in Health 8:94–104. https://doi.org/10.1111/j.1524-4733.2005.04054.x

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      Accessed 27 Apr 2020

7. Article #2

Youth depression and inflammatory markers:

cross-sectional network analyses in a population-based sample

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ABSTRACT

Background: Inflammation-related markers constitute a promising avenue in studying biological correlates of major depressive disorder (MDD). However, MDD is a heterogeneous condition – a crucial aspect to be considered in association studies. We examined whether inflammatory markers are associated with categorical diagnosis, a dimensional total sum-score, and specific depressive symptoms among youths.

Methods: We analyzed data from the 1993 Pelotas Birth Cohort, a population-based study in Brazil that followed individuals up to age 22 years. Categorical psychiatric diagnoses were derived using adapted modules of the Mini International Neuropsychiatric Interview (MINI). Dimensional symptomatology was assessed using the Brazilian Portuguese version of the Center for Epidemiological Studies– Depression Scale–Revised (CESD-R). We estimated network structures that included individual depressive symptoms as measured by CESD-R items, peripheral inflammatory markers (C-Reactive Protein [CRP] and Interleukin-6 [IL-6]), as well as relevant covariates.

Results: There were no associations between concentrations of inflammatory markers and categorical diagnosis of MDD or with CESD-R total sum-scores. However, CRP was connected to poor sleep, fatigue and weight loss. IL-6 was positively associated with reduced appetite, low mood and poor sleep.

Discussion: We found cross-sectional connections of two commonly studied inflammatory markers and specific depressive symptoms. Conducting symptom-specific analyses in relation to biological markers might advance our understanding of the heterogeneity of MDD.

Keywords: depressive symptoms; adolescence; inflammation; network analysis

INTRODUCTION

Inflammatory markers are considered a promising avenue in uncovering depression's biological underpinnings (1). Despite evidence from clinical samples showing interleukin-6 (IL-6) and C-Reactive Protein (CRP) levels to be increased among individuals with major depressive disorder (MDD) in comparison with healthy controls (2), differences in non-clinical samples (3,4) and associations with specific symptoms are less consistent (5–7). Studies in population-based and clinical samples found associations of specific somatic, but not cognitive, symptoms with IL-6 (8) and CRP (6). Additionally, studies have more frequently focused on either categorical clinical diagnosis (2) or total sum dimensional measures.

MDD is as a heterogeneous construct in its phenomenological presentation (9), and distinct clinical profiles had been associated with specific neurobiological correlates (10). Accordingly, there may be specific aspects of depression more closely linked to inflammatory activity, which would also relate to why only a subset of individuals with MDD show heightened inflammation levels (3,11,12). It is possible that relying on categorical diagnoses or dimensional total sum-scores, which assume symptoms to be equivalent or interchangeable, may hide important biological associations (13,14). Thus, understanding the condition as a combination of interconnected symptoms and biopsychosocial factors, rather than a monolithic construct, is a promising way forward (6,15).

The study of depression using a network perspective provides the opportunity to examine specific associations between symptoms and inflammatory markers, as well as the role of relevant covariates (6,7,16). By focusing on individual symptoms instead of categorical diagnoses or total sum-scores, network analyses allow for an

examination of the relationship between inflammation and depressive symptoms as part of a complex systems.

We examined, in a population-based sample of youths, the links between IL-6/CRP and three levels of depression assessment: (A) clinician-derived categorical diagnoses; (B) total dimensional sum-scores; and (C) specific items of a self-report dimensional instrument. We hypothesize that investigating individual symptoms may highlight associations hidden in categorical or total sum-score analyses.

METHODS

Sample description

We used data from the 1993 Pelotas Birth Cohort, an ongoing longitudinal study in which all children born in the city of Pelotas, Brazil, in 1993 (n=5,249) were assessed at multiple timepoints. We analyzed cross-sectional data from the cohort's latest assessment at 22 years old, with 76.3% retention (17). Further details on the cohort's design and methods can be found elsewhere (17,18). Participants or their legal guardians provided written informed consent, and data was coded to ensure anonymity. The study had approval from the Ethics Committee of the Universidade Federal de Pelotas (ethics approval number 1.250.366). We excluded from analyses participants with corticosteroid use in the previous 3 months of assessment because as per recent literature suggesting a possible confounding effect (19).

Measures

Psychiatric categorical diagnoses

Trained clinical psychologists applied specific modules of the Brazilian Portuguese version of the Mini International Neuropsychiatric Interview (MINI) (20),

adapted to be aligned with DSM criteria (21). We focused on the prevalence of current (i.e., in the past 15 days) unipolar major depressive episode (MDE) at age 22. Attention-deficit/hyperactivity disorder, antisocial personality disorder, generalized anxiety disorder or social anxiety disorder were assessed as comorbid covariates. For all analyses, we excluded participants with missing data for either IL-6 or CRP and/or a lifetime diagnosis of bipolar disorder and/or post-traumatic stress disorder.

Dimensional measure of depressive symptoms

The Center for Epidemiological Studies–Depression Scale–Revised (CESD-R) is an instrument with 20 items on depressive symptomatology. It has five Likert-style response options, ranging from "not at all or less than 1 day", "1–2 days", "3–4 days", "5–7 days", "nearly every day for 2 weeks". Importantly, the CESD-R has individual items on MDD DSM-5 compound symptoms (such as reduced/increased sleep, reduced appetite/weight loss, psychomotor agitation/retardation). The Brazilian Portuguese version of the CESD-R exhibited good indices of validity and reliability in this sample (22).

Inflammatory markers

Non-fasting blood samples were drawn by cubital vein venipuncture. IL-6 was measured in pg/L by the Quantikine® HS Human IL-6 immunoassay kit (R&D Systems®, Inc.; Minneapolis, USA), while CRP was measured by immunoturdimetric assay (Labtest Diagnóstica SA, Minas Gerais, Brazil) in mg/L. Because biomarkers concentrations were non-normally distributed, we conducted non-paranormal transformation on IL-6 and CRP for all analyses (6).

Statistical analyses

For categorical analyses, we conducted multiple logistic regression with CRP/IL-6 and covariates as independent variables the DSM diagnosis of MDD as the dependent variable. For total-sum dimensional analyses we ran multiple linear regression with CRP/IL-6 measures and covariates as independent variables and the CESD-R sum-score as the dependent variable.

For symptom-specific analysis, we estimated network structures with individual CESD-R items, inflammatory biomarkers and covariates (6,16). We estimated symptomatic networks using L1-regularized partial correlations – all variables regressed on each other adjusting for the effect of every other variable. Because our data had continuous and categorical variables, we used mixed graphical models (mgm) (23) for network estimation. Regularized partial correlation networks address issues of multiple testing through a *lasso* (least absolute shrinkage and selection operator) regularization that shrinks small connections to zero by defining a λ (lambda) tuning parameter. This tuning parameter is selected through the Extended Bayesian Information Criteria (EBIC), which in turn has a hyperparameter γ (gamma), here set to 0.25, in accordance to previous literature (6). Thus, edges are considered significant and plotted only if present after regularization (24). Network accuracy was assessed with bootstrapping procedures (6,24).

We followed recommendations from a recent systematic review in choosing covariates (8). We included the following variables as covariates for categorical, dimensional and network analyses: body mass index (weight mass divided by the square of height; kg/m^2); family income (the sum of every household member's income in Brazilian *reais*, R$); education years (sum of years dedicated to formal schooling);

current smoking (defined as endorsing the questions "Have you ever had the habit of smoking?" and "Do you still smoke every day?"); alcohol consumption (the AUDIT questionnaire(25)); a MINI diagnosis of either one of attention-deficit/hyperactivity disorder, antisocial personality disorder, generalized anxiety disorder or social anxiety disorder; and a clinical diagnosis of hypertension, asthma, and/or diabetes. Analyses were performed in R (26) and code is available at https://osf.io/5u9qy/.

RESULTS

The final sample consisted of 2,586 participants (51.3% male; see Figure S1 for recruitment information and reasons for exclusions and Table S1 for descriptive data). As expected, IL-6 and CRP concentrations were correlated (r=0.52, p<0.001).

Results from categorical and dimensional analysis are presented in Table 1. In adjusted categorical analysis, neither CRP nor IL-6 were associated with MDD at age 22. Using a dimensional sum-score approach, neither CRP nor IL-6 were associated with CESD-R total scores.

------ INSERT TABLE 1 ABOUT HERE -----

Figure 1 shows the symptom network structure of CRP, IL-6 and specific CESD-R items, adjusting for covariates. CRP was connected to poor sleep (item 5: "my sleep was restless"), fatigue (item 16: "I was tired all the time") and weight loss (item 18: "I lost a lot of weight without trying to"). IL-6 was associated with reduced appetite (item 1: "my appetite was poor"), low mood (Item 2: "I could not shake off the blues") and poor sleep (item 5).

------ INSERT FIGURE 1 ABOUT HERE -----

DISCUSSION

Using data from a population-based cohort, we examined the cross-sectional associations of two inflammatory biomarkers with depression among youth in the south of Brazil. We did not find elevated levels of inflammatory markers to be associated with categorical MDD diagnoses or with dimensional depression total sum-scores. However, by conducting in-depth symptom analyses, there were small, positive associations of CRP and IL-6 concentrations with specific symptoms. Although categorical nosology serves a clear purpose in clinical practice, to fine-tune research into progressively more precise and observable dimensional elements is considered increasingly important to uncover potentially hidden associations (6,15,16).

In accordance with previous literature (2,5,6,8) on inflammatory biomarkers and depressive symptomatology, we found connections between CRP and IL-6 and specific symptoms, but not total sum-scores. We replicated previous findings of CRP being connected to somatic symptoms (i.e. poor sleep, fatigue and weight loss). This is in agreement with literature suggesting CRP plays a crucial role in the human organism's maintenance (1). IL-6 was connected to reduced appetite and poor sleep. In addition to more established findings of inflammatory markers to be connected to somatic symptoms (10,27), we also found IL-6 to also be linked to low mood. Differential symptom associations of IL-6 and CRP are also in line with recent discussions of complex roles of these markers in psychoimmunology given distinct signaling pathways (1). As IL-6 is permeable through the blood-brain barrier, it is hypothesized to have direct behavioral effects in chronic, low-intensity inflammatory

activity (28). Furthermore, brain targets of inflammatory markers are in line with possible effects of IL-6 on depressed mood (28,29). CRP, on the other hand, may not may not as directly affect neurobiology, although recent data show a possible correlation between plasma and central CRP levels(30). It is thus possible that CRP may be more reflective of somatic alterations in MDD while IL-6 could be connected to a broader range of symptoms.

Our results come at a time of great interest in understanding potential biological depression subtypes (5,31). Even though genetic studies question the causal links between inflammation and depression diagnosis (32), it is possible that inflammatory activity is linked to specific symptoms that are more likely to be present in a subset of patients (5). Although past decades have greatly advanced our understanding of biological correlates of depression, embracing the multifaceted biopsychosocial nature of the disorder (15) through symptom-specific methods might be crucial for disentangling symptom-marker biological pathways.

Limitations and strengths

Our study is not without limitations. Studying a youth sample may limit detection of low-intensity inflammation effects that may be more prominent later in the lifespan (2). It is also possible that examining the point-prevalence of depression (i.e., the MINI diagnosis of a MDE) may miss associations between chronic presentations of MDD and inflammatory markers. Furthermore, the cross-sectional nature of our study warrant caution in causally interpreting associations since reverse causality and bidirectionality cannot be excluded (2,5,13). Finally, even if conducting the appropriate statistical adjustments, network analyses could potentially inflate type I errors by relying on single-item measures of individual symptoms (13) .

Even so, our study had several strengths. Examining population-based samples allow for a better evaluation of depression-inflammation associations in real-world settings, unbiased by the severity and referrals potentially present in clinical samples. Furthermore, regularized network structures allow for assessing conditional independence between items, inflammation markers and covariates – i.e., a connection between two nodes is only plotted if partial correlation is still present after accounting for the influence of every other node and regularization techniques (16). By applying symptom-level analyses, we were able to disentangle symptom-biomarker relations that may be attenuated in categorical or sum-score approaches.

CONCLUSION

In a time of growing interest in studying the heterogeneity of MDD clinical presentation and biological correlates, we studied the association of two inflammatory markers examining three levels of analysis (clinician-derived diagnoses, total sum-scores, and specific symptoms). Our results are concordant with studies showing CRP and IL-6 to be cross-sectionally linked to specific depressive symptoms (2,5–7). Avoiding one-size-fits-all approaches and conducting specific-symptom analyses can be crucial in dealing with depression's multicausal, heterogenous nature.
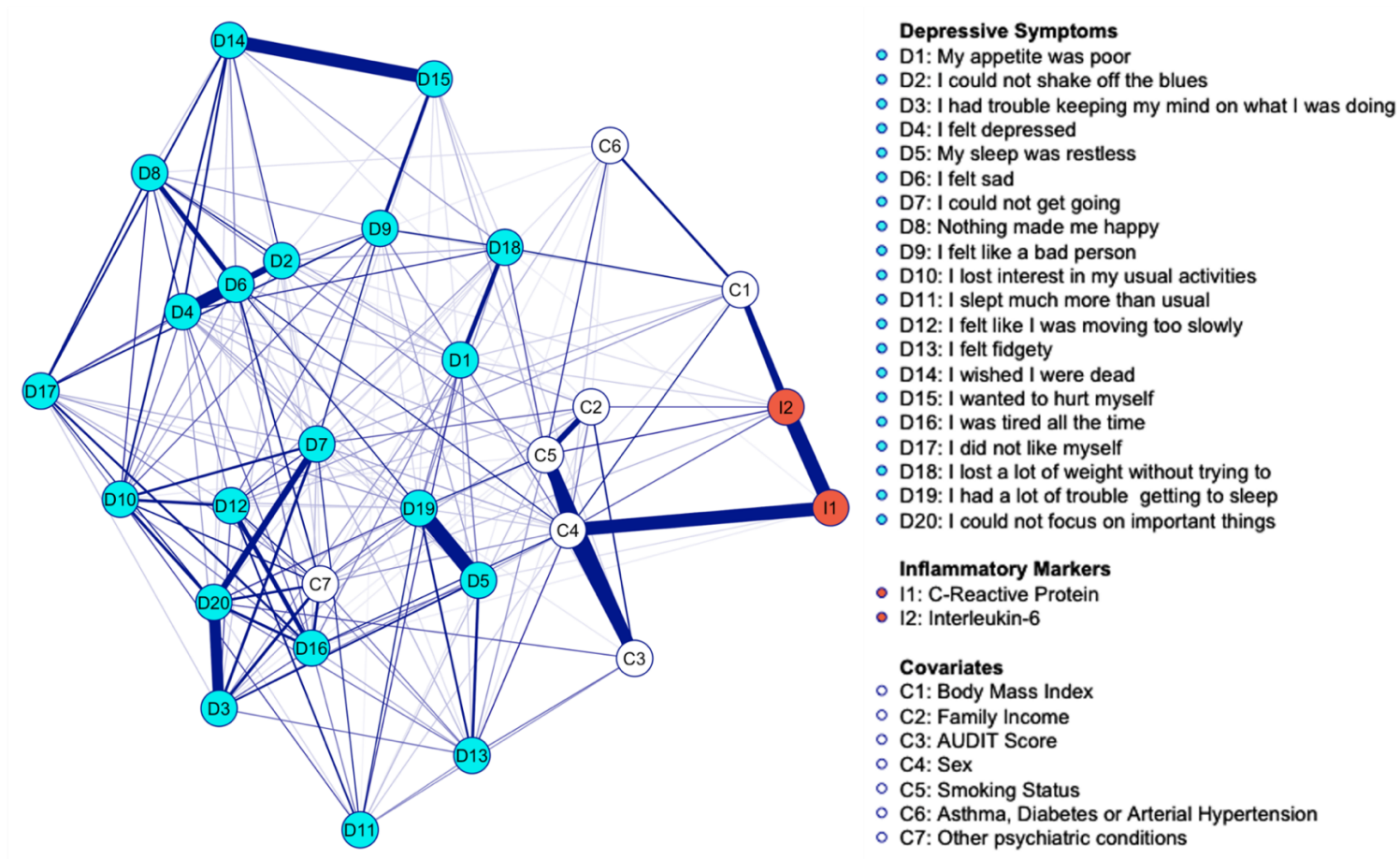
DECLARATIONS

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Figure 1. Network structure of depressive symptoms, inflammatory markers and covariates

Depressive Symptoms
- D1: My appetite was poor
- D2: I could not shake off the blues
- D3: I had trouble keeping my mind on what I was doing
- D4: I felt depressed
- D5: My sleep was restless
- D6: I felt sad
- D7: I could not get going
- D8: Nothing made me happy
- D9: I felt like a bad person
- D10: I lost interest in my usual activities
- D11: I slept much more than usual
- D12: I felt like I was moving too slowly
- D13: I felt fidgety
- D14: I wished I were dead
- D15: I wanted to hurt myself
- D16: I was tired all the time
- D17: I did not like myself
- D18: I lost a lot of weight without trying to
- D19: I had a lot of trouble getting to sleep
- D20: I could not focus on important things

Inflammatory Markers
- I1: C-Reactive Protein
- I2: Interleukin-6

Covariates
- C1: Body Mass Index
- C2: Family Income
- C3: AUDIT Score
- C4: Sex
- C5: Smoking Status
- C6: Asthma, Diabetes or Arterial Hypertension
- C7: Other psychiatric conditions

Light blue nodes are CESD-R items, orange nodes are inflammatory markers and white nodes are covariates. Blue lines represent positive associations.

Line thickness and saturation represent partial correlation magnitude. AUDIT: Alcohol Use Disorders Identification Test. CESD-R: Center for Epidemiological Studies–Depression Scale–Revised. CRP: C-Reactive Protein. IL-6: Interleukin-6.

Table 1. Regression models of depression and inflammatory markers

(A) Logistic regression for MDE diagnosis			
	Odds Ratio	**95%CI**	*p*
CRP	0.95	0.69-1.32	0.78
IL-6	1.08	0.77-1.50	0.66
(B) Linear regression for CESD-R total score			
	Standardized Estimate	**Standard Error**	*p*
CRP	0.13	0.18	0.48
IL-6	0.27	0.17	0.12

All models adjusted for body mass index, family income, education years, current smoking, alcohol consumption and a clinical diagnosis of hypertension, asthma and/or diabetes. (A) Logistic regression of inflammatory markers predicting a major depressive episode according to the MINI. (B) Linear regression of inflammatory markers predicting CESD-R total sum-score. 95%CI: 95% confidence interval for the odds ratio; SE: standard error; CRP: C-Reactive Protein; IL-6: interleukin-6; CESD-R: Center for Epidemiological Studies–Depression Scale–Revised.

Supplementary material

Figure S1. Pelotas birth cohort follow-up flowchart
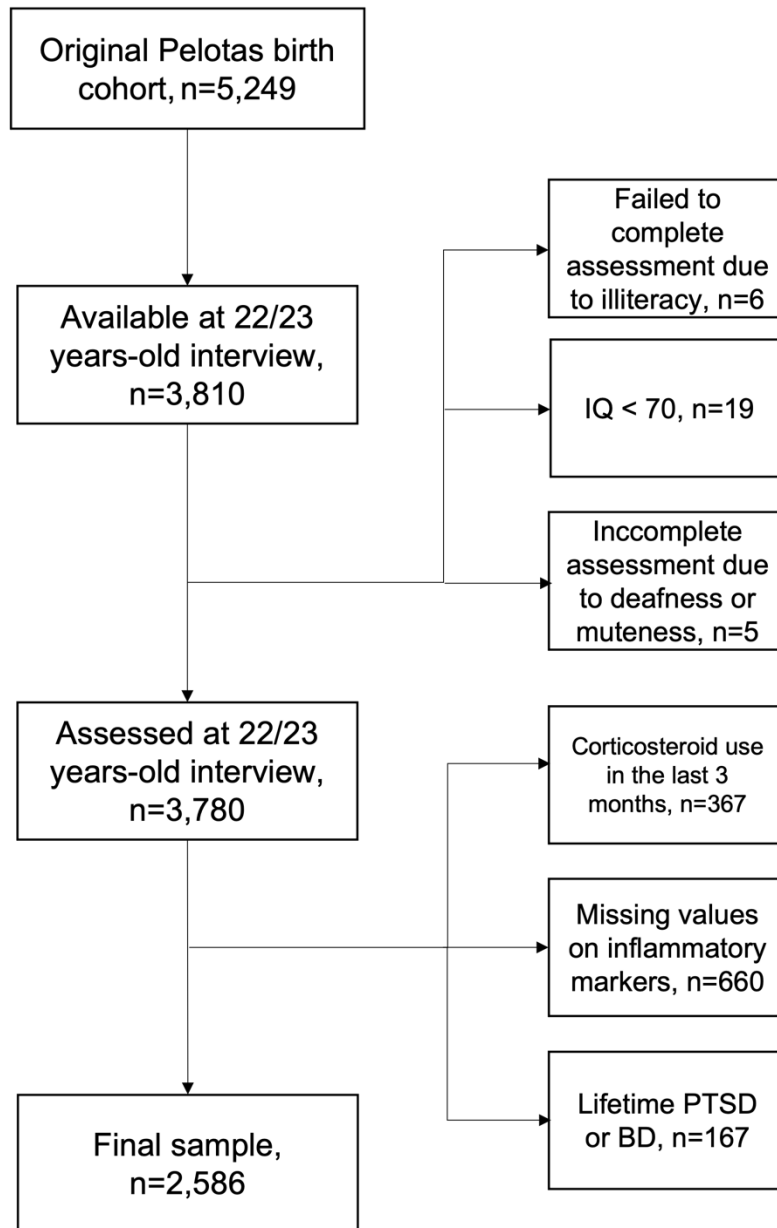
The Pelotas birth cohort is an ongoing longitudinal study in which all children born in Pelotas, in the south of Brazil, during 1993 (5,249 individuals) were assessed at multiple timepoints until 22 years old (2015). Further sample details can be found at (17).

Table S1. Descriptive statistics for the analyzed sample and for excluded participants

	Sample (N=2,586)	Excluded (N=1,194)
Males (%)	1,328 (51.3)	431 (36.0)
Mean Years of Education (SD)	9.78 (2.3)	9.94 (2.4)
Mean Family Income (SD)	3.09 (3.0)	3.50 (4.4)
Mean CESD-R at 22 (SD)	7.81 (8.26)	12.71 (11.9)
Mean AUDIT (SD)	4.15 (4.7)	4.67 (5.2)
Current smokers (%)	424 (16.3)	224 (17.8)
Mean BMI (SD)	25.12 (5.1)	25.53 (5.6)
Asthma, diabetes or hypertension (%)	713 (27.5)	702 (58.7)
Corticosteroid use in the last 3 months (%)	343 (12.2)	160 (16.5)
MDE diagnosis at 22 (%)	53 (2.04)	66 (4.9)
Other psychiatric conditions (%)	317 (12.2)	307 (25.7)
Mean CRP in mg/L (SD)	2.72 (6.7)	3.53 (7.9)
Mean IL-6 in pg/L (SD)	1.67 (1.7)	1.78 (2.0)

Excluded sample: participants with corticosteroid use in the last 3 months, missing data for either CRP or IL-6, and/or a lifetime diagnosis of bipolar disorder or post-traumatic stress disorder. For parsimony, family income is presented in 1,000 Brazilian *reais* (BRL); AUDIT: Alcohol Use Disorders Identification Test; MDE: major depressive episode; other psychiatric conditions: MINI diagnosis of either one of antisocial personality disorder, attention-deficit/hyperactivity disorder, generalized anxiety disorder or social anxiety disorder.

8. Article #3

Adolescent depression beyond DSM definition: a network analysis

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DECLARATIONS

Conflicts of interest: Dr. Valeria Mondelli has received research funding from Johnson & Johnson, a pharmaceutical company interested in the development of anti-inflammatory strategies for depression, but the research described in this paper is unrelated to this funding. All other 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.

Availability of data and material: data is available upon reasonable request.

Code availability: All R code for analysis on the main text and on the Online Resources are available at the Open Science Framework https://osf.io/uvbh3/

Ethics approval: The study was approved by the Brazilian National Ethics Committee (CAAE 50473015.9.0000.5327).

Consent to participate: Participants and/or primary caregivers provided written dissent terms if they refused to participate.

Consent for publication: not applicable.

ABSTRACT

Calls for refining the understanding of depression beyond diagnostic criteria have been growing in recent years. We examined the prevalence and relevance of DSM and non-DSM depressive symptoms in two Brazilian school-based adolescent samples with two commonly used scales, the Patient Health Questionnaire (PHQ-A) and the Mood and Feelings Questionnaire (MFQ). We analyzed cross-sectional data from two similarly recruited samples of adolescents aged 14 to 16 years, as part of the Identifying Depression Early in Adolescence (IDEA) study in Brazil. We assessed dimensional depressive symptomatology using the PHQ-A in the first sample (n=7,720) and the MFQ in the second sample (n=1,070). We conducted network analyses to study symptom structure and centrality estimates of the two scales. Additionally, we compared centrality of items included (e.g., low mood, anhedonia) and not included in the DSM (e.g., low self-esteem, loneliness) in the MFQ. Sad mood and worthlessness items were the most central items in the network structure of the PHQ-A. In the MFQ sample, self-hatred and loneliness, two non-DSM features, were the most central items and DSM and non-DSM items in this scale formed a highly interconnected network of symptoms. Furthermore, analysis of the MFQ sample revealed DSM items not to be more frequent, severe or interconnected than non-DSM items, but rather part of a larger network of symptoms. A focus on symptoms might advance research on adolescent depression by enhancing our understanding of the disorder.

Keywords: Depressive Symptoms; Adolescence; Psychometrics; Diagnostic and Statistical Manual of Mental Disorders; Patient Outcome Assessment

INTRODUCTION

Depressive disorders constitute a leading cause of health-related burden globally[1]. Depression tends to have its onset in adolescence[2] and is commonly chronic and recurrent, with lifetime cumulative prevalence estimates reaching 25%[3]. As a time of profound biopsychosocial changes, adolescence is an important period for the evaluation of mental health problems. Understanding unique characteristics of depression during this period can be crucial for alleviating its life-long repercussions, especially in low- and middle-income settings, where the majority of global youth live, but the minority of mental health research is conducted [4, 5].

The heterogenous nature of Major Depressive Disorder (MDD) poses, however, multiple challenges towards this goal. The Diagnostic and Statistical Manual (5th edition; DSM-5) criteria for MDD among adolescents requires the presence of at least five out of nine possible symptoms, with one of those being low/irritable mood or anhedonia[6]. In adults, these criteria allow for over two hundred symptom permutations that meet the current DSM diagnosis[7] – though such analysis has not been performed among adolescents, even greater heterogeneity would be theoretically expected given the additional criterion of irritability. MDD's multitude of symptom profiles also impacts its understanding from neurobiological[8] and psychosocial[9] perspectives. Furthermore, a non-negligible portion of people receiving psychotherapeutic and/or pharmacological interventions – strategies usually employed following a one-size-fits-all approach to treatment – only partially benefit from them[10].

Suboptimal outcomes may in part stem from an over-focus on criteria that do not adequately consider patient priorities[11]. Items listed in the DSM may not fully capture the experience of living with depression in youth, as, historically, the DSM is a consensus-based operationalization of psychopathology[12] rather than an evidence- or data-driven one. Commonly used instruments for assessing depression dimensionally reflect such heterogeneity. Scales frequently reflect clinically significant symptoms that represent authors' clinical views. For instance, the Children's Depression Inventory (CDI) features items on self-deprecation, pessimism and loneliness that are not explicitly present in the DSM criteria but, much like its original adult version (the Beck Depression Inventory), reflects Beck's cognitive model[13]. Conversely, the Children Depression Rating Scale (CDRS), based

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on the Hamilton Depression Rating Scale, prioritizes somatic symptoms[14], common among hospitalized patients with depression.

Despite the DSM's binary approach to mental illness being undeniably relevant for decision-making in research and clinical settings[15], calls for better understanding of psychiatric symptomatology beyond categorical criteria have gained momentum in recent years. One promising avenue is the adoption of symptom-level, data-driven methods. The network framework[16] offers an alternative to the common cause model of disease, in which symptoms are caused by an underlying latent variable (e.g., low mood, anhedonia, concentration difficulties, insomnia and weight loss are all equally caused by "depression" in the same way a bacteria causes pneumonia). Alternatively, the network perspective considers symptoms as mutually reinforcing entities by focusing on symptoms rather than syndromes. In line with most of the research landscape[5], network analytic investigations of adolescent depression are also more commonly conducted in high-income settings[17–19], more specifically Western Educated Industrialized Rich and Democratic (WEIRD) populations with English-speaking samples[20]. Additionally, even though they are not mutually exclusive[21], most studies to date have examined depression symptoms either from a latent or a network approach.

Therefore, with the growing emphasis in the literature on understanding depression symptomatology beyond current DSM criteria and its interest in the generalizability of psychological findings[22], symptom-level analysis of MDD symptoms in adolescence is a promising avenue to move the field forward. Following from research in adult, clinical samples [23, 24], we hypothesize that symptoms of adolescent depression may be uniquely interconnected and may not follow strict DSM criteria. We here aimed to examine, in two school-based samples of Brazilian adolescents, the symptom structure of two commonly used dimensional depression scales.

METHODS

Sample description

We analyzed cross-sectional data from two samples recruited from public state schools in Porto Alegre, Brazil. Both samples were composed of adolescents aged 14 to 16 years and both completed the same identification and sociodemographic questionnaire, but each had a different instrument to

capture depressive symptomatology: one the Patient Health Questionnaire–Adolescent Version (PHQ-A)[25] the other, the Mood and Feelings Questionnaire (MFQ)[26]. The PHQ-A sample (n=7,720) was recruited from June 2018 to November 2019, while the MFQ sample (n=1,070) was recruited from August 2016 to December 2016. For the PHQ-A sample, 101 schools were visited; for the MFQ sample, 7 schools were visited. All schools in the MFQ sample were also visited for the PHQ-A sample. This report is part of the Identifying Depression Early in Adolescence (IDEA) study, a multi-national collaborative effort to advance the early identification of MDD in adolescents[27, 28]. As inclusion criteria for this study, adolescents had to be enrolled in grades 8 to 11 and be aged 14 to 16 years on the day of school recruitment. Participants and/or primary caregivers provided written dissent terms if they refused to participate and all data was coded to ensure anonymity in database handling. Independently of further inclusion in the IDEA study [28], trained psychologists and child psychiatrists contacted participants who reported suicidality, physical or sexual trauma for in-depth clinical evaluation and referral to appropriate care if needed in accordance with Brazilian legislation. The study was approved by the Brazilian National Ethics Committee (CAAE 50473015.9.0000.5327).

Measures

Sociodemographic variables

Participants completed a questionnaire on age, gender, skin color, school information and parental age. Skin color followed the Brazilian Institute of Geography and Statistics (IBGE) census categorization as white, black, yellow, brown or indigenous. Adolescents also answered questions on variables which are part of a composite risk score for the risk of developing depression in adolescence, the Identifying Depression Early in Adolescence Risk Score[28, 29], though these were not included in the current analysis.

Patient Health Questionnaire-9 – Adolescent Version (PHQ-A)

The PHQ-A is an adapted version of the Patient Health Questionnaire-9 (PHQ-9) for use with adolescents and is commonly employed as a screening tool in clinical and research settings[25]. The questionnaire consists of nine questions with Likert-type response options "none", "several days",

"more than half the days" and "nearly every day". The nine items were designed to represent the DSM-IV criteria for a major depressive episode. We performed the process of translation and cultural adaptation of the scale following the TRAPD (Translation, Review, Adjudication and Documentation) steps proposed for questionnaire translation and assessment[30]. In the PHQ-A sample, 3.1% of participants had missing values; therefore, we conducted multiple imputation, with no significant differences in the imputed sample and the whole sample regarding proportion of males/females, age, skin color, mean PHQ-A score or maltreatment history (Online Resources Table S1).

Mood and Feelings Questionnaire (MFQ)

The MFQ is a 33-item self-report questionnaire with three response options ("not true", "sometimes true" and "true") designed to assess mood symptomatology[26], recently translated and adapted to Brazilian Portuguese by our group[31]. It evaluates features included in the DSM criteria and those not explicitly included in the criteria (e.g., "I felt lonely"). We classified MFQ items as "non-DSM" according to previous studies[12, 23, 24]. Items 12 and 20 were categorized as social isolation; item 14 as easy crying; items 15, 22 and 28 as pessimism; items 23 and 25 as self-derogation; item 24 as self-accusation; item 26 as somatic complaints; item 27 as loneliness; item 30 as low-confidence and pessimism; item 31 as feelings of inadequacy/failure. To allow for comparable analysis between the PHQ-A and the MFQ, we combined DSM items using an "or" rule (e.g., items on reduced and increased appetite were combined to form one item reflecting the DSM A3 criterion; see Online Resources Table S2 for a full description). Since 5.1% of participants had missing values on the MFQ items we conducted multiple imputation, with no significant differences in the imputed sample and the whole sample regarding proportion of males/females, age, skin color, mean MFQ score or maltreatment history (Online Resources Table S1).

Statistical analysis

We calculated mean and standard deviations (SD) for continuous variables, as well as frequencies and percentages for categorical variables. To evaluate possible school-level influence in questionnaire responses, we analyzed the intraclass correlation coefficient (ICC) by school for both

samples[32]. We conducted Wilcoxon-Mann-Whitney tests to compare MFQ and PHQ-A median scores for boys and girls. We compared means, SD and centrality estimates between DSM and non-DSM features with permutation tests that compare the observed variables to a distribution of possible differences between groups.

Latent variable analysis

We used confirmatory factor analysis (CFA) to identify factor structure and dimensionality of the PHQ-A and the MFQ[21]. To test if PHQ-A and MFQ items could be reduced to a single "depressive symptomatology" factor, we tested unidimensional solutions. Model fit was evaluated based on traditional fit measures[33]: Comparative Fit Index (CFI) and Tucker-Lewis Index (TLI) ≥0.95; and root mean square error approximation (RMSEA) ≤0.06. We derived reliability estimates from CFA using McDonald's omega (ω)[34] and the estimator was weighted least squares with adjusted for mean and variances (WLSMV).

Network analysis

Networks consist of nodes (i.e. questionnaire items) connected through edges (associations) estimated using L1-regularized partial correlations (all nodes are regressed on each other adjusting for the effect of every other node). An L1-penalty is imposed on regression coefficients to balance goodness of fit and parsimony (also called the least absolute shrinkage and selection operator-*lasso*). Small edges are set to zero, which enables finding the sparsest (parsimonious) network and controls for multiple testing. As recommended, we used a tuning lambda=0.25[35]. We focused our analysis on expected influence node centrality, deemed more stable than other centrality measures[36]. We used multidimensional scaling for all graphs due to node distance interpretability (i.e., strongly associated nodes appear closer together, while weakly/negatively associated ones are more distant)[37]. We tested the accuracy of the networks using non-parametric bootstrapping procedures with n=1000 runs. For centrality measures, we used a case-dropping bootstrap and evaluated the correlation coefficient of stability (CS (cor=0.7)), which should be above 0.25, ideally above 0.5[35]. Because PHQ-A and MFQ

items may assess closely related constructs, we used the *goldbricker* procedure on each scale to check the data for node redundancy and possible item reduction[38]. Furthermore, in order to see if MFQ DSM and non-DSM items would cluster together or independently, we used the *walktrap* algorithm[39] to detect item clusters. Lastly, we used the network comparison test (NCT)[40] to compare PHQ-A and MFQ networks (the M statistic) according to sex. The same analysis was done for examining PHQ-A items and DSM items derived from the MFQ. Analyses were conducted in *R*, version 3.6.1[41]. The R code is available in the Online Resources Material.

RESULTS

Descriptive statistics

The PHQ-A sample included 7,720 participants (54.9% females), with a median PHQ-A total score of 8 (IQR=10; Table S1). Over half (59.9%) of participants self-reported as white (Table S1). Females had higher median PHQ-A total scores than males (11 and 6, respectively; Mann-Whitney U-statistic=446, p<0.001). The most commonly endorsed items in the "nearly every day" option were sleep problems (27.3%), fatigue (23.5%) and feelings of worthlessness (23.4%). The average correlation between items was r=0.39 (range *r*=0.31 to *r*=0.62; Online Resources Figure S1). There was negligible evidence of school-clustering (ICC=0.009, 95% CI 0.004-0.017).

The MFQ sample included 1,070 participants (55.5% females), with a median MFQ total score of 19 (IQR=20; Table S1). Females had higher median MFQ total scores than males (25 and 14, respectively; Mann-Whitney U-statistic=744, p<0.001). The most commonly endorsed items in the "always true" category were "It was hard to make decisions" (32.9%), followed by "I felt lonely" (26.1%) and "I felt sulky or upset with my parents" (24.7%). The average correlation between items was *r*=0.31 (range *r* = -0.25 to *r* = 0.69; see Figure S2 for a correlation matrix). DSM and non-DSM features were not different regarding medians (Mann-Whitney U-statistic=133, p=0.999) or standard deviations (Mann-Whitney U-statistic=121, p=0.615), suggesting neither group was more severe or variable than the other. There was a close to zero effect of school-clustering (ICC=-0.004, 95% CI -0.005-0.006).

Confirmatory factor analysis for the PHQ-A

The unidimensional solution for the PHQ-A had good fit indices (CFI=0.982, TLI=0.976, RMSEA=0.064) with adequate reliability (ω=0.854, 95% CI 0.849-0.859). Items assessing suicidality had the highest initial thresholds (i.e., required higher depression severity to endorse the response option "Several days" over "None"), followed by psychomotor changes and concentration difficulties (Online Resources Table S4).

PHQ-A Network analysis

Figure 1 presents the PHQ-A network structure. There were 35 non-zero edges out of 36 possible edges, with a mean weight of 0.10. There were strong partial correlations between low mood, feelings of worthlessness and suicidality items. Suicidality, low mood and feelings of worthlessness had the highest expected centrality indices (Figure 1b). There was no suggestion of node redundancy from the *goldbricker* procedure. Males and females did not have different network structures (M=0.068, p=0.126), but there was a significant difference in overall connectivity, with females showing higher values than males (S=0.201, p<0.001; Online Resources Figure S3).

--- INSERT FIGURE 1 HERE ---

MFQ Confirmatory factor analysis

The unidimensional solution for the MFQ had adequate fit indices (CFI=0.953, TLI=0.949, RMSEA=0.057) with good reliability estimates (ω=0.941, 95% CI 0.936-0.946). Items assessing concentration difficulties had the lowest initial thresholds, while items reflecting psychomotor retardation ("I spoke slower than usual") and suicidality ("I thought about killing myself") had the highest initial thresholds (Online Resources Table S5).

MFQ Network analysis

Figure 2 presents the MFQ sample network structure. There were 271 non-zero edges out of 528 possible edges, with a mean weight of 0.02. In contrast to the PHQ-A sample, low mood was not

among the most central items. Rather, "hated myself", "I felt lonely" and "I did not sleep as well as I usually sleep" were the most central items (Figure 3). However, two of the three least central items were also non-DSM criteria ("I worried about aches and pains" and "I did not want to see my friends"). DSM and non-DSM items did not differ regarding their mean centrality (W=151, p=0.529), suggesting groups were not differentiated based on expected influence. The *walktrap* algorithm did not suggest DSM and non-DSM items to cluster independently – rather, as a complex, highly interconnected network of symptoms. Analyzing the network structure using an "or" rule to estimate DSM criteria from the MFQ items, the most central items were the same as in the full scale analysis in Figures 2 and 3. Additionally, in a DSM-only MFQ analysis using an "or" rule, worthlessness, low mood and suicidality were the most central items (Online Resources Table S2 and Figures S4-S6). This is consistent with results from the PHQ-A analysis.

Males and females had different network structures (M=0.272, p<0.001), with no difference in overall connectivity (S=0.400, p=0.379). "I hated myself" was the most central items for boys and girls, followed by "I felt lonely" and "I thought bad things would happen to me" for males and "I felt I was no good anymore" and "I thought life was not worth living" for females (Online Resources Figure S7). Items M2 ("I did not enjoy anything at all"), M14 ("I cried a lot") and M17 ("I thought about death and dying") were more central for females, while items M4 ("I ate more than usual") and M33 ("I slept a lot more than usual") were more central for males. Examining only MFQ DSM items, there was no significant differences in network structure (M=0.122, p=0.73) or connectivity (S=0.084, p=0.33) for either sex.

--- INSERT FIGURE 2 HERE ---

--- INSERT FIGURE 3 HERE ---

Network accuracy

The PHQ-A and the MFQ showed adequate network structure accuracy, with non-zero weights in bootstrapped difference tests ($\alpha = 0.05$). For both scales, most edges were significantly different. Centrality estimates for both the PHQ-A and the MFQ expected influence had optimal levels of stability

(CS-coefficient >0.75) and were not biased by node variance (PHQ-A: r=-0.111, p=0.777. MFQ: r=-0.042, p=0.814). All graphs are available upon request.

DISCUSSION

In two similarly recruited independent school-based samples from Brazil, we examined, using latent and network analyses, the characteristics of adolescent depression features that are and are not included in the formal DSM criteria for MDD. In the PHQ-A sample – including exclusively DSM items – we found low mood and feelings of worthlessness as the two most central items. In the MFQ sample, we found DSM items to be part of a complex and interconnected network that also includes items not explicitly captured by the DSM criteria for MDD. In this sample, the two most central features were self-hatred and loneliness – features not overtly captured by the DSM.

Depression is widely acknowledged as a heterogeneous construct[7, 12]. We attempted to tackle such heterogeneity by examining two dimensional measures of depressive symptoms: the PHQ-A, a widely used instrument reflecting strict DSM adolescent MDD criteria; and the MFQ, which includes those criteria as well as features not included in the DSM. The PHQ-9, from which the PHQ-A is derived and closely related to, is one of the standardized mental health outcomes recently proposed by the Wellcome Trust and the National Institute of Mental Health as an attempt to harmonize data from different research settings[42]. Meanwhile, the MFQ was used as the main outcome for the largest clinical trial of psychotherapy in adolescents with depression[43].

Our work is in agreement with previous findings from high-income countries showing self-hatred and loneliness as among the most interconnected items in community-based samples of adolescents [17, 36]. Our results are also in line with a previous report of middle- and high-school students in the United States that found self-hatred, loneliness, sadness and worthlessness as the most central symptoms of adolescent depression using the short version of the MFQ [18]. Moreover, our work replicates and expands on findings from two studies that show non-DSM features to be as important in depression networks as DSM criteria[23, 24] – results derived from adult clinical samples. Our report adds to these studies by applying both latent and network approaches to two non-clinical, school-based adolescent samples from a middle-income country.

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An important implication of our findings is the question of whether the DSM, through its consensus-based operationalization of adolescent MDD, is capturing all features of depression that are important to the young people experiencing this disorder. In the PHQ-A sample, excessive guilt and/or feelings of worthlessness was a highly central item, while anhedonia, one of the cardinal symptoms of MDD, was not. In the MFQ sample, self-hatred and low self-esteem were highly central nodes, though neither is explicitly and adequately captured by the DSM's criteria A7 of "feelings of worthlessness and/or excessive guilt". Both are, however, predictors and/or markers of negative outcomes longitudinally associated with depression[44, 45]. The same holds true for loneliness, also found to be highly central in our report and not mentioned as one of the nine MDD DSM criteria[44]. A recent qualitative meta-synthesis also identified loneliness as a central experience among young people with depression[46]. Moreover, findings from developmental social neuroscience research suggest that adolescence is a period of increased vulnerability to perceived loneliness, and loneliness is associated with heightened adverse responses to social cues in functional neuroimaging studies[47].

Interestingly, three of the five most central items in the MFQ network ("I hated myself", "I thought life was not worth living", "I thought bad things would happen to me") parallel Beck's cognitive triad of negative views about the self, the world and the future[48]. Furthermore, hopelessness, considered by 11th version of the International Classification of Diseases (ICD-11) as an accessory symptom of depression[49] and shown to be highly central in our adolescent sample, was shown to better differentiate depressed and non-depressed adults according to DSM-IV criteria[50]. Our results come at a time of growing interest in understanding outcomes based on patients' needs and priorities. In accordance with our results, Chevance and colleagues found, among other domains, improvements in feelings of loneliness, low self-esteem and social isolation to be commonly cited expected benefits of depression treatment[11]. A systematic review of qualitative studies of adults showed only seven out of fifteen frequently mentioned features of depression from worldwide samples are part of the DSM criteria for MDD diagnosis, with loneliness notably being the fourth most frequently mentioned symptom among Western and non-Western populations[51]. Symptoms tended to have significant variability across cultures, suggesting DSM criteria may also miss important information in culturally-diverse settings.

Although useful for clinical and research purposes, there has been growing skepticism regarding the adequacy of the consensus-based approach to psychopathology used by the DSM[15]. Different conceptualizations of depression, with empirical decisions to add or drop symptoms, are common within the history of psychiatry[15]. It is possible that, given the biopsychosocial particularities of adolescence as a life period, simply extending the definition of MDD for adulthood to adolescence, with the inclusion of irritability as an alternative to depressed mood in the A1 criterion[6], may not fully encompass particular characteristics of how young people experience depressive symptomatology. Highly central nodes in our results such as pessimism and hopelessness are important clinical features of depression[11, 12, 48], but neither is adequately captured by the DSM A7 criteria of excessive guilt and worthlessness[12]. Importantly, a recent study of depressed parents and their offspring did not support irritability as being more common in adolescents than in adults, though it did find different symptomatic profiles according to age[52]. Indeed, irritability has been suggested as an antecedent of low mood in longitudinal research and/or as a marker of severity[53]. In the PHQ-A sample, the item questioning low mood or irritability was highly central - though, following DSM criteria, there was a single item simultaneously questioning both symptoms. In the MFQ sample, irritability was not a specially interconnected node.

The past decade has seen the rise of data-driven methods for more refined understanding of depressive phenotypes. We used network analysis as an exploratory approach for studying relations among depressive symptoms in adolescence. Other data-driven approaches have been used to better understand symptom clusters of treatment response in adolescents[54]. However, a systematic review exposed difficulties in finding data-driven subtypes that may stem from the over-reliance on DSM criteria as well as on the common cause model[55]. As an alternative to these shortcomings, the network approach advances psychopathological research by considering symptoms as mutually reinforcing entities[16]. By combining individuals with very different symptom profiles into an unweighted sum-score, we risk losing important connections that are fundamental to continue progress in depression research[16]. Interestingly, results from our MFQ sample did not support a clear separation of DSM and non-DSM criteria. By using regularized partial correlations, which calculate symptom-symptom correlations adjusting for every other symptom in the network, we found all items to be part of a highly

interconnected network. Though increasing the number of symptoms contemplated by the DSM certainly could increase MDD's heterogeneity, not properly evaluating important non-DSM features also hinders understanding of how young people experience the disorder. Although most of the network literature to date has used cross-sectional data, these can be useful for exploring singular patterns of symptom association as a data-driven, hypothesis-generating approach. Further studies assessing longitudinal datasets will be crucial to better understand the developmental presentation of depressive symptomatology in adolescence.

Even though we are considering MFQ non-DSM items as part of the depression spectrum, it is conceivable that non-DSM MFQ items may capture a different construct, not necessarily depression, but related to a comorbid mental disorder. It is plausible that the MFQ, even if *a priori* designed to encompass symptoms of depression, actually captures anxiety symptoms or broader psychopathological distress. As much as our findings suggest a potential expansion of the depressive syndrome, stakeholders may share different propositions on an even larger expansion, not exclusively or fully captured by psychopathology research using more traditional measurements[11]. This is important in a larger discussion on the distinction between what are the disorder's diagnostic criteria and the disorder itself. Our argument of a potential insufficiency of DSM criteria for adolescent MDD is in line with an indexical view of nosology[13] – symptoms suggest the presence of the disorder, but they are not fully explanatory of it. Rather, these are possible alterations reflective of the condition. If we consider that the diagnostic criteria (i.e., DSM criteria for adolescent MDD) are the only means of identifying depression, we may miss more detailed information of the range of depressive experiences in teenagers (i.e., features included and not included in the DSM criteria). These concerns have been previously raised in network examinations of adult samples [23, 24] and are even more pertinent in studies of adolescent features of depression. Despite the DSM's numerous contributions and for allowing multiple advances in psychopathology research, interpreting the diagnostic criteria as full descriptions of the syndrome of depression among adolescents may be insufficient for understanding its uniqueness and peculiarities. Acknowledging limitations of psychopathology research[11] and a possible overlook on what is most important to patients is crucial for advancing depression research.

A number of limitations must be noted. Firstly, our results are based on cross-sectional data from school-based samples, which simultaneously precludes necessary generalization of findings to other populations or clinical samples and highlights the need for longitudinal research for further disentangling of results as specific features of adolescent depression. Although both samples were recruited using closely related protocols, respondents were different participants, which impedes direct comparisons between scales, as well as possible risk factor exposition (see Table S1). Also, it is worth noting the high frequency of endorsement of the seven questions on maltreatment (see reference [28] for details) in both samples – which is a limitation in terms of external generalizability but also emphasizes importance of studying adolescent depression in socially vulnerable populations (i.e., public state schools in a middle-income country). Furthermore, comparisons between the PHQ-A and DSM items derived from the MFQ were drawn from an "or" rule based on face validity and item content, suggesting caution in evaluating these results. It is worth mentioning that there were significant differences in network structure between the two scales, but not of centrality estimates. This may be due to a potential impact of the number of questionnaire items on response pattern of a 9-item and a 33-item questionnaire, the "or" rule used to derive DSM features from the MFQ and the different samples. Consequently, the replicability and longitudinal dynamics of network characteristics, influence of context and number of items in network estimation are matters of continued interest that deserve further investigation[56, 57]. Additionally, the PHQ-9, from which the PHQ-A is derived, has been under heavy criticism for its accuracy and psychometric properties[58]. Both the PHQ-A and the MFQ, as self-report instruments, may lead to biases in terms of symptom reporting when compared to clinician-rated scales or structured interviews[59]. Because this report is based on data from the screening phase of a larger [28], clinical diagnosis was not possible for either sample. We are not aware of any other study examining depressive symptoms with the PHQ-A or the MFQ in Brazilian adolescents, thus limiting comparisons between universal and local symptom conceptualizations. Finally, we used only one instrument to examine the centrality of DSM and non-DSM criteria, which could have biased the findings.

In light of these limitations, and considering we are at the early stages of implementing network techniques to adolescent psychopathology, we believe our study had several strengths. The use of two

large, community-based samples allows for the study of depression symptom presentation in a setting that is closer to the real-world and, therefore, may enhance our comprehension of the dimensional presentation of depression in adolescence. Furthermore, by recruiting adolescents in the school environment, we avoid a severity bias from clinical referrals and selection bias in contexts of scarcer resources. Additionally, the somewhat narrow age range of participants (14 to 16 years-old), despite limiting to some extent immediate extrapolations to younger or older individuals, increases sample homogeneity. Furthermore, the analysis of two different scales with two different but complementary analytical approaches allows for an in-depth examination of MDD's heterogeneity in outcome measures[60], as well as an investigation of the relations of DSM and non-DSM items. Even though DSM and non-DSM criteria tend to be related, the use of regularized partial correlations allow for multiple comparison adjustment and finding the most parsimonious network structure and centrality estimates. By combining MFQ items to more closely resemble DSM criteria using the "or" rule, we were better suited to distinguish between DSM and non-DSM criteria and allowed some comparability between the PHQ-A and the MFQ scales. Additionally, applying data-driven symptom-level techniques acknowledges growing support for the study of particular symptoms instead of unweighted sum-scores[16]. Nevertheless, we should mention the importance of replicating our findings in other settings (e.g., more resource-deprived countries), in other populations (e.g., in- and out-patient depressed adolescents or community-based youths) and with longitudinal study designs.

In summary, the present report aimed to examine the dimensional structure of two commonly used depression scales in two similarly recruited independent adolescent samples in a middle-income setting. Our study expands on previous literature in adult samples showing DSM and non-DSM features to be part of an interconnected network of symptoms[23, 24]. Our findings suggest DSM criteria for MDD not to be more frequent, more severe or more interconnected than non-DSM items, but instead both appear to be part of a larger network of adolescent depression symptoms. Refining our insights into clinical presentation of depressive symptoms in adolescence may have significant clinical implications for our understanding of such a burdensome condition for young people.

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FIGURES

Fig. 1 Network structure (a) and expected influence centrality (a) for the PHQ-A sample (n=7,720).
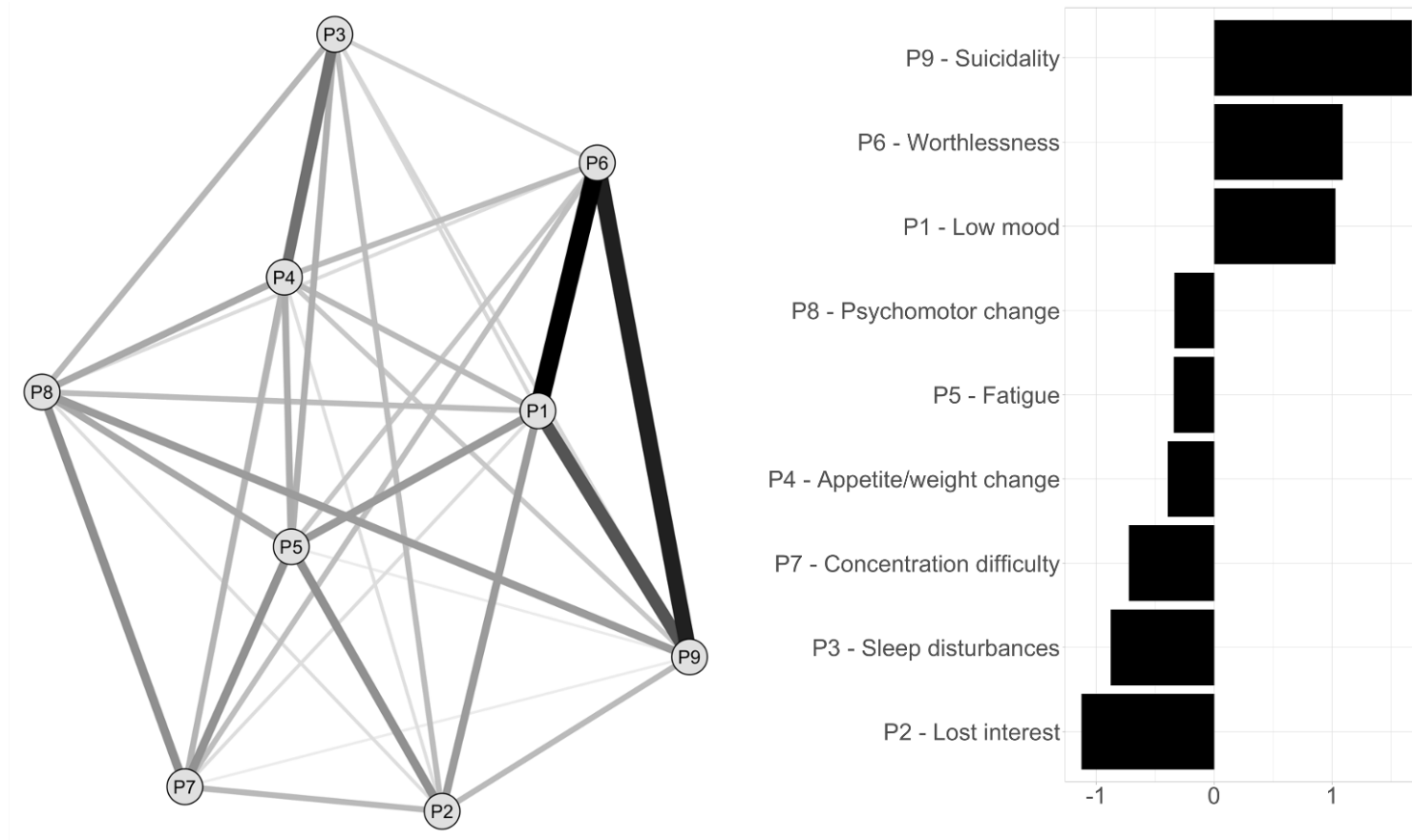
Note. PHQ-A: Patient Health Questionnaire – Adolescent Version. In Figure 1A, the lines represent positive associations. Line thickness and saturation represent correlation magnitude. The graph's layout is based on multidimensional scaling, meaning closely associated nodes are placed closer together. In Figure 1B, the Y-axis shows PHQ items ordered from highest to lowest expected influence centrality; on the X-axis are z-standardized expected influence centrality values with zero as the mean value.

Fig. 2. Network structure for the MFQ (n=1,070).
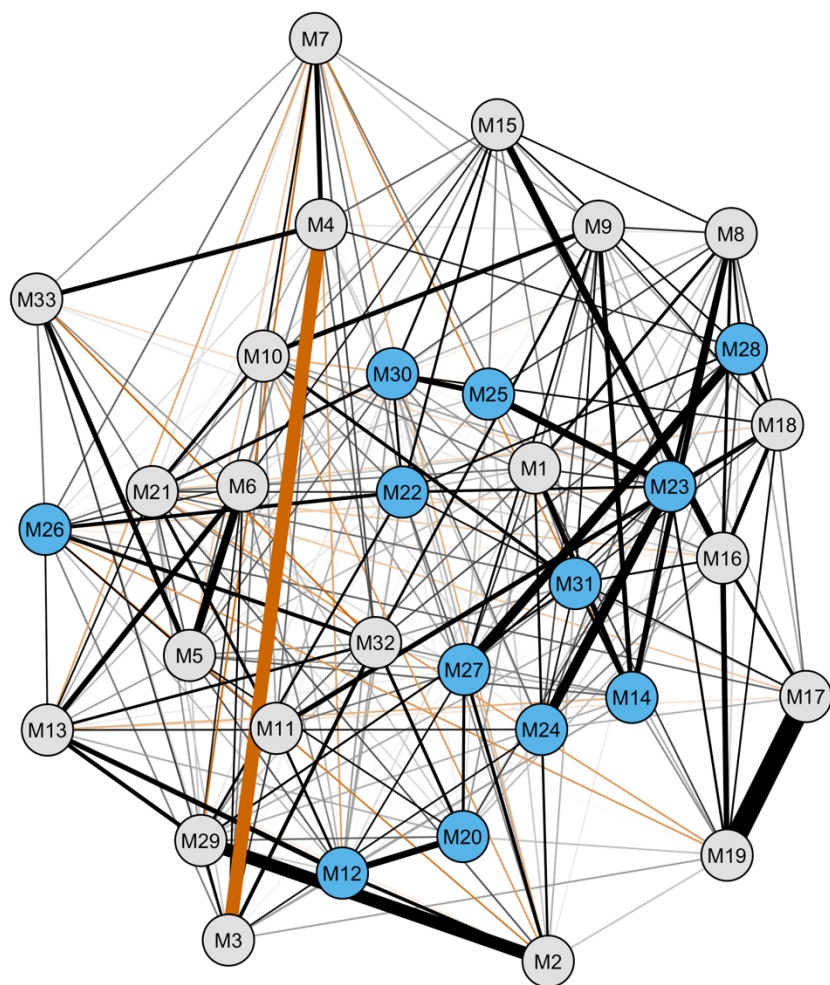
DSM Features
- M1: I felt miserable or unhappy
- M2: I did not enjoy anything at all
- M3: I was less hungry than usual
- M4: I ate more than usual
- M5: I felt so tired I just sat around and did nothing
- M6: I was moving and walking more slowly than usual
- M7: I was very restless
- M8: I felt I was no good anymore
- M9: I blamed myself for things that were not my fault
- M10: It was hard for me to make up my mind
- M11: I felt grumpy and cross with my parents
- M13: I spoke slower than usual
- M15: I thought there was nothing good for me in the future
- M16: I thought life was not worth living
- M17: I thought about death and dying
- M18: I thought family would be better off without me
- M19: I thought about killing myself
- M21: I found it hard to think properly or concentrate
- M29: I did not have any fun in school
- M32: I did not sleep as well as I usually sleep
- M33: I slept a lot more than usual

Non-DSM Features
- M12: I felt like talking less than usual
- M14: I cried a lot
- M20: I did not want to see my friends
- M22: I thought bad things would happen to me
- M23: I hated myself
- M24: I felt I was a bad person
- M25: I thought I looked ugly
- M26: I worried about aches and pains
- M27: I felt lonely
- M28: I thought nobody really loved me
- M30: I thought I could never be as good as other kids
- M31: I did everything wrong

Note. MFQ: Mood and Feelings Questionnaire. Gray nodes are symptoms included in the Diagnostic and Statistical Manual of Mental Disorders (5th edition) criteria for major depressive disorder, while blue nodes are symptoms not included in it. Black lines represent positive associations, while orange lines represent negative associations. Line thickness and saturation represent correlation magnitude. The layout is based on multidimensional scaling, meaning closely associated nodes are placed closer together.

Fig. 3. Expected influence centrality derived from the MFQ network (n=1,070).
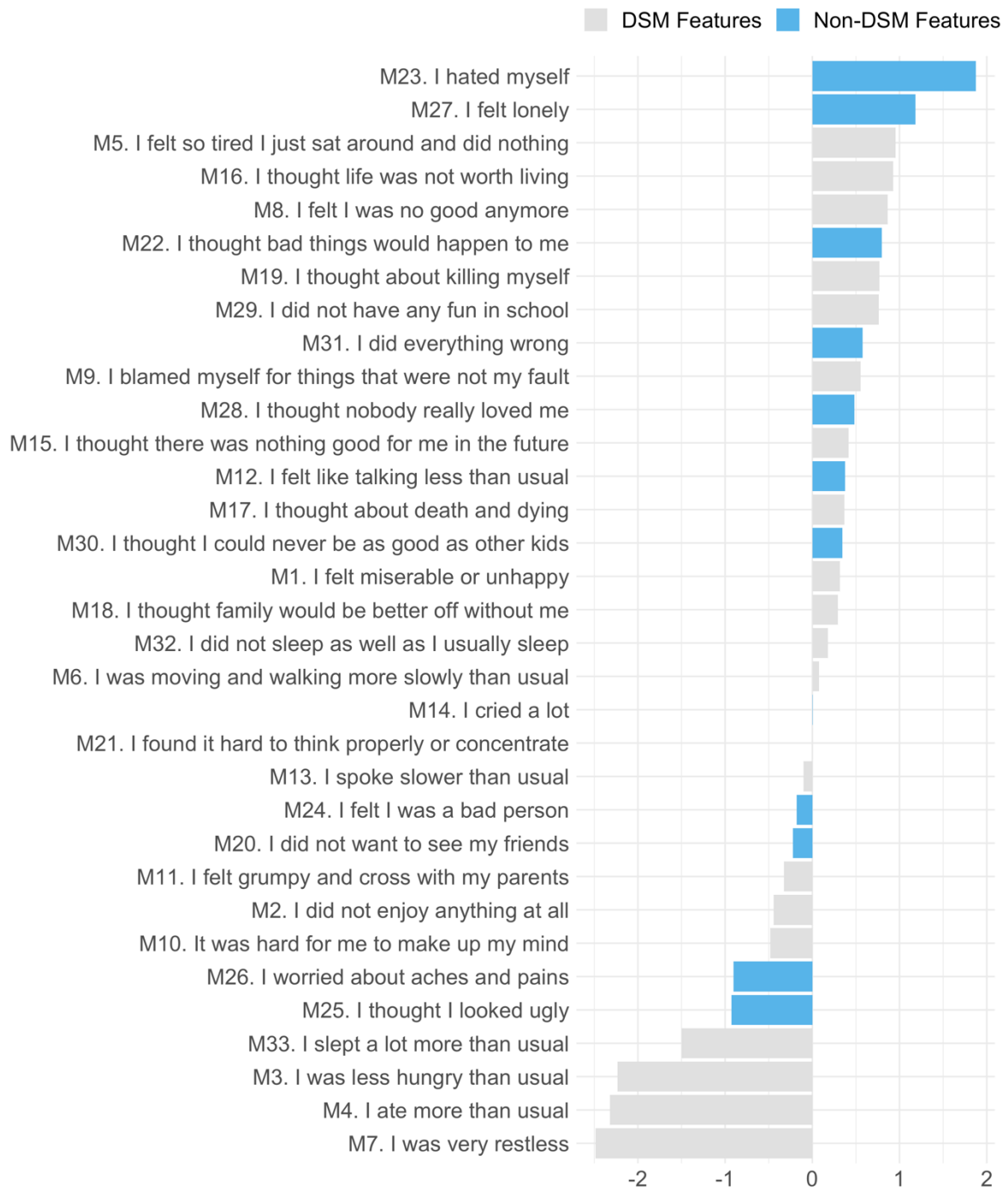
Note. Gray bars represent items included in the Diagnostic and Statistical Manual of Mental Disorders (5th edition) major depressive disorder criteria, while blue bars represent items not included in the DSM. On the Y-axis, MFQ items are ordered by highest to lowest expected influence centrality; on the X-axis are the z-standardized expected influence centrality values with zero as the mean value.

Supplementary materials for **Adolescent depression beyond DSM definition: a network analysis**

Pedro H. Manfro, Rivka B. Pereira, Martha Rosa, Hugo Cogo-Moreira, Helen L. Fisher, Brandon A. Kohrt, Valeria Mondelli, Christian Kieling

All R code for analysis on the main text and on the supplementary material are available at the Open Science Framework https://osf.io/uvbh3/

Supplementary Table S1. Descriptive statistics for the PHQ-A (n=7,720) and the MFQ (n=1,070) samples

	Non-imputed PHQ-A sample (n=7,288)	PHQ-A Sample (n=7,720)	Non-imputed MFQ sample (n=944)	MFQ Sample (n=1,070)
Females (%, 95%CI)	4,022 (55.2, 54.0-56.3%)	4,241 (54.9%, 53.8-56.0%)	518 (54.9%, 51.6-58.1%)	594 (55.5%, 52.5-58.4%)
Mean Age (SD, 95%CI)	15.73 (0.52, 15.70-15.76)	15.74 (0.8, 15.72-15.75)	15.73(0.76, 15.70-15.76)	15.75 (0.74, 15.70-15.79)
Childhood maltreatment (%, 95%CI)				
None	2047 (28.1%, 27.1-29.1%)	2157 (27.9%, 26.9-28.9%)	432 (45.8%, 42.5-49.0%)	487 (45.5%, 42.5-48.5%)
Probable	1643 (22.5%, 21.6-23.5%)	1743 (22.5%, 21.6-23.5%)	222 (23.5%, 20.8-26.4%)	243 (22.7%, 20.3-25.3%)
Severe	3728 (51.1%, 50.0-52.2%)	3820 (49.4%, 48.3-50.5%)	290 (30.7%, 27.8-33.7%)	340 (31.7%, 29.0-34.6%)
Median PHQ-A (SD, 95%CI)	8 (6.53, 9.00-9.50)	8(6.52, 9.00-9.53)	-	-
Range PHQ-A (IQR)	0-27 (4-14)	0-27 (4-14)	-	-
Skewness PHQ-A sum-score (kurtosis)	0.62(-0.47)	0.63 (-0.46)	-	-
Median MFQ (SD, 95%CI)	-	-	19 (13.62, 19.99-21.99)	17(13.92, 20.00-20.92)
Range MFQ (IQR)	-	-	0-66 (11-31)	0-66 (11-31)
Skewness MFQ sum-score (kurtosis)	-	-	-0.67(0.44)	0.68 (-0.45)
Skin color (white, %, 95%CI)	4,399 (60.4%, 59.2-61.5%)	4,630 (59.9%, 58.8-61.0%)	563 (59.6, 56.4-62.8%)	635 (59.3%, 56.3-62.2%)

Note. PHQ-A: Patient Health Questionnaire – Adolescent Version. MFQ: Mood and Feelings Questionnaire. 95%CI: 95% confidence interval. SD: standard deviation. The maltreatment variable is divided into "none" (no positive answer for items on emotional abuse, emotional neglect, physical abuse, physical neglect or sexual abuse), "probable" (one positive answer) and "severe" (two or more positive answer) as per previous literature[1,2]. The skin color item followed Brazilian official census (IBGE) of self-reported categories (white/yellow/indigenous/brown/black). For analyses, two categories (white vs. non-white) were formed. IQR: Interquartile range

Supplementary Table S2. DSM, PHQ-A and MFQ item comparison

DSM items	PHQ-A items	MFQ items
A1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)	P1. Feeling down, depressed, irritable, or hopeless?	M1. I felt miserable or unhappy. M11. I felt grumpy and cross with my parents. M14. I cried a lot. M15. I thought there was nothing good for me in the future.
A2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).	P2. Little interest or pleasure in doing things?	M2. I didn't enjoy anything at all. M29. I didn't have any fun in school.
A3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)	P4. Poor appetite, weight loss, or overeating?	M3. I was less hungry than usual. M4. I ate more than usual.
A4. Insomnia or hypersomnia nearly every day.	P3. Trouble falling asleep, staying asleep, or sleeping too much?	M32. I didn't sleep as well as I usually sleep. M33. I slept a lot more than usual.
A5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).	P8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you were moving around a lot more than usual?	M6. I was moving and walking more slowly than usual. M7. I was very restless. M13. I was talking more slowly than usual.
A6. Fatigue or loss of energy nearly every day.	P5. Feeling tired, or having little energy?	M5. I felt so tired I just sat around and did nothing.

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A7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).	P6. Feeling bad about yourself – or feeling that you are a failure, or that you have let yourself or your family down?	M8. I felt I was no good anymore. M9. I blamed myself for things that weren't my fault. M24. I felt I was a bad person. M25. I thought I looked ugly. M28. I thought nobody really loved me. M30. I thought I could never be as good as other kids. M31. I did everything wrong.
A8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).	P7. Trouble concentrating on things like school work, reading, or watching TV?	M10. It was hard for me to make up my mind. M21. I found it hard to think properly or concentrate.
A9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide	P9. Thoughts that you would be better off dead, or of hurting yourself in some way?	M16. I thought that life wasn't worth living. M17. I thought about death or dying. M18. I thought my family would be better off without me. M19. I thought about killing myself.

PHQ-A: Patient Health Questionnaire – Adolescent Version. MFQ: Mood and Feelings Questionnaire. MFQ items range: 0 (not true), 1 (sometimes true), 2 (true). For comparison between PHQ-A and MFQ items, we used an "or" rule to estimate 9 DSM criteria from the 33 MFQ items – e.g., if any one of items M16 *or* M17 *or* M18 *or* M19 were endorsed as 2 (true), we considered it equivalent to endorsing the A9 criteria of suicidality as 2 (true); if three of the four aforementioned items were endorsed as 1 (sometimes true) and one of them was considered as 2 (true), we also considered it equivalent to endorsing the A9 criteria as 2 (true); if any three of the four items were endorsed as 0 (not true) and one was endorsed as 1 (sometimes true), we considered it equivalent to endorsing the A9 criteria as 1 (sometimes true).

Supplementary Table S3. Non-DSM MFQ items
MFQ12. I felt like talking less than usual.
MFQ14. I cried a lot.
MFQ15. I thought there was nothing good for me in the future.
MFQ20. I didn't want to see my friends.
MFQ22. I thought bad things would happen to me.
MFQ23. I hated myself.
MFQ24. I felt I was a bad person.
MFQ25. I thought I looked ugly.
MFQ26. I worried about aches and pains.
MFQ27. I felt lonely.
MFQ28. I thought nobody really loved me.
MFQ30. I thought I could never be as good as other kids.
MFQ31. I did everything wrong.
MFQ: Mood and Feelings Questionnaire. We classified MFQ items as "non-DSM" according to previous studies [3–5].

Supplementary Table S4. Summary statistics for the PHQ-A and MFQ items

PHQ-A items	Mean	SD	MFQ items	Mean	SD
P1 - Low mood	1.25	1.06	M1 - I felt miserable or unhappy	0.74	0.67
P2 - Lost interest	1.23	1.01	M2 - I did not enjoy anything at all	0.29	0.52
P3 - Sleep disturbances	1.32	1.19	M3 - I was less hungry than usual	0.51	0.73
P4 - Appetite/weight change	1.02	1.13	M4 - I ate more than usual	0.77	0.75
P5 - Fatigue	1.39	1.07	M5 - I felt so tired I just sat around and did nothing	0.89	0.79
P6 - Worthlessness	1.18	1.17	M6 - I was moving and walking more slowly than usual	0.48	0.70
P7 - Concentration difficulty	0.79	1.03	M7 - I was very restless	0.82	0.73
P8 - Psychomotor change	0.73	0.99	M8 - I felt I was no good anymore	0.51	0.73
P9 - Suicidality	0.57	0.96	M9 - I blamed myself for things that were not my fault	0.70	0.79
			M10 - It was hard for me to make up my mind	1.08	0.75
			M11 - I felt grumpy and cross with my parents	0.82	0.80
			M12 - I felt like talking less than usual	0.74	0.79
			M13 - I spoke slower than usual	0.24	0.53
			M14 - I cried a lot	0.53	0.73
			M15 - I thought there was nothing good for me in the future	0.61	0.76
			M16 - I thought life was not worth living	0.39	0.68
			M17 - I thought about death and dying	0.51	0.74
			M18 - I thought family would be better off without me	0.42	0.69
			M19 - I thought about killing myself	0.28	0.61

M20 - I did not want to see my friends	0.34	0.60
M21 - I found it hard to think properly or concentrate	0.89	0.72
M22 - I thought bad things would happen to me	0.70	0.76
M23 - I hated myself	0.53	0.75
M24 - I felt I was a bad person	0.51	0.72
M25 - I thought I looked ugly	0.81	0.80
M26 - I worried about aches and pains	0.66	0.77
M27 - I felt lonely	0.82	0.81
M28 - I thought nobody really loved me	0.52	0.75
M29 - I did not have any fun in school	0.34	0.57
M30 - I thought I could never be as good as other kids	0.66	0.79
M31 - I did everything wrong	0.52	0.70
M32 - I did not sleep as well as I usually sleep	0.76	0.81
M33 - I slept a lot more than usual	0.75	0.80

PHQ-A: Patient Health Questionnaire – Adolescent Version. MFQ: Mood and Feelings Questionnaire. SD: standard deviation. PHQ-A range: 0 (none), 1 (several days), 2 (more than half the days) and 3 (nearly every day). MFQ items range: 0 (not true), 1 (sometimes true), 2 (true). Of note, the PHQ-A has 4 response options, while the MFQ has 3; therefore, PHQ-A items will have higher means and standard deviations than MFQ's.

Supplementary Figure S1. Spearman correlation matrix from the PHQ-A items
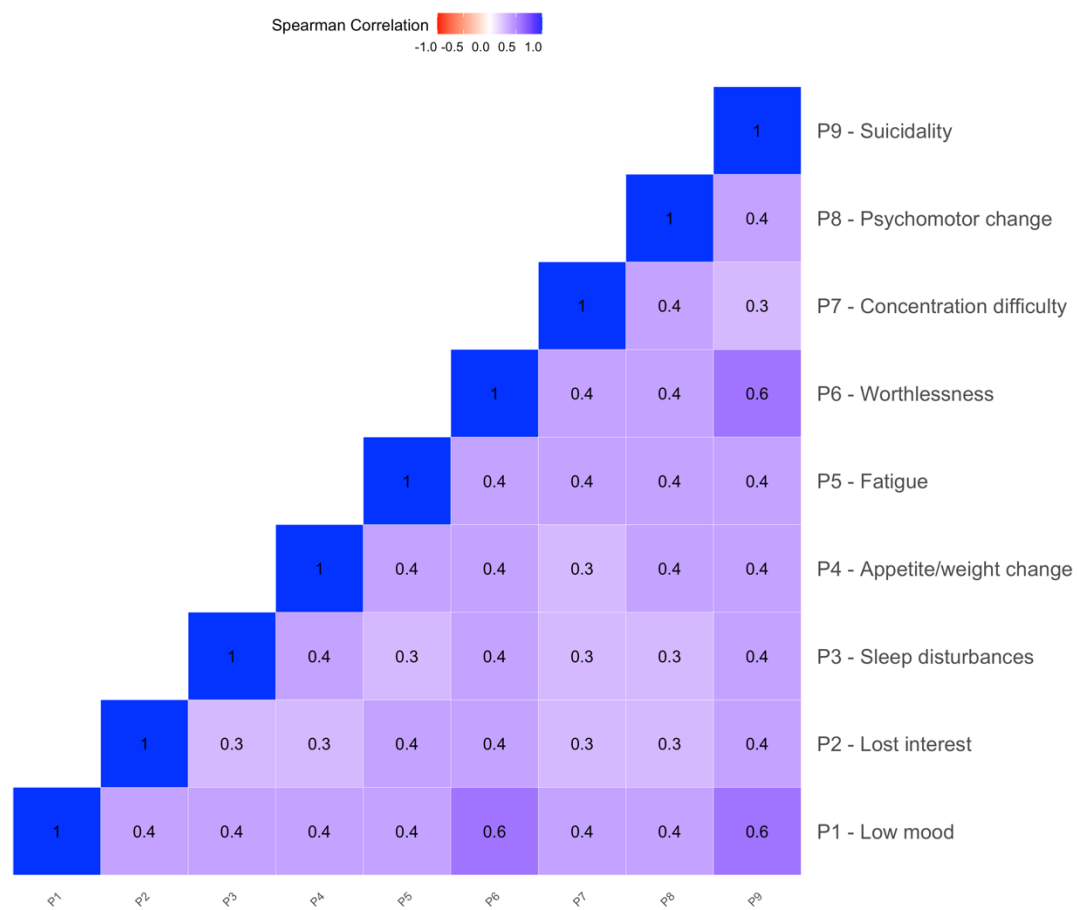
Note. PHQ-A: Patient Health Questionnaire – Adolescent Version. The color gradient goes from blue (positive correlations) to red (negative correlations). Darker shades represent stronger correlations than lighter ones.

Supplementary Figure S2: Spearman correlation matrix from the MFQ items
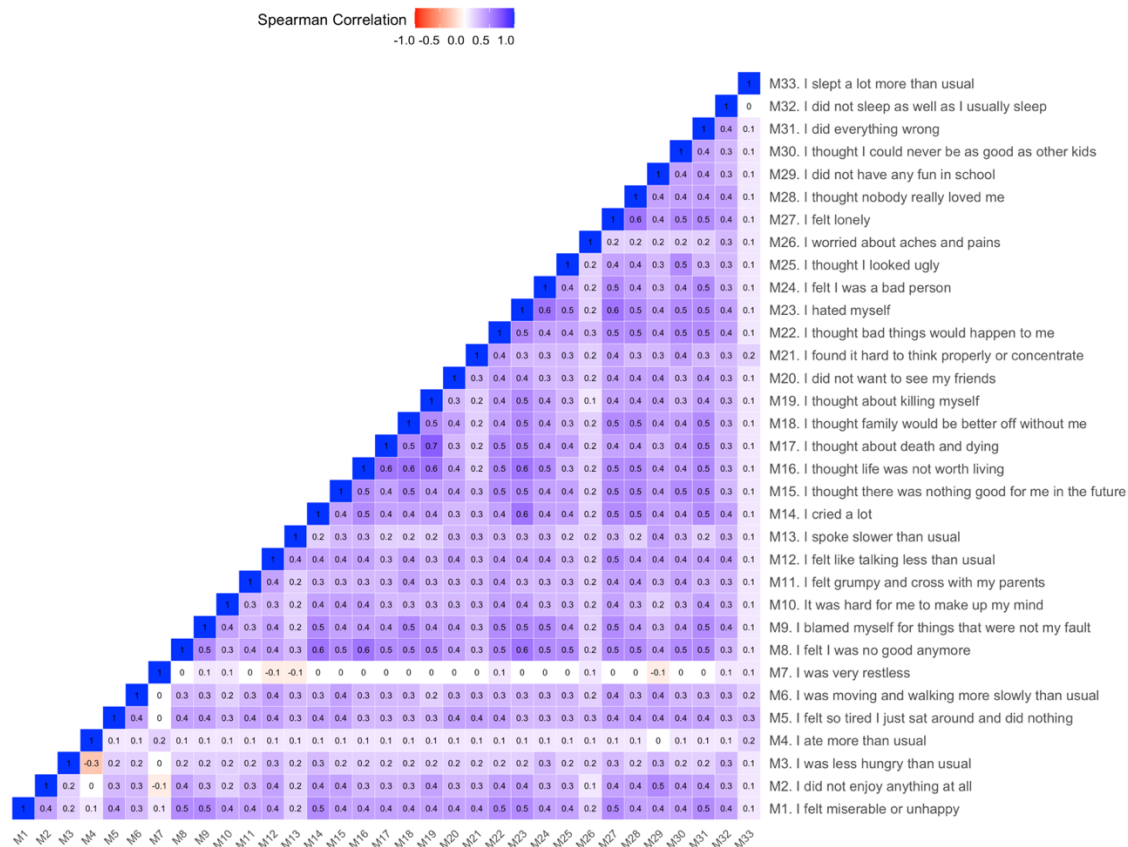
Note. MFQ: Mood and Feelings Questionnaire. As in Figure S1, the color gradient goes from blue (positive correlations) to red (negative correlations). Darker shades indicate stronger correlations.

Supplementary Table S5. Confirmatory factor analysis (CFA) factor loadings, reliability and fit indices for the PHQ-A

| PHQ-A items	Factor loadings (ƛ)	Thresholds (ƛ)		
		1 (several days)	2 (more than half the days)	3 (nearly every day)
P1 - Low mood	0.821	-0.604	0.443	0.867
P2 - Lost interest	0.616	-0.630	0.417	1.015
P3 - Sleep disturbances	0.592	-0.406	0.251	0.648
P4 - Appetite/weight change	0.647	-0.104	0.507	0.958
P5 - Fatigue	0.650	-0.747	0.279	0.761
P6 - Worthlessness	0.831	-0.273	0.393	0.766
P7 - Concentration difficulty	0.603	0.095	0.767	1.198
P8 - Psychomotor change	0.654	0.164	0.848	1.281
P9 - Suicidality	0.846	0.452	1.016	1.302

Note. PHQ-A: Patient Health Questionnaire – Adolescent Version. Factor loadings, fit indices and thresholds are presented for the unidimensional solution CFA results. Factor loadings, fit indices and thresholds are presented for the unidimensional solution CFA results. Fit indices for the unidimensional solution: McDonald's Omega=0.854; CFI=0.982; TLI=0.976; RMSEA=0.064. Omega cut-off close to or above 0.7; CFI and TLI cut-offs close to or larger than 0.950; RMSEA cut-off close to or smaller than 0.060. Thresholds represent the necessary standardized latent value required to endorse a "harder" response option than an "easier" one (i.e., required higher depression severity in order to endorse the response option "Several days" over "None").

Supplementary Figure S3. Expected influence centrality of males and females from the PHQ-A network structure
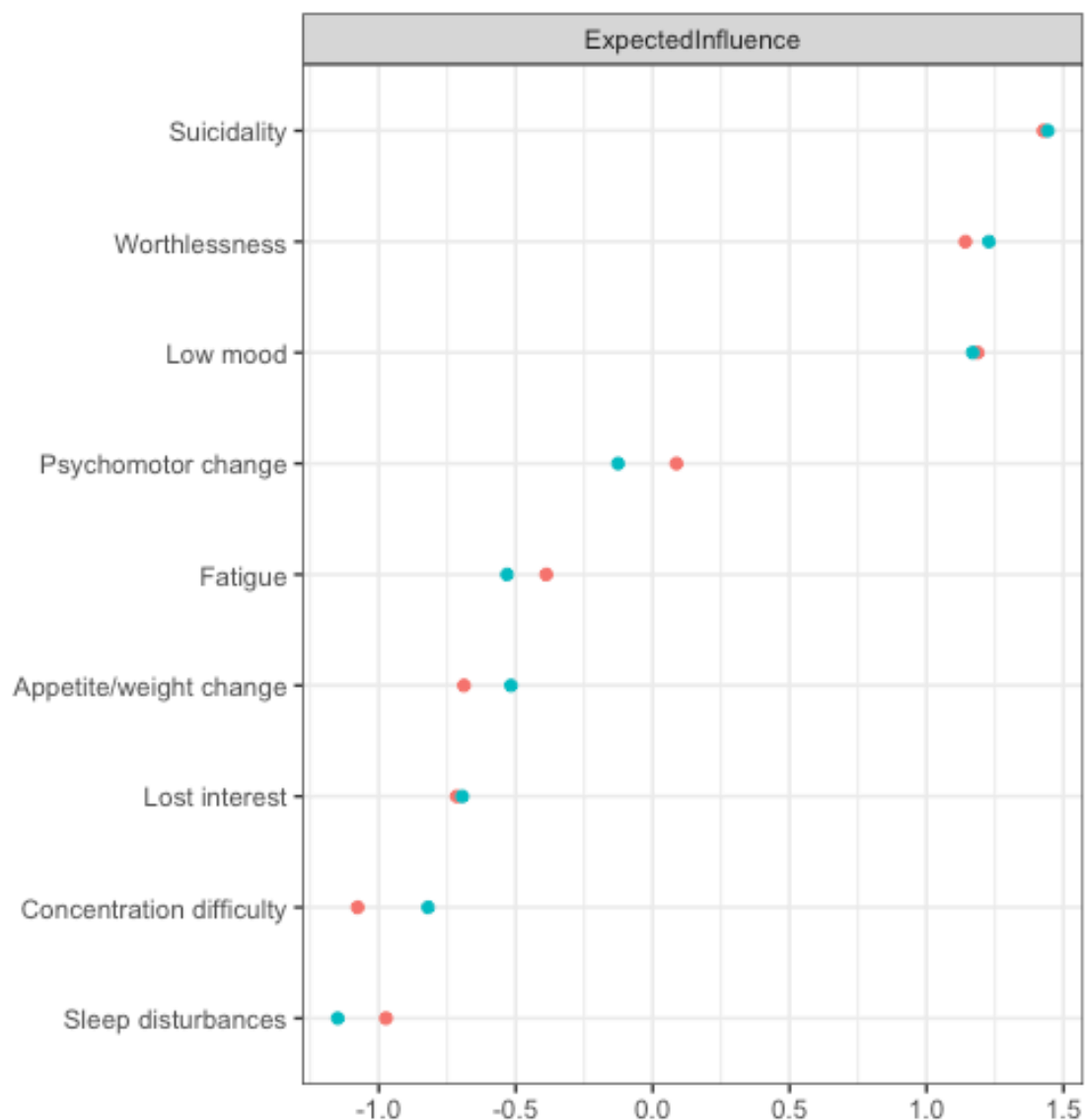
Note. PHQ-A: Patient Health Questionnaire – Adolescent Version. Blue points represent expected influence centrality derived from the PHQ-A network structure of males. Red points represent expected influence centrality derived from the PHQ-A network structure of females. Suicidality, worthlessness and low mood were the most central item for boys and girls. On the Y-Axis, PHQ-A items ordered by highest to lowest expected influence centrality; on the X-Axis are z-standardized expected influence centrality values with zero as the mean value.
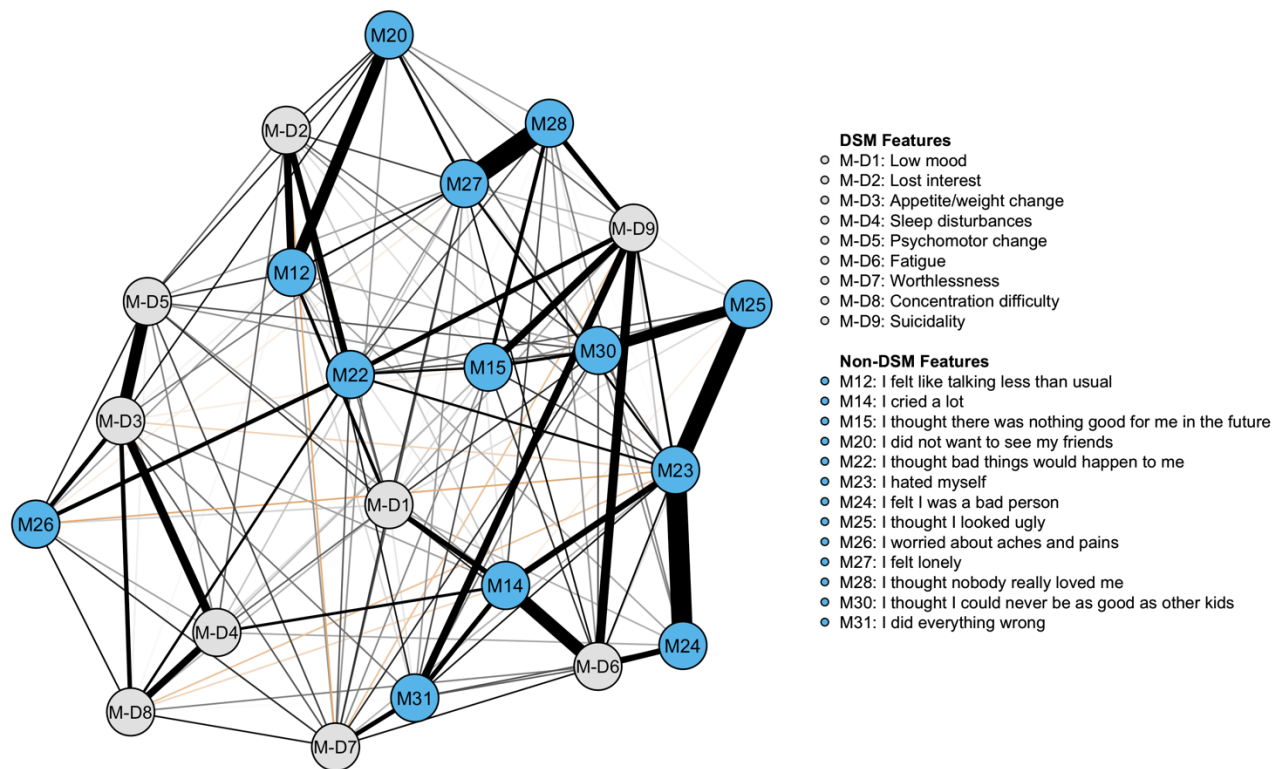
Supplementary Table S6. CFA factor loadings, reliability and fit indices for the MFQ

	Factor loadings (λ)	Thresholds (λ)	
		1 (Sometimes True)	2 (True)
M1 - I felt miserable or unhappy	0.767	-0.292	1.131
M2 - I did not enjoy anything at all	0.686	0.655	1.817
M3 - I was less hungry than usual	0.436	0.337	1.063
M4 - I ate more than usual	0.172	-0.193	0.848
M5 - I felt so tired I just sat around and did nothing	0.646	-0.327	0.624
M6 - I was moving and walking more slowly than usual	0.589	0.351	1.158
M7 - I was very restless	0.029	-0.332	0.865
M8 - I felt I was no good anymore	0.840	0.339	1.051
M9 - I blamed myself for things that were not my fault	0.756	0.023	0.799
M10 - It was hard for me to make up my mind	0.587	-0.667	0.443
M11 - I felt grumpy and cross with my parents	0.603	-0.189	0.685
M12 - I felt like talking less than usual	0.694	-0.063	0.786
M13 - I spoke slower than usual	0.574	0.879	1.623
M14 - I cried a lot	0.777	0.278	1.047
M15 - I thought there was nothing good for me in the future	0.772	0.155	0.935
M16 - I thought life was not worth living	0.838	0.573	1.201
M17 - I thought about death and dying	0.810	0.354	1.019
M18 - I thought family would be better off without me	0.782	0.500	1.177
M19 - I thought about killing myself	0.850	0.848	1.372
M20 - I did not want to see my friends	0.683	0.613	1.455

M21 - I found it hard to think properly or concentrate	0.560	-0.451	0.783
M22 - I thought bad things would happen to me	0.772	-0.049	0.896
M23 - I hated myself	0.872	0.317	0.988
M24 - I felt I was a bad person	0.751	0.297	1.101
M25 - I thought I looked ugly	0.657	-0.160	0.682
M26 - I worried about aches and pains	0.389	0.056	0.889
M27 - I felt lonely	0.823	-0.155	0.641
M28 - I thought nobody really loved me	0.782	0.344	0.995
M29 - I did not have any fun in school	0.727	0.560	1.605
M30 - I thought I could never be as good as other kids	0.723	0.108	0.822
M31 - I did everything wrong	0.792	0.263	1.149
M32 - I did not sleep as well as I usually sleep	0.603	-0.052	0.709
M33 - I slept a lot more than usual	0.227	-0.054	0.724

Note. PHQ-A: Patient Health Questionnaire – Adolescent Version. MFQ: Mood and Feelings Questionnaire. Factor loadings, fit indices and thresholds are presented for the unidimensional solution CFA results. Fit indices for the unidimensional solution: McDonald's Omega=0.941; CFI=0.951; TLI=0.948; RMSEA=0.058. Omega cut-off close to or above 0.7; CFI and TLI cut-offs close to or larger than 0.950; RMSEA cut-off close to or smaller than 0.060. Thresholds represent the necessary standardized latent value required to endorse a "harder" response option than an "easier" one (i.e., required higher depression severity in order to endorse the response option "Sometimes true" over "Not true").

Supplementary Figure S4. Network structure for the MFQ (n=1,070) with DSM and non-DSM features

DSM Features
- M-D1: Low mood
- M-D2: Lost interest
- M-D3: Appetite/weight change
- M-D4: Sleep disturbances
- M-D5: Psychomotor change
- M-D6: Fatigue
- M-D7: Worthlessness
- M-D8: Concentration difficulty
- M-D9: Suicidality

Non-DSM Features
- M12: I felt like talking less than usual
- M14: I cried a lot
- M15: I thought there was nothing good for me in the future
- M20: I did not want to see my friends
- M22: I thought bad things would happen to me
- M23: I hated myself
- M24: I felt I was a bad person
- M25: I thought I looked ugly
- M26: I worried about aches and pains
- M27: I felt lonely
- M28: I thought nobody really loved me
- M30: I thought I could never be as good as other kids
- M31: I did everything wrong

Note. MFQ: Mood and Feelings Questionnaire. Gray nodes are the DSM criteria created from the MFQ items with an "or" rule (see Table S2), while blue nodes are symptoms not contemplated by the DSM.

Supplementary Figure S5: Expected influence centrality for the MFQ (n=1,070) with DSM and non-DSM features
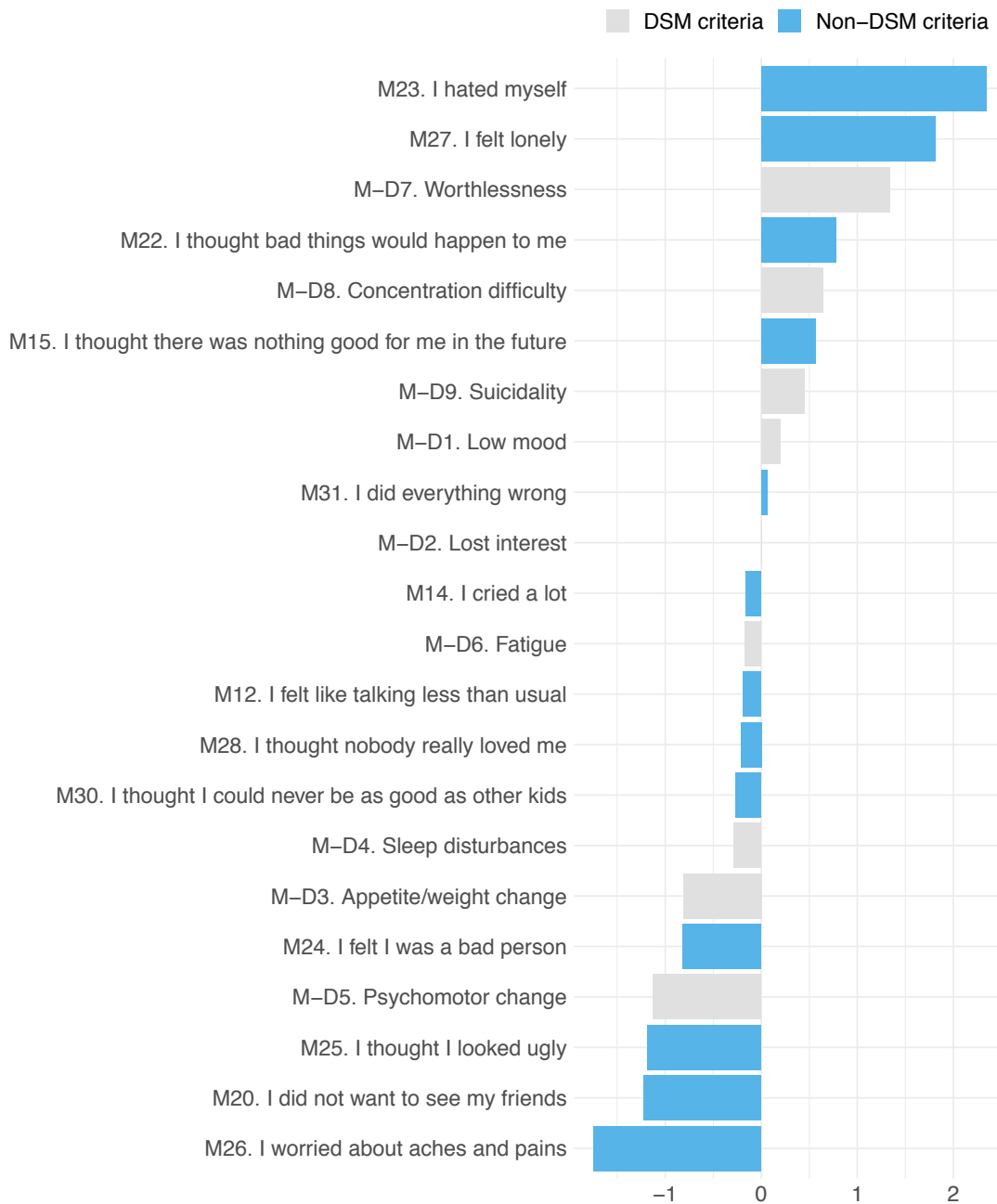
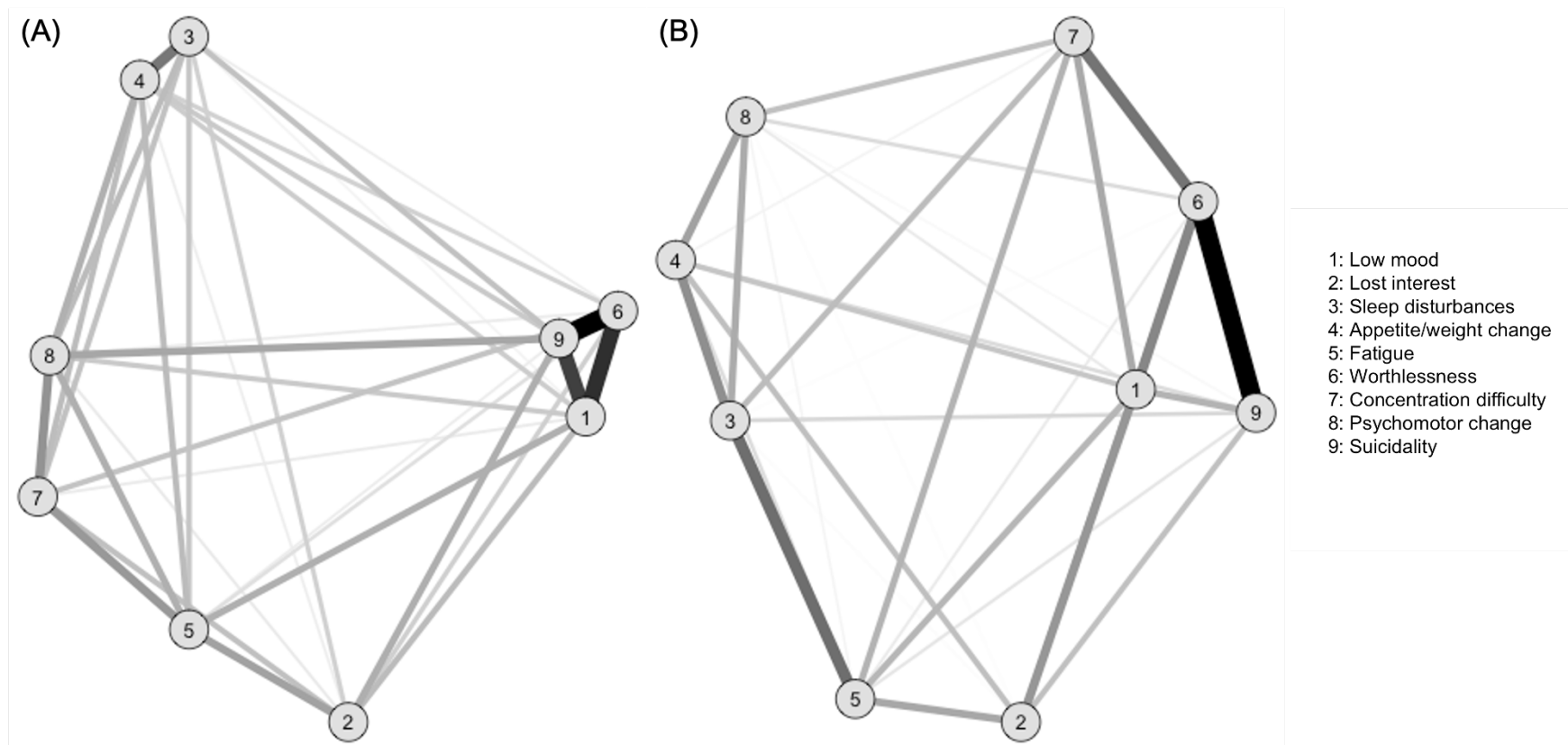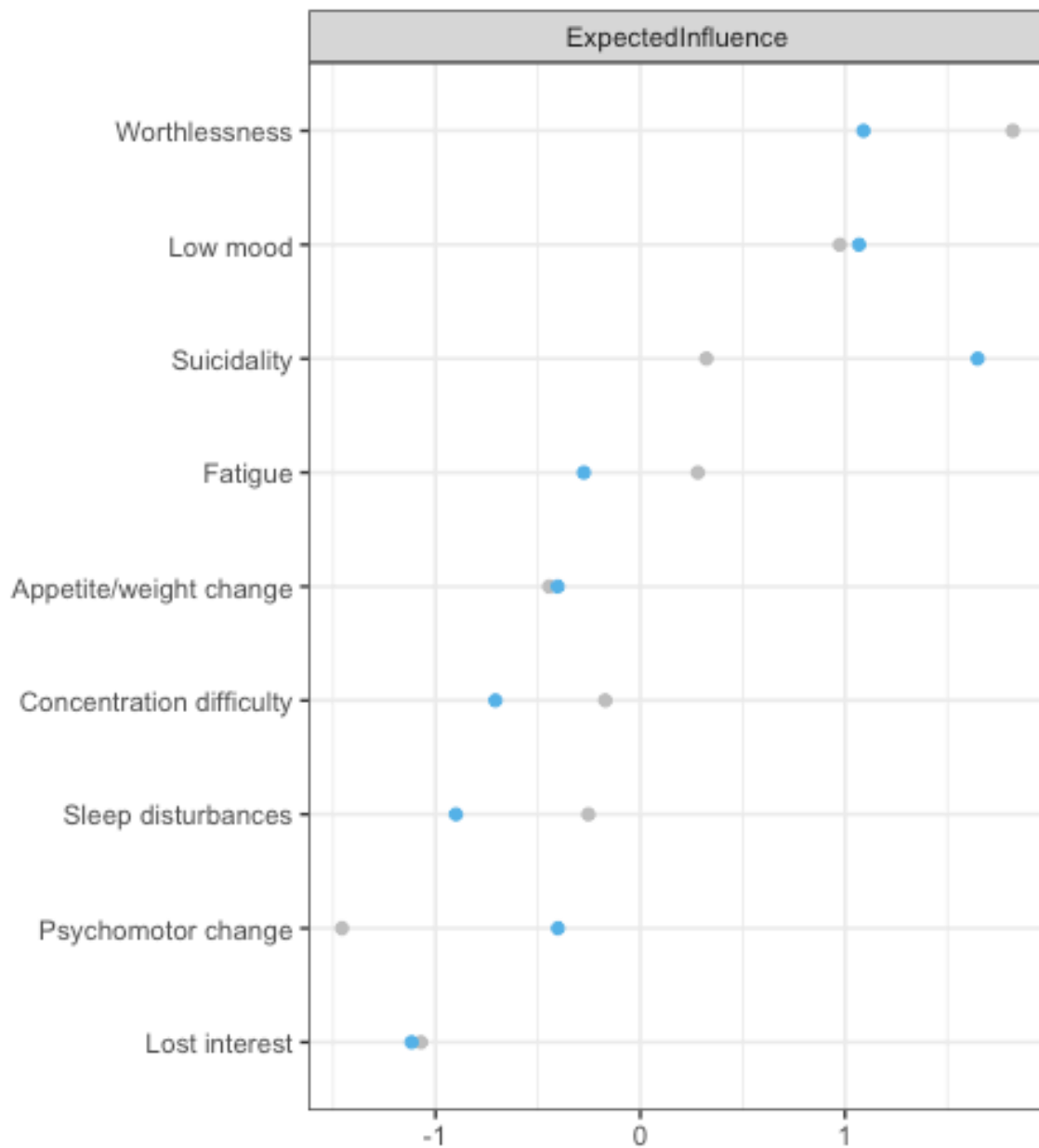Note. MFQ: Mood and Feelings Questionnaire. Gray nodes are DSM criteria created from the MFQ items with an "or" rule (see Table S2), while blue nodes are symptoms not contemplated by the DSM. On the Y-Axis, MFQ items ordered by highest to lowest expected influence centrality; on the X-Axis are z-standardized expected influence centrality values with zero as the mean value.

Supplementary Figure S6. Network structure of PHQ-A items (A) and DSM items derived from the MFQ with an "or" rule (B; see Table S1 for a full explanation)

1: Low mood
2: Lost interest
3: Sleep disturbances
4: Appetite/weight change
5: Fatigue
6: Worthlessness
7: Concentration difficulty
8: Psychomotor change
9: Suicidality

Note. PHQ-A: Patient Health Questionnaire – Adolescent Version. MFQ: Mood and Feelings Questionnaire. Lines represent positive associations. Line thickness and saturation represent correlation magnitude. Both Figure S6.A and S6.B's layout are based on multidimensional scaling. Network comparison test (NCT) between the two graphs showed graphs to have different overall structures (i.e. connections between the nine DSM items change from the PHQ-A sample to the MFQ sample; S=0.128, p=0.01) although there was no difference in total connectivity (i.e. partial correlations were not larger in one graph than another; M=0.058, p=0.282).

Supplementary Figure S7. Expected influence centrality of PHQ-A items and DSM items derived from the MFQ with an "or" rule

Note. PHQ-A: Patient Health Questionnaire – Adolescent Version. MFQ: Mood and Feelings Questionnaire. Gray points represent PHQ-A item centrality estimates; blue points represent DSM criteria derived from the MFQ items. On the Y-Axis, MFQ items ordered by highest to lowest expected influence centrality; on the X-Axis are z-standardized expected influence centrality values with zero as the mean values.

Supplementary Figure S8. Expected influence centrality of males (blue) and females (red) from the MFQ network
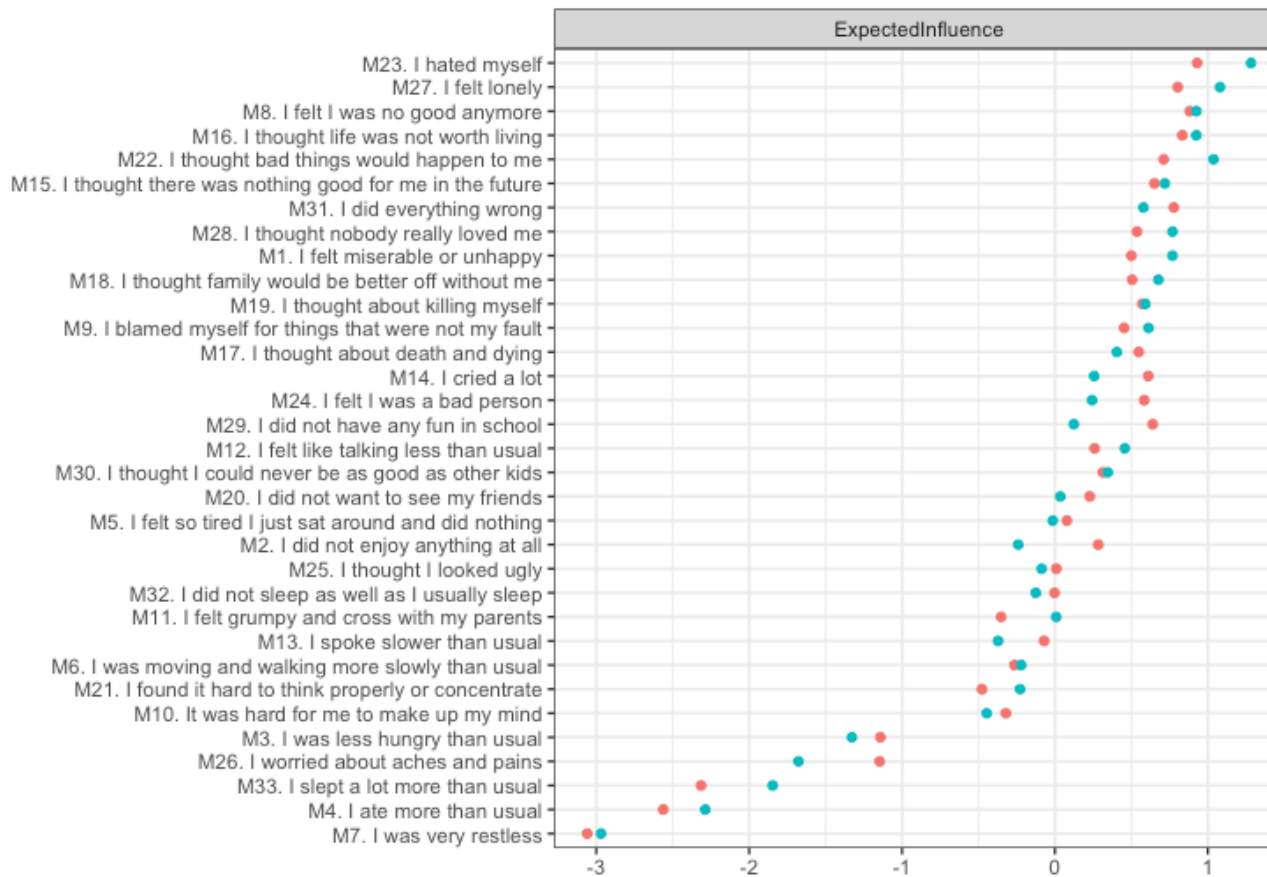
Note. MFQ: Mood and Feelings Questionnaire. "I hated myself" was the most central item for boys and girls, followed by "I felt lonely" and "I thought bad things would happen to me" for males; "I felt I was no good anymore" and "I thought life was not worth living" was the most central item for females. On the Y-Axis, MFQ items ordered by highest to lowest expected influence centrality; on the X-Axis are z-standardized expected influence centrality values with zero as the mean values.

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9. CONSIDERAÇÕES FINAIS E PERSPECTIVAS FUTURAS

Neste trabalho foram apresentados três artigos com o objetivo de avaliar aspectos referentes a apresentação fenomenológica do TDM na adolescência e no início da vida adulta. Buscamos ampliar o entendimento do TDM na juventude ao contemplar a complexidade clínica, nosológica e biológica por meio de análises epidemiológicas e psicométricas clássicas assim como modelos de rede recentemente aplicados na pesquisa em psicopatologia.

O primeiro estudo avaliou, em uma amostra populacional de 3.780 jovens de 22-23 anos de idade da Coorte de Nascidos Vivos de 1993, a prevalência-ponto do diagnóstico categórico de TDM, usando a entrevista estruturada MINI, e a sintomatologia dimensional, por meio da Center for Epidemiological Studies– Depression Scale–Revised (CESD-R). Esse artigo incluiu análises tradicionais da epidemiologia, como prevalência-ponto, valor preditivo positivo e área sob a curva ROC; além de análises da psicometria clássica, como análise fatorial confirmatória e suas métricas, e análises de rede. Encontramos prevalência-ponto coerente com estudos internacionais para a faixa etária investigada. Além disso, a escala CESD-R mostrou-se uma escala confiável, com ótimos índices de ajuste a um modelo bifatorial em que um fator geral de "sintomas depressivos" explicou a maior parte da variância de itens. Em análise específica de itens, encontramos itens de culpa excessiva e suicidalidade como os mais "difíceis" de endossar. Por último, encontramos humor deprimido e anedonia como os dois itens mais centrais da rede de sintomas nessa amostra, corroborando os sintomas cardinais do TDM como os mais interconectados.

Apesar de serem muitos os estudos sobre a prevalência de TDM no mundo, uma parcela majoritária desses resultados advém de países de alta renda, que, apesar de concentrar apenas cerca de 10% da população jovem do mundo, produzem

a maior parte dos estudos dessa população (Kieling et al., 2011). Além disso, uma parcela importante dos estudos de prevalência de depressão utiliza escalas autopreenchidas de sintomas depressivos, que levam a potencial superestimativa de até 2,5 vezes nas taxas de prevalência (Levis 2020). No artigo #1, encontramos prevalência-ponto de 2,9% com a entrevista MINI, compatível com outras estimativas epidemiológicas tradicionais oriundas de países de alta renda (Auerbach et al., 2018; Kessler et al., 2005). Mostramos também que a escala CESD-R tem uma área sob a curva ROC de 92% comparando um ponto de corte de 16 ao diagnóstico por meio da MINI. No entanto, por meio de análises comparando estimativas de prevalência por meio da entrevista MINI e da escala CESD-R, mostramos que utilizar esta escala com ponto de corte de 16 levaria a uma inflação de até seis vezes (19,2%). Mesmo seguindo o algoritmo diagnóstico disponível no site da escala (CESD-R: Center for Epidemiologic Studies Depression Scale Revised Online Depression Assessment), haveria uma potencial superestimação de 2,3 vezes da prevalência-ponto.

Com o atual foco da literatura em avaliar amostras transculturais a fim de otimizar a generalização dos achados, adotamos métodos psicométricos tradicionais e de rede para a análise de sintomas específicos do TDM. É essencial considerar que os dados para esse estudo foram coletados e processados no Brasil, país de média renda com grande população jovem. Ao avaliar a sintomatologia depressiva em amostra de diversos contextos culturais (Haroz et al., 2017), possibilitamos ampliar o entendimento da fenomenologia do TDM. Por meio de análises latentes (CFA) e de rede, mostramos que a avaliação específica de sintomas pode trazer novas percepções do TDM na vida jovem. Achados baseados no modelo latente e os baseados em modelos de rede confirmam uma ideia dimensional a sintomas depressivos medidos por meio da CESD-R. Além disso, nosso estudo foi apenas o

segundo a aplicar modelos de rede em amostras de países de baixa e média renda (Wasil et al., 2020) e o primeiro a focar-se na transição da adolescência para a vida adulta. Assim, concluímos que o estudo dimensional e enfocando sintomas pode trazer informações originais ao entendimento do TDM nessa faixa etária que podem futuramente influenciar em estratégias preventivas e terapêuticas.

No segundo artigo, avançamos a investigação da fenotipagem de sintomas depressivos reportados por jovens de 22-23 anos da Coorte de Nascidos Vivos de Pelotas por meio de análises de rede de sintomas, dois marcadores inflamatórios (IL-6 e PCR) avaliados em dois pontos (aos 18 e aos 22-23 anos) e suas associações com covariáveis frequentemente estudadas. Ao usar análises de rede para examinar a relação de sintomas depressivos com marcadores inflamatórios, não encontramos relações longitudinais (marcadores inflamatórios aos 18 anos e sintomas aos 22-23 anos) ou transversais (marcadores inflamatórios e sintomas aos 22-23 anos) entre PCR ou IL-6 com o diagnóstico categórico por meio da entrevista MINI ou com a soma total da CESD-R. Contudo, ao realizarmos análise específica de sintomas com os marcadores e ajustando estatisticamente para covariáveis biológicas e sociais, encontramos relações específicas longitudinalmente de IL-6 associada com humor deprimido, alterações psicomotoras, fadiga e sentimento de culpa excessiva. Na avaliação transversal, sintomas de apetite, alterações psicomotoras e sentimentos de culpa excessiva e IL-6.

Importantemente, as associações encontradas foram de pequeno tamanho de efeito, em linha com a literatura moderna que sugere participação importante de covariáveis biológicas e sociais na influência de vias inflamatórias nos sintomas depressivos (Fried et al., 2019; Jokela et al., 2016; Moriarty et al., 2020). Acreditamos

que estudar elementos progressivamente mais detalhados, precisos e observáveis pode conferir novas compreensões sobre vias inflamatórias do TDM na vida jovem.

No terceiro artigo, estudamos duas amostras de adolescentes de 14 a 16 anos de escolas públicas de Porto Alegre, recrutadas com protocolos semelhantes. Em ambas as amostras, conduzimos análises latentes e de rede para estudar as propriedades e as interrelações de cada item. Encontramos resultados compatíveis com a literatura prévia (Gijzen et al., 2021; Mullarkey et al., 2019): na amostra que respondeu a PHQ-A (n=7.720), escala composta por nove itens correspondentes aos nove critérios do DSM-5, itens de humor triste e de culpa excessiva foram os mais centrais da rede. Na amostra que respondeu ao MFQ (n=1.070), por outro lado, itens de ódio a si mesmo e de sentimento de solidão, ambos classificados como não explicitamente contemplados no DSM de acordo com a literatura prévia, foram os mais centrais da rede de sintomas. Nossos resultados sugerem que os critérios do DSM-5 não são mais frequentes, mais graves ou mais interconectados do que sintomas não contemplados pelo DSM-5 – pelo contrário, itens DSM e não-DSM formam uma rede altamente interconectada de sintomas.

Neste terceiro artigo, buscamos ampliar o conhecimento da estrutura fenomenológica do TDM expandindo dois artigos recentes que conduziram análises de rede em amostras de adultos (Fried, Epskamp, et al., 2016; Kendler et al., 2018). Ambos esses artigos aplicaram exclusivamente estratégias de análise de rede em amostras de adultos, enquanto nosso terceiro artigo avaliou adolescentes de amostras oriundas de escolas, que responderam a duas escalas diferentes porém complementares, por meio de análises latentes e de rede. Nossos resultados reforçam a importância de avaliar sintomas além dos critérios DSM-5, definidos por consenso de experts, e buscar uma aproximação de características do TDM que

possam ser cruciais aos pacientes mas que vão além da atual compreensão psicopatológica da doença (Chevance et al., 2020). Em um estudo qualitativo recente utilizando amostra transcultural de pacientes, cuidadores e profissionais da saúde, aspectos considerados importantes pelos pacientes não só não são captados adequadamente por escalas comumente utilizadas em ensaios clínicos como por vezes são distintos do que priorizaram os profissionais (Chevance et al., 2020). Isso vai ao encontro de outro estudo mostrando que pacientes com maior discordância com seus profissionais da saúde sobre prioridades do tratamento para depressão tendem a ter pior resposta clínica (Demyttenaere et al., 2015a, 2015b). Conforme mencionado na introdução, a conceptualização de depressão ao longo da história sofreu mudanças aparentemente empíricas principalmente baseadas em consensos (Maj, 2018). Sendo assim, é possível que definições que não contemplem as particularidades biopsicossociais e culturais da depressão na adolescência lentifiquem o progresso no entendimento da doença em um período crucial para prevenção e identificação precoce (Davey & McGorry, 2019). Implementar múltiplas técnicas analíticas para dados psicopatológicos, biológicos e sociais, em amostras de culturas diversas, é primordial para enriquecer nossa compreensão da experiência do TDM na vida jovem.

Para continuar avançando nosso entendimento da depressão no período da vida jovem, acreditamos ser crucial a aproximação à complexidade nosológica, da fenomenológica e biológica do TDM. Reconhecer as limitações da pesquisa atual em psicopatologia, estudar de maneira complexa temas complexos e rejeitar simplificações são tarefas cruciais para futuras linhas de pesquisa (Borsboom et al., 2018). Os estudos que compuseram essa tese têm o objetivo de mostrar a importância de avaliar o conceito "depressão" de maneira plural, acolhendo por meio

de variadas estratégias analíticas e embasamentos filosóficos subjacentes a heterogeneidade natural ao TDM.

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