JÚLIA DE SOUZA RODRIGUES

Estudo dos fatores de risco associados ao comprometimento das funções executivas na adolescência: Coorte de Nascimentos de Pelotas 2004

Estudio de los factores de riesgo asociados al deterioro de las funciones ejecutivas en la adolescencia: Cohorte de Nacimientos de Pelotas 2004

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo e à Universidad Miguel Hernández de Elche para obtenção do título de Doutor em Ciências

Programa de Pós-graduação em Saúde Coletiva (FMUSP)
Orientadora: Profª Drª Alicia Matijasevich

Programa de Doctorado em Salud Pública, Ciencias Médicas y Quirúrgicas (Universidad Miguel Hernández de Elche)
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São Paulo
2024

Dados Internacionais de Catalogação na Publicação (CIP)

Preparada pela Biblioteca da
Faculdade de Medicina da Universidade de São Paulo

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Rodrigues, Júlia de Souza

Estudo dos fatores de risco associados ao comprometimento das funções executivas na adolescência : Coorte de Nascimentos de Pelotas 2004 = Estudio de los factores de riesgo asociados al deterioro de las funciones ejecutivas en la adolescencia : Cohorte de Nacimientos de Pelotas 2004 / Júlia de Souza Rodrigues; Alicia Matijasevich Manitto e María Asuncion Pastor Valero, orientadoras. -- São Paulo; Elche, 2024.

Tese (Doutorado) – Programa de Saúde Coletiva. Faculdade de Medicina da Universidade de São Paulo. Programa de Salud Pública, Ciencias Médicas y Quirúrgicas. Universidad Miguel Hernandes de Elche, 2024.

1. Desenvolvimento infantil 2. Cognição 3. Depressão pós-parto 4. Parentalidade 5. Estudo de coorte 6. Adolescência I. Manitto, Alicia Matijasevich, orient. II. Pastor Valero, María Asuncion, orient. III. Título.

USP/FM-DBD-355/24

Responsável: Daniela Amaral Barbosa, CRB-8 7533

La presente Tesis Doctoral, titulada "Estudio de los factores de riesgo para el deterioro de las funciones ejecutivas en la adolescencia: Cohorte de Nascimientos de Pelotas 2004", se presenta bajo la modalidad de **tesis por compendio** de los siguientes **artículos publicados:**

- Rodrigues JS, Valero MP, Trambaiolli LR, Bozzini AB, Matijasevich A. Impact of maternal depressive symptoms on offspring executive functions: a systematic review. Revista brasileira de psiquiatria. São Paulo, Brazil. 2024 Mar 1.

- Rodrigues JS, Matijasevich A, Tovo-Rodrigues L, Munhoz TN, Santos IS, Pastor-Valero M. Risk factors for executive function impairment in adolescence: 2004 Pelotas Birth Cohort study. Revista Brasileira de Psiquiatria. São Paulo, Brazil. 2023 Jan 1.

Otra publicación derivada de esta tesis doctoral:

- Rodrigues JS, Pastor-Valero M, Maruyama JM, Munhoz TN, Santos IS, Barros AJD, Tovo-Rodrigues L, Matijasevich A. Examining Pathways Between Trajectories of Maternal Depressive Symptoms, Harsh Parenting, and Adolescent Executive Functions: Insights from the 2004 Pelotas Birth Cohort. 2024. *Currently under peer review in the Journal of Affective Disorders Reports.*

La Dra. Dña. María del Mar Masiá Canuto, Coordinadora del Programa de Doctorado en Salud Pública, Ciencias Médicas y Quirúrgicas

INFORMA:

Que Dña. Júlia de Souza Rodrigues ha realizado bajo la supervisión de nuestro Programa de Doctorado el trabajo titulado “Estudio de los factores de riesgo asociados al deterioro de las funciones ejecutivas en la adolescencia: Cohorte de Nacimientos de Pelotas 2004” conforme a los términos y condiciones definidos en su Plan de Investigación y de acuerdo al Código de Buenas Prácticas de la Universidad Miguel Hernández de Elche, cumpliendo los objetivos previstos de forma satisfactoria para su defensa pública como tesis doctoral.

Lo que firmo para los efectos oportunos, en Alicante a 26 de septiembre de 2024

Profa. Dra. Dña. María del Mar Masiá Canuto

Coordinadora del Programa de Doctorado en Salud Pública, Ciencias Médicas y Quirúrgicas

La Dra. Dña. María Asunción Pastor-Valero directora, y a Dra. Dña. Alicia Matijasevich Manitto, codirectora de la tesis doctoral titulada “Estudio de los factores de riesgo asociados al deterioro de las funciones ejecutivas en la adolescencia: Cohorte de Nacimientos de Pelotas 2004”.

INFORMAN:

Que Dña. Júlia de Souza Rodrigues ha realizado bajo nuestra supervisión el trabajo titulado “Estudio de los factores de riesgo asociados al deterioro de las funciones ejecutivas en la adolescencia: Cohorte de Nacimientos de Pelotas 2004” conforme a los términos y condiciones definidos en su Plan de Investigación y de acuerdo al Código de Buenas Prácticas de la Universidad Miguel Hernández de Elche, cumpliendo los objetivos previstos de forma satisfactoria para su defensa pública como tesis doctoral.

Lo que firmamos para los efectos oportunos, en Alicante a 26 de septiembre de 2024.

Directora de la tesis	Codirector/a de la tesis
Dra. Dña. María Asunción Pastor-Valero	Dra. Dña. Alicia Matijasevich Manitto

Esta tese foi desenvolvida no âmbito do Convênio de Dupla Titulação de Doutorado Internacional entre o Programa de Doctorado en Salud Pública, Ciencias Médicas y Quirúrgicas da Facultad de Medicina da Universidad Miguel Hernández de Elche na Espanha e o Pograma de Pós-graduação em Saúde Coletiva da Faculdade de Medicina da Universidade de São Paulo.

Esta tesis fue desarrollada en el marco del Convenio de Doble Titulación de Doctorado Internacional entre el Programa de Doctorado en Salud Pública, Ciencias Médicas y Quirúrgicas de la Facultad de Medicina de la Universidad Miguel Hernández de Elche en España y el Programa de Posgrado en Salud Colectiva de la Facultad de Medicina de la Universidad de São Paulo.

AGRADECIMENTOS

Gostaria de agradecer às minhas orientadoras, as professoras Alicia Matijasevich e María Pastor-Valero pelo constante apoio, incentivo e confiança. O suporte de vocês foi fundamental para o desenvolvimento deste trabalho.

À minha mãe Mônica e ao meu pai Alfredo, por serem presença, sabedoria e amor. Obrigada por me ensinarem tanto sobre a vida.

Às minhas irmãs Victoria, Isabella e Cecília, minhas grandes parceiras.

Às minhas amigas e amigos por serem refúgio, apoio e carinho.

Às minhas colegas de pós-graduação Jéssica e Ana por toda troca ao longo desses anos de pesquisa.

Agradeço, também, a todos os pesquisadores, professores, alunos e colegas de profissão que cruzaram a minha caminhada durante o meu doutorado e cujas trocas me fizeram crescer em vários âmbitos da vida.

Aos alunos, professores e funcionários do Departamento de Medicina Preventiva da Faculdade de Medicina da USP, e do *Programa de Doctorado en Salud Pública, Ciencias Médicas y Quirúrgicas* da *Facultad de Medicina* da *Universidad Miguel Hernández* por todo suporte e assistência.

Aos alunos, professores e funcionários da Universidade Federal de Pelotas pelo acolhimento, excelência e trabalho excepcional.

A todas as famílias participantes da Coorte de Nascimentos de Pelotas de 2004.

À Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), pela bolsa de doutorado direto e pela Bolsa de Estágio de Pesquisa no Exterior (Processos FAPESP Nº 2020/13425-3, 2023/00522-9).

NORMALIZAÇÃO ADOTADA

Esta tese está de acordo com as diretrizes para apresentação de dissertações e teses da Universidade de São Paulo, em vigor no momento desta publicação.

Referências: Adaptado de *International Comitte of Medical Journal Editors (Vancouver)*.

Tese: Universidade de São Paulo. Faculdade de Medicina. Divisão de Biblioteca e Documentação. Guia de apresentação de dissertações, teses e monografias. Elaborado por Annelise Carneiro da Cunha, Maria Julia de A.L. Freddi, Maria F. Crestana, Marinalva de Souza Aragão, Suely Campos Cardoso, Valéria Vilhena. 3ª edição. São Paulo: Divisão de Biblioteca e Documentação; 2011.

Abreviatura dos títulos dos periódicos de acordo com *List of Journal Indexed in Index Medicus*.

NORMALIZACIÓN ADOPTADA

Esta tesis está de acuerdo con las directrices para la presentación de disertaciones y tesis de la Universidad de São Paulo, vigentes en el momento de esta publicación.

Referencias: Adaptado del *International Committee of Medical Journal Editors (Vancouver).*

Tesis: Universidade de São Paulo. Faculdade de Medicina. División de Biblioteca y Documentación. Guía de presentación de disertaciones, tesis y monografías. Elaborado por Annelise Carneiro da Cunha, Maria Julia de A.L. Freddi, Maria F. Crestana, Marinalva de Souza Aragão, Suely Campos Cardoso, Valéria Vilhena. 3ª edición. São Paulo: División de Biblioteca y Documentación; 2011.

Abreviatura de los títulos de los periódicos de acuerdo con la *List of Journals Indexed in Index Medicus.*

SUMÁRIO

LISTA DE ABREVIATURAS E SIGLAS

ANOVA	Análise de Variância
CANTAB	*Cambridge Neuropsychological Test Automated Battery*
CTSPC	*Parent-Child Conflict Tactics Scales*
FE	Função Executiva
GRADE	*Grading of Recommendation, Assessment, Development, and Evaluation*
HPA	Hipotálamo-hipófise-adrenal
IBGE	Instituto Brasileiro de Geografia e Estatística
IC 95%	Intervalo de Confiança de 95%
LILACS	Literatura Latino-Americana e do Caribe em Ciências da Saúde
LMIC	*Low and Middle-Income Country*
NIH	*National Institutes of Health*
OR	*Odds Ratio*
PAL	*Paired Associated Learning*
PeNSE	Pesquisa Nacional de Saúde do Escolar
PRISMA	*Preferred Reporting Items for Systematic reviews and Meta-Analyses*
PSE	Posição Socioeconômica
RVP	Rapid Visual Processing
SWM	Spatial Working Memory
TEA-Ch	*Test of Everyday Attention for Children*

RESUMO

Rodrigues JS. *Estudo dos fatores de risco associados ao comprometimento das funções executivas na adolescência: Coorte de Nascimentos de Pelotas 2004* [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2024.

As funções executivas são um conjunto de habilidades cognitivas que permitem o controle e a execução de processos mentais, atencionais e comportamentais em situações de conflito ou distração. Investigar os fatores que influenciam o desenvolvimento dessas habilidades durante a infância e a adolescência é fundamental para a formulação de intervenções que promovam a saúde mental e o bem-estar da população. Os objetivos do presente estudo foram: (i) realizar uma revisão sistemática da literatura sobre o impacto da depressão materna no desenvolvimento das funções executivas dos filhos durante a infância e a adolescência; (ii) investigar potenciais fatores de risco associados ao comprometimento do controle atencional, atenção seletiva e flexibilidade cognitiva aos 11 anos, e da memória de trabalho aos 15 anos; (iii) estimar os efeitos das trajetórias de sintomas depressivos maternos sobre a atenção sustentada, memória de trabalho e memória episódica aos 15 anos, examinando o papel mediador da parentalidade negativa aos 11 anos. Esta tese é composta por três manuscritos. O primeiro deles consistiu em uma revisão sistemática, conduzida de acordo com o Protocolo PRISMA. Uma busca por estudos de coorte publicados em revistas indexadas foi realizada nas bases de dados Pubmed, ScienceDirect, LILACS, PsychINFO e SciELO. A qualidade dos estudos foi avaliada utilizando a Ferramenta de Avaliação de Qualidade do Instituto Nacional do Coração, Pulmão e Sangue dos Estados Unidos para Estudos de Coorte Observacionais e Transversais. A qualidade das evidências foi analisada utilizando o sistema GRADE. Trinta e três estudos de coorte foram analisados, dos quais vinte e quatro confirmaram a hipótese de que os sintomas depressivos maternos têm um efeito prejudicial no desempenho das funções executivas das crianças. A programação fetal, fatores epigenéticos e as práticas parentais foram descritos como possíveis mecanismos que explicariam o impacto dos sintomas depressivos maternos no comprometimento das funções executivas. O segundo artigo que compõe esta tese utilizou dados da Coorte de Nascimentos de Pelotas de 2004 (N=4.231). As exposições incluíram características sociodemográficas, do nascimento e da infância. Os desfechos incluíram o controle atencional, a flexibilidade

cognitiva e a atenção seletiva, medidos aos 11 anos por meio do Teste de Atenção Cotidiana para Crianças (TEA-Ch, do inglês *Test of Everyday Attention for Children*). A memória de trabalho espacial foi medida aos 15 anos pela Bateria Automatizada de Testes Neuropsicológicos de Cambridge (CANTAB, do inglês *Cambridge Neuropsychological Test Automated Battery*). Modelos de regressão logística foram construídos com o intuito de investigar a relação entre as exposições e o comprometimento das funções executivas. Os resultados indicaram que a baixa escolaridade materna teve o maior impacto negativo nas funções executivas. Aos 11 anos, estave associada à diminuição do controle atencional e, aos 15 anos, ao comprometimento da memória de trabalho. A amamentação, independentemente da duração, foi identificada como um fator protetor contra o comprometimento da flexibilidade cognitiva aos 11 anos. O terceiro artigo analisou dados de 1.949 adolescentes pertencentes à Coorte de Nascimentos de Pelotas de 2004, acompanhados desde o nascimento até os 15 anos. Sintomas depressivos maternos foram avaliados pela Escala de Depressão Pós-Natal de Edimburgo dos 3 meses aos 11 anos. A parentalidade negativa foi medida utilizando a Escala de Táticas de Conflito entre Pais e Crianças aos 11 anos. As funções executivas de atenção sustentada, memória de trabalho e episódica foram avaliadas aos 15 anos por meio do CANTAB. As análises de caminho foram conduzidas no software MPlus utilizando modelagem de equações estruturais. Os resultados revelaram que mães com sintomas depressivos crônicos e elevados durante a infância apresentaram comportamentos parentais mais negativos, o que, por sua vez, esteve associado a pior atenção sustentada e memória episódica. Ao considerar a parentalidade negativa como mediador, observou-se que adolescentes cujas mães apresentaram sintomas depressivos elevados desde os 3 meses até os 11 anos mostraram pior atenção sustentada e pior memória episódica aos 15 anos. Como conclusão, o desenvolvimento das funções executivas na infância e adolescência é negativamente impactado por variáveis sociodemográficas, principalmente pela baixa escolaridade materna, e pelos sintomas depressivos maternos elevados, medidos desde os 3 meses até os 11 anos. A parentalidade emergiu como um importante alvo para intervenções e futuras políticas públicas destinadas a promover o desenvolvimento cognitivo saudável de adolescentes, especialmente daqueles em situação de vulnerabilidade. **Descritores:** Desenvolvimento infantil. Cognição. Depressão pós-parto. Parentalidade. Estudo de coorte. Adolescência.

ABSTRACT

Rodrigues JS. *Study of risk factors associated with impairment of executive functions in adolescence: 2004 Pelotas Birth Cohort* [thesis]. São Paulo: "Faculdade de Medicina, Universidade de São Paulo"; 2024.

Executive functions are a set of cognitive skills that enable the control and execution of mental, attentional, and behavioral processes in situations of conflict or distraction. Investigating the factors that influence the development of these skills during childhood and adolescence is crucial for formulating interventions that promote mental health and well-being in the population. The objectives of this study were: (i) to conduct a systematic review of the literature on the impact of maternal depression on the development of children's executive functions during childhood and adolescence; (ii) to investigate potential risk factors associated with impairments in attentional control, selective attention, and cognitive flexibility at age 11, and working memory at age 15; (iii) to estimate the effects of maternal depressive symptoms over time on sustained attention, working memory, and episodic memory at age 15, examining the mediating role of harsh parenting at age 11. This thesis is composed of three manuscripts. The first consisted of a systematic review conducted in accordance with the PRISMA Protocol. A search for cohort studies published in indexed journals was carried out in the databases Pubmed, ScienceDirect, LILACS, PsychINFO, and SciELO. The quality of the studies was assessed using the NIH National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-sectional Studies. The quality of the evidence was evaluated using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system. Thirty-three cohort studies were analyzed, of which twenty-four confirmed the hypothesis that maternal depressive symptoms have a detrimental effect on children's executive function performance. Fetal programming, epigenetic factors, and parental practices were identified as possible mechanisms explaining the impact of maternal depressive symptoms on executive function impairment. The second article in this thesis used data from the 2004 Pelotas Birth Cohort (N=4,231). The exposures included sociodemographic, birth, and childhood characteristics. The outcomes included attentional control, cognitive flexibility, and selective attention measured at age 11 using the Test of Everyday Attention for Children (TEA-Ch). Spatial

working memory was assessed at age 15 using the Cambridge Neuropsychological Test Automated Battery (CANTAB). Logistic regression models were constructed to investigate the relationship between the exposures and the impairments in the analyzed executive functions. The results indicated that low maternal education had the most significant negative impact on executive functions. At age 11, it was associated with decreased attentional control, and at age 15, with impaired working memory. Breastfeeding, regardless of duration, was identified as a protective factor against impairments in cognitive flexibility at age 11. The third article in this thesis analyzed data from 1,949 adolescents from the 2004 Pelotas Birth Cohort, followed from birth to age 15. Maternal depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale from 3 months to 11 years. Harsh parenting was measured using the Parent-Child Conflict Tactics Scale at age 11. The executive functions of sustained attention, working memory, and episodic memory were assessed at age 15 using the CANTAB. Path analyses were conducted in the MPlus software using structural equation modeling. The results revealed that mothers with elevated depressive symptoms during childhood exhibited more negative parenting behaviors, which were in turn associated with poorer sustained attention and episodic memory. Considering harsh parenting as a mediator, it was observed that adolescents whose mothers had elevated depressive symptoms from 3 months to 11 years showed worse sustained attention and worse episodic memory at 15 years. In conclusion, the development of executive functions in childhood and adolescence is negatively impacted by sociodemographic variables, particularly low maternal education, and elevated maternal depressive symptoms, measured from 3 months to 11 years. Parenting emerged as an important target for interventions and future public policies aimed at promoting the healthy cognitive development of adolescents, especially those in vulnerable situations. **Keywords:** Child development. Cognition. Post-partum depression. Parenting. Cohort study. Adolescence.

RESUMEN

Rodrigues JS. *Estudio de los factores de riesgo asociados al deterioro de las funciones ejecutivas en la adolescencia: Cohorte de Nacimientos de Pelotas 2004* [tesis]. São Paulo: "Faculdade de Medicina, Universidade de São Paulo"; 2024.

Las funciones ejecutivas son un conjunto de habilidades cognitivas que permiten el control y la ejecución de procesos mentales, atencionales y conductuales en situaciones de conflicto o distracción. Investigar los factores que influyen en el desarrollo de estas habilidades durante la infancia y la adolescencia es crucial para formular intervenciones que promuevan la salud mental y el bienestar en la población. Los objetivos de este estudio fueron: (i) realizar una revisión sistemática de la literatura sobre el impacto de la depresión materna en el desarrollo de las funciones ejecutivas de los niños durante la infancia y la adolescencia; (ii) investigar los posibles factores de riesgo asociados con el deterioro del control atencional, la atención selectiva y la flexibilidad cognitiva a los 11 años, y la memoria de trabajo a los 15 años; (iii) estimar los efectos de los síntomas depresivos maternos a lo largo del tiempo sobre la atención sostenida, la memoria de trabajo y la memoria episódica a los 15 años, examinando el papel mediador de los malos tratos a los 11 años. Esta tesis se compone de tres manuscritos. El primero consistió en una revisión sistemática realizada de acuerdo con el Protocolo PRISMA. Se realizó una búsqueda de estudios de cohortes publicados en revistas indexadas en las bases de datos Pubmed, ScienceDirect, LILACS, PsychINFO y SciELO. La calidad de los estudios se evaluó utilizando la herramienta de evaluación de calidad del Instituto Nacional del Corazón, los Pulmones y la Sangre de los NIH para estudios de cohortes y estudios transversales. La calidad de la evidencia se evaluó utilizando el sistema GRADE (Grading of Recommendations, Assessment, Development, and Evaluation). Se analizaron treinta y tres estudios de cohortes, de los cuales veinticuatro confirmaron la hipótesis de que los síntomas depresivos maternos tienen un efecto perjudicial en el rendimiento de las funciones ejecutivas de los niños. La programación fetal, los factores epigenéticos y las prácticas parentales se identificaron como posibles mecanismos que explican el impacto de los síntomas depresivos maternos en el deterioro de las funciones ejecutivas. El segundo artículo de esta tesis utilizó datos de la Cohorte de Nacimientos de Pelotas 2004 (N=4.231). Las exposiciones incluyeron características sociodemográficas, de nacimiento y de la

infancia. Los resultados incluyeron el control atencional, la flexibilidad cognitiva y la atención selectiva medida a los 11 años utilizando el Test de Atención Cotidiana para Niños (TEA-Ch). La memoria de trabajo espacial se evaluó a los 15 años utilizando la Batería Neuropsicológica Automatizada de Cambridge (CANTAB). Se construyeron modelos de regresión logística para investigar la relación entre las exposiciones y el deterioro de las funciones ejecutivas analizadas. Los resultados indicaron que la baja escolaridad materna tuvo el impacto negativo más significativo en las funciones ejecutivas. A los 11 años, se asoció con una disminución del control atencional, y a los 15 años, con un deterioro de la memoria de trabajo. La lactancia materna, independientemente de su duración, se identificó como un factor protector contra el deterioro de la flexibilidad cognitiva a los 11 años. El tercer artículo de esta tesis analizó datos de 1.949 adolescentes de la Cohorte de Nacimientos de Pelotas 2004, seguidos desde el nacimiento hasta los 15 años. Los síntomas depresivos maternos se evaluaron utilizando la Escala de Depresión Postnatal de Edimburgo desde los 3 meses hasta los 11 años. Los malos tratos se midieron utilizando la Escala de Tácticas de Conflicto entre Padres e Hijos a los 11 años. Las funciones ejecutivas de atención sostenida, memoria de trabajo y memoria episódica se evaluaron a los 15 años utilizando el CANTAB. Se realizaron análisis de trayectorias en el software MPlus utilizando modelos de ecuaciones estructurales. Los resultados revelaron que las madres con síntomas depresivos elevados durante la infancia exhibían comportamientos parentales más negativos, lo que a su vez se asociaba con una peor atención sostenida y memoria episódica. Considerando los malos tratos como mediador, se observó que los adolescentes cuyas madres presentaron síntomas depresivos elevados desde los 3 meses hasta los 11 años mostraron peor atención sostenida y peor memoria episódica a los 15 años. En conclusión, el desarrollo de las funciones ejecutivas en la infancia y adolescencia se ve negativamente impactado por variables sociodemográficas, especialmente por la baja escolaridad materna, y por los síntomas depresivos maternos elevados, medidos desde los 3 meses hasta los 11 años. La parentalidad emergió como un objetivo importante para intervenciones y futuras políticas públicas destinadas a promover el desarrollo cognitivo saludable de los adolescentes, especialmente de aquellos en situación de vulnerabilidad. **Palabras clave:** Desarrollo infantil. Cognición. Depresión postparto. Parentalidad. Estudio de cohorte. Adolescencia.

APRESENTAÇÃO

A presente tese é composta por uma introdução ao tema da pesquisa, abordando os conceitos básicos sobre as funções executivas e seu desenvolvimento ao longo da infância e adolescência. Em seguida, apresento os dados sobre a epidemiologia da depressão materna, exposição principal da presente tese. Além disso, descrevo brevemente a relação entre a depressão materna e o emprego de estratégias parentais e demonstro as evidências existentes acerca dos impactos das trajetórias de sintomas depressivos maternos sobre as funções executivas dos filhos.

Integram também esta tese as justificativas para o estudo e os objetivos gerais e específicos. Os resultados são compostos pelo resumo breve de três artigos científicos, dos quais dois estão publicados e um submetido em revistas indexadas:

Artigo 1: *Impact of maternal depressive symptoms on offspring executive functions: a systematic review.*

Artigo 2: *Risk factors for executive function impairment in adolescence: 2004 Pelotas Birth Cohort study.*

Artigo 3: *Examining Pathways Between Trajectories of Maternal Depressive Symptoms, Harsh Parenting, and Adolescent Executive Functions: Insights from the 2004 Pelotas Birth Cohort. 2024*

Para encerrar, apresento uma discussão dos achados de cada artigo e as considerações finais com limitações e ponderações, recomendações e conclusões geradas ao longo da tese. Os artigos na íntegra se encontram nos apêndices da presente tese de doutorado.

1. INTRODUÇÃO

1.1 Funções executivas: conceitos básicos

As funções executivas (FEs, também chamadas de controle executivo ou controle cognitivo) representam um conjunto de habilidades cognitivas auto-regulatórias que permitem o controle e execução de processos mentais, atencionais, comportamentais e emocionais diante de situações de conflito ou distração (Best & Miller, 2011; Diamond, 2014a). As FEs estão relacionadas com a capacidade de racionalizar, planejar, resolver problemas, controlar impulsos e manter o foco (Diamond, 2014a). Essas habilidades fazem parte do desenvolvimento cognitivo, social e psicológico, o que as tornam essenciais para a saúde física e mental durante todo o ciclo da vida. Apesar dos constructos teóricos sobre as FEs diferirem amplamente na literatura (Goldstein et al., 2014; Snyder et al., 2015), há um consenso de que as FEs são compostas por pelo menos três subcomponentes interdependentes: memória de trabalho, controle inibitório, e flexibilidade cognitiva (Diamond, 2013; Lehto et al., 2003).

A memória de trabalho é subdividida em duas dimensões: verbal e não-verbal (visoespacial) (Baddeley & Hitch, 1994). A dimensão verbal representa a capacidade de reter informações, relacioná-las e processá-las em um curto intervalo de tempo. Exemplos incluem somar números ditados ou ouvir uma lista de letras ou números e recitá-los de trás para frente. A dimensão não-verbal representa a habilidade de armazenar e resgatar estímulos visuais, auditivos, táteis, olfativos e gustativos não disponíveis de forma perceptiva no ambiente e relacioná-los de forma estratégica como, por exemplo, relacionar um cheiro a uma memória passada. Durante a primeira infância, os estímulos sensoriais e a comunicação verbal são fatores que influenciam no desenvolvimento da memória de trabalho (Stedron et al., 2005). As habilidades relacionadas à memória de trabalho são essenciais no processo de aprendizagem, pois permitem a realização de atividades sequenciais sem o uso de lembretes, reorganização de tarefas, formulação de estratégias em jogos de regras, operacionalização de números e compreensão da linguagem oral e escrita (Diamond, 2012).

O controle inibitório refere-se à capacidade de regular e controlar a atenção, o comportamento e as predisposições mentais e emocionais, visando evitar distrações e suprimir impulsos (Diamond, 2013). As distrações ou respostas automáticas podem ter

origem interna (do próprio indivíduo) ou externa (do ambiente). O controle inibitório abrange três dimensões autorregulatórias: controle inibitório da atenção (também denominado atenção seletiva ou atenção executiva), inibição cognitiva e autocontrole (Diamond, 2014a). O controle inibitório da atenção é a capacidade de suprimir estímulos externos para manter o foco em um objeto/situação. Por exemplo, ao ler uma placa de trânsito enquanto dirige, mesmo com distrações ao redor. A inibição cognitiva é a habilidade de bloquear representações mentais predominantes, como resistir a pensamentos involuntários ou a memórias indesejadas. O autocontrole envolve a regulação comportamental e emocional interna para suprimir tentações e evitar ações impulsivas, permitindo ao indivíduo realizar tarefas não prazerosas para alcançar um objetivo e manter uma boa conduta em situações de tensão. A memória de trabalho e o controle inibitório atuam mutuamente e exercem papéis importantes no funcionamento das FEs. O trabalho em conjunto dessas habilidades permite que o indivíduo seja capaz de selecionar os estímulos a serem inibidos a partir do foco em um objetivo e também que seja capaz de manter o foco mesmo que haja estímulos distratores (Diamond, 2014a).

A flexibilidade cognitiva representa a capacidade de alternar entre diferentes tarefas ou objetivos, permitindo que os indivíduos regulem seus pensamentos e ações de maneira adaptativa (Best & Miller, 2010). Essa habilidade depende diretamente do controle inibitório e da memória de trabalho, uma vez que é necessário inibir uma perspectiva anterior e manipular mentalmente a informação para visualizá-la de um ponto de vista diferente. Essa habilidade é muito importante para o desenvolvimento da criatividade, resolução de conflitos, reconhecimento de erros e avaliação de oportunidades. No desenvolvimento escolar, essa habilidade se faz fundamental para, por exemplo, analisar diferentes métodos para resolver uma equação matemática (Diamond, 2014a).

Outro aspecto da atenção relacionado às FEs é a atenção sustentada, que se refere à capacidade de manter o foco e a concentração em uma tarefa específica ou estímulo por um período prolongado de tempo (A. V. Fisher, 2019). Seu correlato neural consiste em um sistema composto pela integração de múltiplas redes cerebrais heterogêneas (Langner & Eickhoff, 2013). Essas redes incluem regiões talâmicas, fronto-parietais, dorsais, e cingulo-opercular (A. V. Fisher, 2019). Problemas na atenção sustentada durante a infância estão

associados a dificuldades acadêmicas ao longo da adolescência, resultando em redução do desempenho acadêmico, e na desvalorização do ambiente escolar (Cruz et al., 2020)

As FEs também exercem um papel fundamental para o armazenamento e a recuperação de memórias episódicas (Meléndez et al., 2019). Essas memórias contêm informações sobre experiências e soluções passadas que podem ser aplicadas como referências ao resolver problemas no presente. A memória episódica é essencial para a realização de tarefas diárias, como lembrar onde se guardou um objeto ou da fala de uma pessoa importante. Além disso, ela fornece a base para a memória autobiográfica (Nelson & Fivush, 2004) e contribui para a sensação de continuidade do eu ao longo do tempo (Buckner & Carroll, 2007). Seu desenvolvimento saudável impacta significativamente a compreensão da leitura e a aprendizagem, com medidas de memória episódica presentes em testes de capacidade intelectual (Ghetti & Bunge, 2012).

1.2 Desenvolvimento das funções executivas na infância e adolescência

Ao longo dos últimos vinte anos, diferentes teorias do desenvolvimento das funções executivas (FEs) emergiram. Estudos que avaliaram gêmeos uni e bivitelinos propuseram que as diferenças individuais nas FEs eram mìnimas ao comparar pares de irmãos, propondo assim, que as FEs possuíam importante influência genetica (Feng et al., 2022; Friedman et al., 2008). No entanto, estudos também observaram que as experiências de vida também influenciavam as diferenças individuais nas FEs, atribuindo relevância ao entorno ambiental e social (Bouyeure & Noulhiane, 2021; Tamura et al., 2020). Além disso, os estudos que buscaram entender o desenvolvimento das FEs revelaram que essas não são fixas ou imutáveis, sendo possível melhora-las com treinamentos específicos (Diamond, 2012). Mais recentemente, modelos ecológicos e biopsicossociais assumem que as FEs estão inseridas dentro de uma combinação de processos biológicos e contextuais de múltiplos níveis (Miguel et al., 2023; Zelazo, 2020).

De acordo com a perspectiva biopsicossocial, a biologia, o comportamento e o ambiente social da criança interagem continuamente ao longo do desenvolvimento (Calkins, 2015). Essa interação dinâmica molda a forma como as FEs se desenvolvem por meio da percepção, interpretação e reação a estímulos. A biologia fornece a base para as habilidades e características individuais, o comportamento reflete as respostas e adaptações às

experiências, e o ambiente social oferece contextos e desafios que podem promover ou limitar o desenvolvimento.

Do ponto de vista neurobiológico, as FEs estão associadas à maturação do córtex pré-frontal e sua conexão com outras regiões corticais, subcorticais e límbicas (Best & Miller, 2011; Diamond, 2014a). Além do aumento na conectividade do córtex pré-frontal, também ocorre uma especialização das áreas de ativação global para regiões de ativação local durante o desenvolvimento das FEs (Fiske & Holmboe, 2019).

O desenvolvimento ontológico das FEs está relacionado ao desenvolvimento neurocognitivo, uma vez que o cérebro humano não está completamente formado na ocasião do nascimento (Courchesne et al., 2000). As funções executivas têm sua origem nos estágios iniciais da infância, com habilidades básicas emergindo nos três primeiros anos de vida (Garon et al., 2008). Durante a primeira infância, o cérebro passa por diversas modificações sinápticas e neuronais, as quais envolvem a maturação de células nervosas e o aumento do número de sinapses (Gilmore et al., 2018). No decorrer do neurodesenvolvimento, as sinapses são selecionadas, o que favorece a especialização de circuitos e consolidação de redes cognitivas (Fiske & Holmboe, 2019). O processo de maturação neuronal e modificação das sinapses no período da infância está relacionado às interações entre os estímulos ambientais e as repostas individuais (Halfon et al., 2001).

Ao longo do desenvolvimento, é possível a detecção de "períodos sensíveis", nos quais ocorre o aumento dramático da plasticidade cerebral e uma consequente facilitação para o desenvolvimento das FEs (Carlson, 2005). A possibilidade de desenvolvimento das FEs é significativamente maior entre os três e cinco anos. Apesar disso, o período entre a adolescência e o início da vida adulta é também considerado um período sensível para o desenvolvimento das FEs (Best & Miller, 2011; Diamond, 2014b). Evidências indicam que a especialização das FEs à medida que o córtex pré-frontal passa por mudanças durante a adolescência se deve especialmente ao processo de mielinização dos axônios (Yakovlev & Lecours, 1967). Esse processo melhora a transmissão de sinais, resultando em um aumento da matéria branca e uma diminuição da matéria cinzenta devido à reorganização sináptica (Gogtay et al., 2004).

Estudos indicam que o primeiro avanço significativo no desempenho das habilidades de controle inibitório ocorre nos anos pré-escolares, tanto em tarefas simples (como a pura

inibição da resposta) quanto em tarefas complexas (como a inibição da resposta seguida de uma resposta alternativa) (Best & Miller, 2010). Um exemplo disso é a capacidade de manipulação de um cartão bidimensional, onde a criança foca em uma dimensão e, em seguida, precisa inibi-la para observar a segunda dimensão. O controle inibitório continua a se aprimorar entre os cinco e oito anos, especialmente em tarefas que combinam controle inibitório e memória de trabalho, como a imitação de um gesto oposto ao realizado pelo instrutor (jogo das mãos) (Gogtay et al., 2004). Estudos indicam que o controle inibitório continua a avançar até os 15 anos (Luna et al., 2015), com exceção das tarefas Stroop (Stroop, 1935), nas quais ganhos funcionais em eficiência continuam a emergir após os 15 anos e durante a fase adulta jovem (Huizinga et al., 2006).

Aos seis anos, a memória de trabalho está suficientemente desenvolvida para permitir a realização de tarefas complexas que exigem a coordenação de várias dimensões, como lembrar de itens específicos de listas ditadas anteriormente (Visu-Petra et al., 2014). A velocidade de processamento em tarefas que envolvem memória de trabalho também tende a aumentar durante o desenvolvimento, influenciando diretamente a flexibilidade cognitiva (Garon et al., 2008). A flexibilidade cognitiva também continua se desenvolvendo durante a adolescência, e atinge uma estabilização por volta dos 14-15 anos (Huizinga et al., 2006). Diversos estudos, utilizando uma variedade de medidas (por exemplo, amplitude de dígitos/letras, n-back e tarefas de busca), encontraram mudanças significativas no desempenho da memória de trabalho e flexibilidade cognitiva desde o início até a adolescência média (Huizinga et al., 2006), e em alguns casos, estendendo-se além dos 18 anos (Boelema et al., 2014).

As relações construídas entre o indivíduo e o ambiente durante a primeira infância são fundamentais para o desenvolvimento das FEs, que serão amadurecidas nas etapas posteriores da vida, à medida que a complexidade dos estímulos ambientais e comportamentais aumentam (Bouyeure & Noulhiane, 2021; Huttenlocher, 2009).

1.3 Fatores de risco para o desenvolvimento das funções executivas

Prejuízos no desenvolvimento cognitivo, particularmente em países de média e baixa renda, são determinados por fatores frequentemente atribuídos à pobreza resultante da falta de recursos ou de sua distribuição desigual (Haft & Hoeft, 2017). Esses fatores são

denominados determinantes distais, pois geralmente atuam através de determinantes proximais inter-relacionados, também conhecidos como variáveis intermediárias ou mecanismos. Os determinantes distais geralmente são representados como variáveis de exposição relacionadas a posição socioeconômica (PSE). A PSE é definida pela combinação de recursos econômicos (como renda e riqueza material) e recursos sociais (como prestígio social e nível de educação). Os determinantes proximais podem ser subdivididos em grupos inter-relacionados de forma hierárquica, como características do nascimento, da primeira infância, da infância e da adolescência.

Estudos de coorte indicam de forma consistente que determinantes distais como baixa renda familiar, baixo nível de escolaridade materna e problemas na estrutura familiar, estão associados a prejuízos nas funções executivas (Best & Miller, 2010; Diamond, 2013). (Hackman et al., 2015; Holochwost et al., 2016; Last et al., 2018; Rhoades et al., 2011).

Uma meta-análise incluindo estudos que examinaram majoriatariamente populações do norte global identificou que crianças e adolescentes cujas família possuíam baixo status socioeconômico apresentavam maiores prejuízos nas FEs em comparação com crianças e adolescentes cujas famílias apresentavam médio ou alto status socioeconômico (Lawson et al., 2018). Andrade et al. (2005) investigaram a associação entre a qualidade de vida domiciliar e o desenvolvimento cognitivo em uma amostra de 350 crianças brasileiras com idades entre 17 e 42 meses. A Escala de Observação Domiciliar para Medição do Ambiente (HOME, do inglês *Home Observation for Measurement of the Environment Scale*) foi utilizada para avaliação da PSE (Elardo & Bradley, 1981) . Os resultados mostraram que crianças com menos de 5 anos que tinham ambos os pais em casa e mães com níveis educacionais mais altos apresentaram os melhores índices de desenvolvimento cognitivo. Outros estudos revelaram um maior impacto da PSE no desenvolvimento da memória de longo prazo, memória de trabalho e habilidades linguísticas em crianças com menos de 9 anos (Piccolo et al., 2016).

A relação entre a PSE e as FEs pode ser explicada por determinantes proximais, tais como estresse (Blair & Raver, 2016), parentalidade (Holochwost et al., 2016), estimulação cognitiva (Rosen et al., 2020) e exposição à linguagem (Merz et al., 2019). Outros aspectos do ambiente familiar em que crianças e adolescentes são criados têm sido identificados como determinantes proximais dos prejuízos nas FEs, incluindo ansiedade e depressão materna,

ausência paterna, maus-tratos, baixa sensibilidade parental e socialização emocional entre a criança e os cuidadores (Fay-Stammbach et al., 2014, 2017; Power et al., 2021). A vulnerabilidade socioeconômica está associada ao estresse materno desde o período pré-natal, o que pode resultar em problemas no cuidado parental, afetando o desenvolvimento das funções executivas desde os primeiros anos de vida (Sarsour et al., 2011). A memória de trabalho (Hackman et al., 2015), atenção (Stevens et al., 2009), controle inibitório e flexibilidade cognitiva (Sarsour et al., 2011) são particularmente vulneráveis a aos efeitos negativos da exposição a esses fatores.

A maneira como esses determinantes afetam as FEs é explicada pela teoria do risco cumulativo, que sugere que a combinação de múltiplos *determinantes distais*, como a pobreza e a baixa escolaridade dos pais, juntamente com *determinantes proximais*, como estresse familiar, exposição à violência, falta de apoio social e problemas de saúde mental dos pais, influenciam negativamente o desenvolvimento das FEs de crianças e adolescentes (Fay-Stammbach et al., 2014; Wade et al., 2018).

1.4 Depressão materna: conceito, epidemiologia e fatores associados

A depressão materna é uma condição psicológica que abrange um espectro de condições depressivas como a depressão pré-natal, depressão pós-parto e psicose pós-parto (Shidhaye & Giri, 2014). A depressão materna, nos últimos anos, emergiu como uma questão de saúde pública global que afeta o bem-estar das mães e de seus filhos (Gelaye et al., 2016a). A sintomatologia da depressão materna é semelhante à sintomatologia do transtorno depressivo maior observado em outras fases da vida, e os sintomas incluem humor deprimido, anedonia, mudanças significativas no peso ou apetite, insônia ou hipersônia, agitação ou retardo psicomotor, fadiga, sentimentos de inutilidade ou culpa, capacidade diminuída de pensar, de concentrar-se, indecisão e pensamentos recorrentes de norte (Ruschi et al., 2007). No Brasil, menos de um quarto das mulheres afetadas recebem tratamento, e apenas metade dos casos de depressão pós-parto é identificada na prática clínica diária (Faisal-Cury et al., 2021).

Globalmente, as taxas de depressão pós-parto variam conforme o nível de renda dos países. A prevalência estimada é de 17,22% (IC 95%: 16,00–18,51) entre as mulheres mundialmente, e de 20,51% (IC 95%: 18,53%–22,65%) no Brasil (Wang et al., 2021). Uma

meta-análise, que incluiu 565 estudos de 80 países, identificou que o tamanho do estudo e a renda do país ou nível de desenvolvimento foram os principais fatores explicativos para a elevada heterogeneidade entre os países (Wang et al., 2021). Nos países de alta renda, a prevalência combinada de depressão pós-parto foi de 15,5%, enquanto nos países de baixa renda foi de 20,0%.

Um estudo transversal realizado no Brasil, envolvendo 23.894 mulheres no período pós-parto entre 6 a 18 meses, identificou diversos fatores de risco associados a sintomas depressivos maternos elevados (Theme Filha et al., 2016). Os fatores incluiram variáveis sociodemográficas e individuais, como a cor de pele parda (OR = 1,15; IC 95% (1,01–1,31)), classe econômica mais baixa (OR = 1,70; IC 95% (1,41–2,06)), uso de álcool (OR = 1,41; IC 95% (1,09–1,84)) e histórico de transtornos mentais (OR = 3,13; IC 95% (1,80–5,44)). Fatores de risco obstétricos também foram identificados, como gravidez não planejada (OR = 1,38; IC 95% (1,20–1,60)), multiparidade (OR = 1,97; IC 95% (1,58–2,47) para 3 ou mais filhos), e atendimento inadequado durante o parto (OR = 2,02; IC 95% (1,28–3,20)) ou do recém-nascido (OR = 2,16; IC 95% (1,51–3,10)).

Diferentes mecanismos pelos quais a depressão materna impacta negativamente as funções executivas vêm sendo identificados por estudos de coorte. Esses mecanismos podem ser compreendidos principalmente em relação ao momento em que a exposição aos sintomas depressivos maternos ocorre: durante a gravidez ou no período pós-parto que se estende ao longo da infância (Glover et al., 2015; Lautarescu et al., 2020; Lawler et al., 2019; Power et al., 2021).

A exposição a sintomas depressivos durante a gravidez está associada a alterações no desenvolvimento cerebral intrauterino, o que pode comprometer o funcionamento executivo na infância e adolescência (Plamondon et al., 2015). Essas mudanças são explicadas pela hipótese de programação fetal, que enfatiza o período crítico para o neurodesenvolvimento durante a fase embrionária e fetal (Glover et al., 2018). Mecanismos biológicos, como a regulação do eixo hipotálamo-hipófise-adrenal (HPA), são sugeridos para explicar os impactos da depressão materna pré-natal no desenvolvimento infantil e no subsequente risco de problemas de saúde mental (Sohr-Preston & Scaramella, 2006). Variações nos níveis de cortisol, influenciadas pela reatividade do cortisol, têm sido associadas a déficits em funções executivas e alterações comportamentais (Fernandes et al., 2015). Além disso, estudos

destacam o papel significativo do gene SLC6A4 na inibição, memória de trabalho e flexibilidade cognitiva em crianças expostas a sintomas depressivos maternos, evidenciando que variações genéticas podem modular a resiliência em face de condições adversas (Weikum et al., 2013).

No período pós-parto, o impacto negativo dos sintomas depressivos nas funções executivas dos filhos é explicado pelas adversidades nos campos emocionais e de interação na relação mãe-filho. Estudos evidenciam que mães depressivas apresentam uma redução na capacidade de fornecer estímulo emocional estável e previsível para a criança (Holochwost et al., 2016; Power et al., 2021). Estudos de mediação identificaram práticas parentais negativas tais como disciplina não violenta, agressão física e psicológica, negligência, e a falta de sensibilidade materna e "calor maternal" como importantes mediadores nesta associação (Baker, 2018; Ku & Feng, 2021). As funções executivas, como o controle inibitório, a flexibilidade cognitiva e o planejamento, são especialmente vulneráveis a essas influências negativas. Crianças e adolescentes expostos aos sintomas depressivos maternos podem apresentar maiores dificuldades na regulação emocional, na atenção e na resolução de problemas, impactando seu desempenho acadêmico e social (Chae et al., 2020; Cilino et al., 2018; Farías-Antúnez et al., 2018).

Examinar o impacto dos sintomas depressivos maternos sobre as funções executivas a partir de estudos de coorte não apenas auxilia na compreensão do desenvolvimento infantil, mas também oferece insights sobre as implicações para o bem-estar e o sucesso a longo prazo dos indivíduos, à medida que enfrentam desafios ao longo da vida. Estudos de coorte são a forma mais robusta de pesquisa médica após experimentos como ensaios controlados randomizados e são os desenhos mais apropriados para estudar essa relação.

1.5 Depressão materna e parentalidade

Os comportamentos parentais mais consistentemente associados às diferenças individuais nas FEs podem ser agrupados em quatro dimensões (Landry et al., 2010; O'Connor, 2002): (a) acompanhamento, (b) estimulação, (c) sensibilidade/responsividade versus hostilidade/rejeição, e (d) controle. Uma revisão sistemática incluiu diversos estudos observacionais que investigaram a relação entre as diferentes dimensões do comportamento parental e as FEs (Fay-Stammbach et al., 2014). Nesta revisão, os autores relataram que os

efeitos das práticas parentais como apoio parental, sensibilidade e estimulação nas FEs dos filhos podem ser explicados, em parte, por mudanças nas capacidades linguísticas das crianças (Clark et al., 2013; Hammond et al., 2012; Matte-Gagne & Bernier, 2011). Déficits nas FEs em crianças cujos pais não proporcionaram um ambiente estimulante foram explicados, em parte, por déficits na capacidade linguística (nomeação de cores) e velocidade de processamento (Clark et al., 2013).

As dificuldades nas interações entre mães com depressão e seus filhos são um fenômeno observado globalmente, afetando culturas e grupos socioeconômicos variados (Field, 2011). Comparado a controles sem distúrbios psiquiátricos, mães deprimidas apresentavam maior frequência de comportamento parental inadequado, incluindo maior hostilidade, maiores taxas de interações negativas com filhos, e episódios de disciplina que tendiam a alternar entre punitiva e rígida a permissiva e relaxada (Gotlib; Goodman, 1999; Lovejoy et al., 2000; Sockol et al., 2013). Mães deprimidas também se mostraram menos responsivas às necessidades infantis, comunicavam-se menos e demonstravam menos sincronia e envolvimento com seus bebês (Lovejoy et al., 2000). A depressão paterna também desempenha um papel crítico, pois ela pode exacerbar os efeitos da depressão materna nos problemas de comportamento infantil (M. W.-L. Cheung, 2019). Além disso, a hostilidade paterna foi associada a um aumento no comprometimento da memória de trabalho, destacando o impacto relevante do comportamento parental negativo nas funções cognitivas das crianças (Lam et al., 2018).

Problemas relacionados às práticas parentais negativas contribuem para a exposição prolongada a ambientes altamente estressantes, o que pode levar ao desenvolvimento de estresse tóxico, uma condição que está ligada a efeitos prejudiciais no sistema nervoso e nos sistemas reguladores de hormônios do estresse (Franke, 2014). O elevado nível de concentração de cortisol, um hormônio glicocorticoide que modula a atividade no córtex pré-frontal, foi identificado como mediador entre as práticas parentais e as FEs durante a infância (Blair et al., 2011). Outro fator de risco para as FEs, associado também a elevados níveis de cortisol em crianças é a exposição a sintomas depressivos maternos (Lawler et al., 2019).

1.6 Trajetórias dos sintomas depressivos maternos e impactos nas funções executivas dos filhos

O impacto negativo da depressão materna nas funções executivas dos filhos não se restringe situações pontuais e/ou de curta duração. A exposição aos sintomas depressivos pode ser entendida como um continuum capaz de influenciar negativamente o neurodesenvolvimento durante a infância e adolescência. Uma estratégia adotada por alguns autores para avaliar a cronicidade/persistência dos efeitos da depressão materna ao longo do tempo foi trabalhar com trajetórias da sintomatologia depressiva (Oh et al., 2020; Park et al., 2018; Rinne et al., 2022). Esses estudos revelaram que as funções executivas foram mais impactadas durante a infância entre aquelas crianças cujas mães apresentavam sintomas de depressão crescente na infância precoce e média ou que tinham trajetórias crônicas e severas de depressão materna.

As trajetórias dos sintomas depressivos maternos ao longo do tempo podem variar em termos de severidade e cronicidade. Para examinar essas heterogeneidades, diversos estudos longitudinais se dedicaram à construção de trajetórias de sintomas depressivos maternos (Ahmed et al., 2019; Campbell et al., 2007; Cents et al., 2013; Chae et al., 2020). Em uma revisão sistemática que incluiu 22 estudos longitudinais, foi identificado que os padrões das trajetórias variaram de duas a seis classes, o momento de início (gestação ou pós-parto), severidade (baixa, média ou alta) e estabilidade (trajetórias estáveis, ascendentes ou descendentes) (H. Santos et al., 2017). Os padrões de baixo nível e altos níveis de sintomas depressivos foram consistentemente identificados, sendo o primeiro incluindo o maior grupo e o segundo o menor grupo das amostras.

Embora o estudo de trajetórias de sintomas depressivos maternos possibilite uma série de ganhos em relação a identificação de períodos sensíveis nos quais as FEs dos filhos podem ser mais afetadas, e na relação entre cronicidade e severidade, estudos dessa natureza ainda são escassos na literatura, principalmente em países de baixa e média renda (Power et al., 2021). Examinar a trajetória dos sintomas de depressão materna pode fornecer informações muito importantes sobre os impactos da duração, intensidade e variabilidade dos sintomas depressivos nas FEs dos filhos ao longo do tempo.

2. JUSTIFICATIVA

As funções executivas (FEs) são fundamentais para o desenvolvimento dos processos de aprendizagem, estando intimamente ligadas a desfechos positivos tanto a curto quanto a longo prazo na saúde mental, vida social e autonomia do indivíduo. A literatura científica é clara ao evidenciar a saúde mental materna como um preditor significativo das FEs, uma vez que o relacionamento saudável e seguro entre mães e filhos constitui o alicerce primordial para a aprendizagem na infância. A presença de transtornos psiquiátricos maternos, como a depressão, pode comprometer esse relacionamento, resultando em impactos adversos no desenvolvimento das FEs e no bem-estar dos filhos ao longo da vida. Alem disso, o desenvolvimento das FEs é influenciado por uma variedade de fatores, incluindo determinantes sociodemográficos, características do nascimento e relações parentais inadequadas.

O estudo das FEs é de suma importância para a saúde individual e coletiva. A análise das FEs na adolescência é especialmente relevante, pois contribui para a compreensão dos impactos a longo prazo de exposições ocorridas na infância. A adolescência é um período crítico do desenvolvimento humano, caracterizado por transformações físicas, bioquímicas, emocionais e sociais. Os padrões comportamentais e os indicadores de saúde estabelecidos durante essa fase são profundamente influenciados por eventos ocorridos nesse período formativo.

Embora a prevalência de depressão materna seja mais elevada em países de baixa e média renda, a maioria dos estudos realizados nas últimas duas décadas tem se concentrado predominantemente em países de alta renda. Isso representa uma lacuna importante na literatura, potencialmente subestimando os efeitos dos fatores de risco populações vulneráveis e/ou marginalizadas. Assim, este estudo visa preencher essa lacuna, fornecendo evidências pioneiras sobre os fatores de risco e generar hipóteses sobre possíveis mecanimos associados às FEs na adolescência em uma população brasileira. A Coorte de Nascimentos de Pelotas de 2004 oferece uma ampla base populacional com uma baixa taxa de perdas no acompanhamento. Esta coorte reúne dados coletados desde o nascimento até os 15 anos de idade, abrangendo diversas exposições identificadas na literatura como importantes preditores das funções executivas. Esta coorte possui dados coletados desde o nascimento até os 15 anos de idade, abrangendo diversas exposições identificadas na literatura como

importantes preditores das funções executivas. Além disso, este estudo investiga diferentes domínios das funções executivas em momentos distintos do desenvolvimento adolescente. Espera-se que esta tese contribua significativamente para a comunidade científica, profissionais de saúde, gestores públicos e formuladores de políticas públicas, visando proporcionar às crianças e adolescentes brasileiros os recursos necessários para um desenvolvimento saudável e promissor desde os primeiros anos de vida.

3. HIPÓTESES

I. A exposição à depressão materna, seja diagnosticada clinicamente ou relatada através de sintomas depressivos autorreferidos desde o nascimento e durante a infância dos filhos, está consistentemente associada a efeitos negativos nas funções executivas das crianças tanto na infância quanto na adolescência.

III. Características adversas nas esferas socioeconômica (como baixa renda familiar e baixa escolaridade materna), familiar (como práticas parentais negativas) e do nascimento (como baixo peso ao nascer e prematuridade) estão independentemente associadas a déficits no controle atencional, atenção seletiva e flexibilidade cognitiva aos 11 anos, bem como na memória de trabalho aos 15 anos de idade, conforme observado na Coorte de Nascimentos de Pelotas de 2004.

II. Trajetórias de sintomas depressivos maternos crescentes ou cronicamente elevadas ao longo da vida dos filhos têm um impacto negativo na atenção sustentada, memória de trabalho e memória episódica aos 15 anos de idade. Este efeito é, em parte, mediado por práticas parentais negativas observadas aos 11 anos de idade na Coorte de Nascimentos de Pelotas de 2004.

4. OBJETIVOS

4.1 Objetivo Geral

Avaliar as trajetórias dos sintomas depressivos maternos desde os três meses até os 11 anos, os fatores de risco e potenciais mediadores associados a prejuízos nas funções executivas (FEs) relacionadas à atenção aos 11 anos, e à atenção e memória aos 15 anos, nos adolescentes da Coorte de Nascimentos de Pelotas de 2004.

4.2 Objetivos Específicos

- Realizar uma revisão sistemática da literatura sobre o impacto da depressão materna, definida por diagnóstico clínico ou sintomas autorreferidos, no desenvolvimento das funções executivas dos filhos durante a infância e adolescência.

- Investigar potenciais fatores de risco associados ao comprometimento do controle atencional, atenção seletiva e flexibilidade cognitiva aos 11 anos, e à memória de trabalho aos 15 anos, na Coorte de Nascimentos de Pelotas de 2004.

- Estimar os efeitos das trajetórias de sintomas depressivos maternos sobre a atenção sustentada, memória de trabalho e memória episódica aos 15 anos, examinando se parte desses efeitos é mediada por práticas parentais negativas observadas aos 11 anos.

5. ASPECTOS ÉTICOS

O projeto foi aprovado pelo Comitê de Ética em Pesquisa da Faculdade de Medicina da Universidade de São Paulo (USP), em sessão no dia 24 de fevereiro de 2022, pelo Comitê de Ética da Universidade Federal de Pelotas (UFPel) e pela Oficina de Investigación Responsable da Universidad Miguel Hernández de Elche (Código de Investigación Responsable: ADH.SPU.MAP.JDSR.23 – ANEXO A). O Termo de Consentimento Livre e Esclarecido das mães ou responsáveis e o Termo de Assentimento dos adolescentes foram obtidos, assim como foi garantido a confidencialidade dos dados, a participação voluntária e a possibilidade de abandonar o estudo a qualquer momento, sem necessidade de justificativa. Os casos de transtornos mentais graves, quando identificados pelos psicólogos, foram encaminhados para serviços de atendimento psicológico e/ou psiquiátricos disponíveis na cidade.

6. METODOLOGIA

6.1 Revisão sistemática: resumo dos métodos para responder ao objetivo específico 1

Para responder a primeira hipótese e objetivo desta tese, realizou-se uma revisão sistemática incluido apenas estudos de coorte, e seguindo as diretrizes do protocolo PRISMA (do inglês *Preferred Reporting Items for Systematic reviews and Meta-Analyses*) (Page et al., 2021). O protocolo do estudo foi registrado no Registro Internacional de Revisões Sistemáticas do Centro de Revisões e Disseminação da Universidade de York (Registro PROSPERO CRD42020221193).

Buscamos artigos científicos a partir da primeira data disponível nas seguintes bases de dados até 20 de agosto de 2023: PubMed, ScienceDirect, LILACS, PsychINFO e SciELO. A equação de busca final foi desenvolvida para uso no PubMed e depois adaptada para o restante das bases de dados consultadas.

Os critérios de inclusão foram: estudos de coorte originais, revisados por pares e escritos em inglês, espanhol, português ou outros idiomas. Em contrapartida, os critérios de exclusão foram: dados sobrepostos, fontes como livros e papers de conferências sem texto completo disponível, artigos não originais (revisões e análises), e artigos que não estivessem alinhados com os objetivos do estudo. A seleção dos estudos relevantes, baseada no título e no resumo, foi realizada usando o aplicativo Rayyan, de forma independente por dois autores. Duplicatas identificadas nas bases de dados bibliográficas eletrônicas foram verificadas manualmente e removidas. A variabilidade interobservador foi calculada usando o coeficiente kappa de Cohen (K).

A extração de dados foi realizada de forma independente por dois autores, e qualquer discordância foi resolvida consultando um terceiro autor. Para extrair as informações mais relevantes, criamos uma planilha de extração de dados com 24 itens agrupados em seis categorias. Os dados extraídos estão disponíveis: (1) Descrição do estudo; (2) Características da população; (3) Características da exposição; (4) Principais desfechos; (5) Resultados, incluindo informações sobre controle de dados para potenciais fatores de confusão e análise de mediação; (6) Conclusão.

A avaliação da qualidade do relato foi realizada usando a Ferramenta de Avaliação de Qualidade do Instituto Nacional do Coração, Pulmão e Sangue (NIH, do inglês *National Institutes of Health*) para Estudos de Coorte Observacionais e Estudos Transversais. Para avaliar a precisão das evidências coletadas, foi criado um resumo das limitações no desenho do estudo (risco de viés), inconsistência dos resultados, indireção das evidências e imprecisão usando o Grading Quality of Evidence and Strength of Recommendations (GRADE, do inglês *Grading of Recommendation, Assessment, Development, and Evaluation*) para revisões sistemáticas.

6.2 Coorte de Nascimentos de Pelotas de 2004: população e critérios de inclusão

Para responder à segunda e terceira hipótese e objetivo, realizaram-se estudos que examinaram dados provenientes da Coorte de Nascimentos de Pelotas de 2004.

A Coorte de Nascimentos de Pelotas de 2004 é um estudo de base populacional, que incluiu crianças nascidas em Pelotas, estado do Rio Grande do Sul, Brasil, entre 1º de janeiro e 31 de dezembro de 2004. Todas as crianças nascidas vivas na zona urbana dos municípios de Pelotas e Capão do Leão (bairro Jardim América), foram identificadas e suas mães convidadas a fazer parte do estudo. A taxa de resposta no recrutamento foi de 99,3% e incluiu 4.231 crianças. Dentro das primeiras 24 horas após o nascimento, as mães foram entrevistadas utilizando um questionário padronizado, com perguntas demográficas, socioeconômicas, comportamentais, sobre características biológicas, histórico reprodutivo e utilização de serviços de saúde. Os recém-nascidos foram examinados por uma equipe especializada e as medidas incluíam comprimento, perímetro cefálico, perímetro torácico e circunferência abdominal. Além da entrevista perinatal, as mães e crianças foram entrevistadas novamente aos 3, 12, 24 e 48 meses em casa, e aos 6, 11, 15 anos no Centro de Pesquisas Epidemiológicas da Universidade Federal de Pelotas. As taxas de seguimento até o acompanhamento de 11 anos variou entre 86,6% e 99,2% (Barros et al., 2006; Santos et al., 2011; Santos et al., 2014a). O acompanhamento de 15 anos se iniciou em novembro de 2019 e prosseguiu até março de 2020, quando as medidas de distanciamento social impostas pela pandemia de COVID-19 entraram em vigor no RS. Até aquele momento, 1949 adolescentes e mães tinham sido entrevistados, correspondendo a 46,1% da coorte original.

6.2.1 Variáveis sociodemográficas, características do nascimento e da infância

As variáveis independentes consistiram em uma série de variáveis medidas no perinatal, salvo se indicado diferentemente:

- Variáveis de posição socioeconômica: renda familiar (medida de forma contínua e categorizada em quintis), educação materna (anos completos de educação formal, categorizados em 0, 1-4, 5-8 e ≥9 anos), cor da pele da mãe auto-reportada (branca, negra, morena ou parda, amarela/asiática/indígena), situação conjugal (mãe sozinha ou vive com o companheiro), e número de irmãos (nenhum, um, dois ou mais);
- Outras características maternas: idade materna (<20, 20-34 and ≥35 anos), paridade (definido como o número de filhos vivos nascidos anteriormente e categorizado como 1, 2 e ≥3);
- Fumo durante a gravidez (fumantes regulares foram definidas como mulheres que fumaram pelo menos um cigarro por dia em qualquer trimestre da gravidez);
- A ausência paterna foi medida nos primeiros 48 meses de vida (nunca ausente, ausente aos 24 meses, ausente aos 48 meses, sempre ausente);
- Variáveis da criança ao nascimento: baixo peso ao nascer (peso ao nascer menor de 2500g), prematuridade (idade gestacional menor de 37 semanas) e sexo.

6.2.2 Trajetórias dos sintomas depressivos maternos

As trajetórias da depressão materna foram construídas utilizando uma abordagem de modelagem semiparamétrica baseada em grupos, conforme proposta por Nagin e Tremblay (1999). Detalhes dos passos e métodos usados para identificar as trajetórias de sintomas depressivos maternos foram relatados em estudos anteriores (Azeredo et al., 2017; Matijasevich et al., 2015). Resumidamente, 90% da coorte com dados de pelo menos três acompanhamentos foi incluída nas análises. Indivíduos com informações ausentes não foram excluídos do modelo devido à capacidade da modelagem baseada em trajetórias de lidar com dados ausentes usando a estimativa de máxima verossimilhança (Nagin, 2005). O número e a forma das trajetórias foram baseados no melhor ajuste do modelo (critério de informação bayesiano máximo, BIC) e na interpretabilidade das trajetórias obtidas (Nagin, 2005). Pontuações de probabilidade posterior (ou seja, a probabilidade individual de pertencer a cada um dos grupos de trajetória) foram usadas para selecionar o modelo apropriado.

Segundo Nagin (2005), uma pontuação de probabilidade média deve ser superior a 0,70 para todos os grupos. Para modelar as trajetórias das pontuações EPDS maternas, as análises foram conduzidas especificando modelos de três, quatro, cinco e seis grupos. O BIC melhorou à medida que mais grupos foram adicionados. Entre os modelos considerados, um modelo de cinco grupos surgiu como o mais adequado e parcimonioso, caracterizado por probabilidades posteriores médias variando de 0,78 a 0,87 entre os Grupos 1 a 5. A inspeção das estimativas dos parâmetros para o modelo de cinco grupos revelou que três trajetórias foram melhor representadas por um termo cúbico, uma trajetória foi linear e outra quadrática. O Grupo 1 (chamado "baixo", N=1239) e o Grupo 2 (chamado "moderadamente baixo", N=1621), representando 74,5% das mães, tiveram pontuações EPDS inferiores a 10 em todos os momentos, sugerindo baixa sintomatologia depressiva. O Grupo 3 (chamado "aumentando") incluiu 9,3% (N=357) das mulheres no estudo, mostrando um aumento consistente nos sintomas depressivos durante o período do estudo. O quarto grupo (chamado "diminuindo") incluiu 11,1% (N=426) das mulheres e, ao contrário do grupo anterior, essas mães mostraram altas pontuações EPDS nos primeiros dois anos pós-parto e uma queda acentuada posteriormente. Finalmente, o quinto grupo (chamado "alto-crônico"), representando 5,2% da população (N=198), exibiu consistentemente altas pontuações EPDS ao longo do período do estudo.

6.2.3 Parentalidade negativa

Cuidadores, predominantemente mães aos 11 anos (92,5%), foram questionados sobre estratégias parentais severas usando a versão de pai-para-filho da Escala de Táticas de Conflito (CTSPC) (Straus et al., 1998). A adaptação transcultural e validação da CTSPC para uso no Brasil foi conduzida por Paiva e Figueiredo (2006) e Reichenheim e Moraes (2003). A CTSPC compreende 22 itens categorizados em cinco subescalas que medem comportamentos parentais em relação à criança nos 12 meses anteriores: disciplina não violenta (4 itens); agressão psicológica (5 itens); e agressão física, incluindo punição corporal (5 itens), maus-tratos físicos (4 itens) e maus-tratos físicos graves (4 itens; não administrados neste estudo). Consistente com dois estudos anteriores, a parentalidade severa foi definida como a soma das pontuações das subescalas de agressão psicológica, punição corporal e maus-tratos físicos (Pinquart, 2017a, 2017b). Cada item foi avaliado em uma escala Likert

de 5 pontos. A pontuação da CTSPC foi calculada somando todas as respostas (intervalo de pontuação: 0–28), com pontuações mais altas indicando episódios mais frequentes de parentalidade severa.

6.2.4 Funções executivas aos 11 e 15 anos

As funções executivas aos 11 anos foram avaliadas por meio da realização de tarefas contidas no Teste de Atenção Diária para Crianças (TEA-Ch, do inglês *Test of Everyday Attention for Children*) (Manly et al., 2001), um teste neuropsicológico desenvolvido para avaliar a natureza multidimensional da atenção e as funções executivas relacionadas em crianças e adolescentes. Aos 15 anos, a atenção sustentada, memoria episódica e memoria de trabalho foram examinadas por meio de subtestes contidos na Bateria Automatizada de Testes Neuropsicológicos de Cambridge (CANTAB, do inglês Cambridge Neuropsychological Testing Automated Battery) (Luciana & Nelson, 2002). As avaliações foram realizadas por uma equipe treinada de psicólogos na clínica de pesquisa.

- **Controle atencional:** aplicou-se uma tarefa de avaliação de velocidade do processamento verbal e controle atencional. A criança foi exposta a uma fileira de 24 elementos, sendo eles os números “1” e “2”. Em um primeiro momento, a criança era instruída a ler os números o mais rápido possível enquanto o instrutor mantinha o dedo próximo a cada número na fileira até que a criança o lesse corretamente. Esta tarefa foi denominada “Same World”. Em um segundo momento, a criança era instruída a ler a fileira de números o mais rápido possível, mas dessa vez dizendo “um” quando o número visto era “2” e dizendo “dois” quando o número visto era “1”. Esta tarefa foi denominada “Oppositive World”. O tempo médio necessário para concluir a tarefa “Same World”, considera-se como a medida da velocidade do processamento verbal. O tempo médio necessário para concluir a tarefa "Opposite World" foi definido como a medida do controle atencional.
- **Atenção seletiva:** esta habilidade foi avaliada pelo tempo de latência na tarefa “Sky-Search”. Inicialmente, a criança foi instruída a selecionar pares de naves espaciais dentre naves espaciais correspondentes e não correspondentes. Na folha de teste, 50% dos pares de naves espaciais eram correspondentes. Foram registrados o tempo total em segundos

para a realização da tarefa (circular todos os pares de naves espaciais) e o número de acertos (pares de naves correspondentes). Em um outro momento, a criança foi instruída a realizar o mesmo procedimento em uma folha de treino que continha apenas pares correspondentes. O tempo total para a realização dessa tarefa e o número de acertos foram registrados. O tempo de latência, utilizado como medida final da atenção seletiva, consistiu na subtração do tempo total no teste contendo pares correspondentes e não correspondentes pelo tempo total no teste contendo apenas pares correspondentes.

- **Flexibilidade cognitiva:** o instrumento de avaliação da flexibilidade cognitiva foi o tempo de latência em uma tarefa de atenção dupla do subteste "Sky-Search", contido no TEA-Ch. Inicialmente, a criança foi instruída a selecionar pares de naves espaciais correspondentes dentre naves correspondentes e não correspondentes contidas na folha de teste. Em seguida, a mesma tarefa foi repetida com a adição de outra tarefa: a criança também foi solicitada a contar o número de ruídos (batidas) emitidos por uma gravação enquanto realizava a tarefa. A diferença no tempo de execução e precisão ao concluir as tarefas com e sem a adição de ruídos foi considerada como medida de indicação de flexibilidade cognitiva.
- **Atenção sustentada:** avalisou-se essa função executiva por meio do subteste de Processamento Visual Rápido (RVP, do inglês *Rapid Visual Processing*). Uma caixa branca no centro da tela exibia dígitos de 2 a 9 em uma ordem pseudorrandômica a uma taxa de 100 dígitos por minuto. Os participantes foram solicitados a detectar sequências-alvo de dígitos (por exemplo, 2-4-6, 3-5-7, 4-6-8). Quando o participante via a sequência-alvo, ele tinha que responder selecionando o botão no centro da tela o mais rápido possível. O nível de dificuldade variava, com os participantes sendo requeridos a monitorar uma ou três sequências-alvo simultaneamente. Foi utilizado como desfecho a variável contínua, no intervalo entre 0,0 e 1,0, representando a sensibilidade do sujeito em detectar sequências-alvo (valores mais altos indicavam maior sensibilidade).
- **Memória episódica:** utilizou-se o subteste de Aprendizado de Associação Pareada (PAL, do inglês *Paired Associated Learning*) para avaliar esta função executiva. Caixas eram exibidas na tela e abertas em uma ordem aleatória, com uma ou mais contendo um padrão. Os padrões eram então exibidos no centro da tela, um de cada vez, e o participante precisava selecionar a caixa onde cada padrão foi inicialmente localizado. Em caso de

erro, as caixas eram reabertas sequencialmente para lembrar o participante das localizações dos padrões. O desfecho consistiu em uma variável contínua representando a frequência de seleções incorretas de caixas para os padrões pelos participantes (valores mais altos indicavam pior desempenho).

- **Memória de trabalho:** esta função executiva foi avaliada utilizando o subteste de Memória de Trabalho Espacial (SWM, do inglês *Spatial Working Memory*). O teste começava com vários quadrados coloridos (caixas) exibidos na tela. O objetivo deste teste era que os participantes localizassem um "token" amarelo em cada uma das várias caixas e os utilizassem para preencher uma coluna vazia no lado direito da tela. O número de caixas exibidas para os participantes procurarem poderia aumentar gradualmente, com base no nível de dificuldade do teste, com um máximo de 12 caixas. Para desencorajar o uso de estratégias de busca estereotipadas, a cor e a posição das caixas variavam de uma tentativa para outra. O desfecho foi definido como uma variável contínua indicando a frequência de revisitas a caixas onde um token havia sido encontrado incorretamente (valores mais altos indicavam pior desempenho).

6.3 Análise dos fatores de risco para as funções executivas na adolescência: resumo dos métodos para responder ao objetivo específico 2

Os desfechos estudados foram as funções executivas de controle atencional, flexibilidade cognitiva e atenção seletiva aos 11 anos e memória de trabalho espacial aos 15 anos coletadas na Coorte de Nascimentos de Pelotas de 2004. Essas variáveis foram dicotomizadas para definir um grupo de baixo desempenho. A categorização das funções executivas relacionadas à atenção foi feita usando um ponto de corte abaixo do 10º percentil, indicando aquelas crianças que levaram mais tempo para completar a tarefa, enquanto a categorização da memória de trabalho espacial foi baseada no ponto de corte do 3º tercil, identificando aqueles com maior número de erros.

As variáveis independentes foram coletadas na entrevista perinatal e incluíram renda familiar (medida como variável contínua e categorizada em quintis), escolaridade materna (categorizada em 0, 1-4, 5-8 e ≥ 9 anos de educação formal), cor da pele materna auto-relatada (branca, preta, parda, amarela/indígena), arranjo domiciliar (sozinha ou com parceiro), idade materna (< 20, 20-34 e ≥ 35 anos), e paridade (definida como o número de

filhos previamente nascidos e categorizada como 1, 2 e ≥ 3). O tabagismo durante a gravidez foi avaliado retrospectivamente no nascimento por relato materno; fumantes regulares foram definidas como mulheres que fumavam pelo menos um cigarro por dia em qualquer trimestre da gravidez.

As variáveis independentes da criança avaliadas ao nascimento foram baixo peso ao nascer (< 2.500 g) e prematuridade (idade gestacional < 37 semanas). A duração da amamentação foi avaliada por relato materno aos 24 meses e categorizada como < 1, 1-3, 3-6, 6-12 ou ≥ 12 meses. Outras variáveis independentes como a ausência do pai (pai social ou biológico), foi medida nos primeiros 48 meses de vida (nunca ausente, ausente aos 24 meses, ausente aos 48 meses, sempre ausente). O número de irmãos mais velhos (nenhum, 1, ≥ 2) foi relatado pela mãe na entrevista perinatal. Também foram utilizadas como variáveis independentes as trajetórias dos sintomas depressivos maternos e parentalidade negativa.

Para a análise estatística, comparações entre características socioeconômicas, maternas e de nascimento entre os participantes dos acompanhamentos de 11 anos (n=3.582) e 15 anos (n=1.950) em relação ao número total de participantes na linha de base (n=4.231) foram realizadas usando o teste do qui-quadrado. A análise descritiva foi realizada calculando as frequências absolutas e relativas das variáveis de interesse. A análise estatística bivariada entre cada exposição e os desfechos do estudo foi realizada por meio do teste do qui-quadrado. Para estudar os potenciais fatores de risco para desempenho prejudicado nas funções executivas relacionadas ao controle atencional, flexibilidade cognitiva, atenção seletiva, e memória de trabalho espacial, modelos de regressão logística foram construídos para cada função executiva analisada e o ajuste foi realizado usando um modelo conceitual hierárquico para determinar os fatores de risco com quatro níveis: 1) nível 1: ajuste para características maternas, socioeconômicas e gestacionais; 2) nível 2: ajuste para variáveis do nível 1 e características ambientais; 3) nível 3: ajuste para variáveis do nível 2 e características de nascimento e amamentação; 4) nível 4: ajuste para variáveis do nível 3 e maus-tratos na infância. Razões de chances (OR) foram usadas para avaliar as associações entre variáveis. Se o nível de significância fosse abaixo de 0,20, a variável permanecia no modelo como um potencial confundidor para o próximo nível. Um nível alfa de 0,05 foi considerado para indicar uma associação. Todas as análises foram conduzidas usando o software Stata, versão 16.1. Uma análise adicional foi conduzida na qual potenciais fatores

de risco foram modelados para dois grupos distintos: participantes pertencentes ao quintil de renda mais baixo, representando o grupo economicamente desfavorecido; e os outros participantes pertencentes do segundo ao quinto quintis de renda.

6.4 Análise das trajetórias dos sintomas depressivos maternos, parentalidade negativa e funções executivas aos 15 anos: resumo dos métodos para responder ao objetivo específico 3

Os desfechos estudados foram a atenção sustentada, memória de trabalho espacial e memória episódica aos 15 anos medidas nos adolescentes da Coorte de Nascimentos de Pelotas de 2004. Os desfechos foram utilizados em forma de variável contínua. Para cada desfecho, foram calculados a média, o desvio padrão, os percentis e a faixa de valores medidos. O tempo total para concluir os três subtestes foi calculado em minutos, subtraindo-se o tempo inicial do tempo final ao término do subteste.

A exposição principal examinada foram as trajetórias dos sintomas depressivos maternos, já descritas anteriormente. O potencial mediador da parentalidade negativa entre as trajetórias dos sintomas depressivos maternos e as funções executivas também foi examinado neste estudo.

Os potenciais fatores de confusão incluíam variáveis coletadas no nascimento do adolescente, como a renda familiar, a escolaridade materna, a cor da pele materna autodeclarada, a idade materna e a paridade. O tabagismo durante a gravidez foi avaliado retrospectivamente no nascimento por meio de relato materno. A idade gestacional foi estimada usando o primeiro dia da última menstruação normal ou por ultrassom obstétrico antes de 20 semanas de gestação, se os dados menstruais fossem pouco confiáveis ou indisponíveis. O nascimento prematuro foi definido como gestação <37 semanas.

As comparações entre as características socioeconômicas, maternas e de nascimento dos participantes no acompanhamento de 15 anos (N=1950) e o número total de participantes na linha de base (N=4231) foram realizadas usando o teste qui-quadrado. A análise descritiva foi feita calculando as frequências absolutas e relativas das variáveis incluídas na análise. A média e o desvio padrão dos desfechos, de acordo com as características maternas e dos adolescentes, foram analisados usando análise de variância (ANOVA).

Uma série de modelos de regressão linear passo a passo foi realizada separadamente entre exposição e mediador, mediador e desfechos, e exposição e desfechos. Em seguida, cada conjunto de possíveis fatores de confusão foi incluído para cada via na análise de mediação. As variáveis foram mantidas no modelo de regressão linear se seu nível de significância fosse abaixo de 0,20 (Maldonado & Greenland, 1993).

Os modelos de análise de mediação foram construídos por meio da análise de caminhos para as três funções executivas dos adolescentes: atenção sustentada, memória episódica e de trabalho (MacKinnon et al., 2007). Para cada modelo, foi quantificado: o caminho direto entre as trajetórias dos sintomas depressivos maternos e a função executiva correspondente (caminho c'); o efeito direto entre as trajetórias dos sintomas depressivos maternos e a parentalidade negativa (caminho a), o efeito direto entre a parentalidade negativa e a função executiva correspondente (caminho b), o efeito indireto (ou seja, o efeito de mediação) por meio da parentalidade negativa (caminho a*b); e o efeito total (caminho c). Inicialmente, as associações entre as trajetórias dos sintomas depressivos maternos e as funções executivas dos adolescentes foram examinadas usando modelos de regressão linear multivariada para cada desfecho (efeitos totais). Subsequentemente, a modelagem de equações estruturais (SEM) foi utilizada para examinar o papel mediador da parentalidade negativa na relação entre as trajetórias dos sintomas depressivos maternos e as funções executivas dos adolescentes. Todos os modelos foram ajustados para os possíveis fatores de confusão identificados previamente. Todas as análises estatísticas foram bicaudais, e a significância foi estabelecida em 0,05. As estatísticas descritivas foram realizadas usando o Stata versão 14.2. A regressão linear e a análise de caminhos foram realizadas no Mplus versão 8.1 com estimador de máxima verossimilhança e erros padrão bootstrap.

7 RESULTADOS

7.1 Resumo dos principais resultados do primeiro artigo: Rodrigues et al, 2024.

Artigo 1: *Rodrigues JS, Valero MP, Trambaiolli LR, Bozzini AB, Matijasevich A. Impact of maternal depressive symptoms on offspring executive functions: a systematic review. Revista brasileira de psiquiatria. São Paulo, Brazil. 2024 Mar 1.*

Usando os critérios de busca, 11.395 estudos foram identificados (2.156 do Science Direct, 2.179 do PsychInfo, 229 do LILACS, 53 do SciELO e 6.778 do Pubmed), dos quais 451 duplicados foram removidos (Anexo B). Após a avaliação dos títulos e resumos, 10.719 artigos foram eliminados. Com base nos critérios de incluso e exclusão, um total de 33 artigos foram incluídos nesta revisão.

Os 33 estudos foram publicados entre 2010 e 2022. Os tamanhos das amostras variaram de 57 a 6.979 participantes. A maioria dos estudos foi conduzida na população geral, com exceção de Comas et al. (2011), Hughes et al. (2012) e Rhoades et al. (2013) que utilizaram coortes de comunidades de baixa renda, e Priel et al. (2014) com uma coorte que incluía apenas famílias de baixo risco, excluindo casos de pobreza, monoparentalidade, nascimento prematuro ou maternidade na adolescência.

As populações dos estudos foram distribuídas geograficamente da seguinte forma: 21 estudos foram realizados na América do Norte, 7 na Europa, 2 na África, 2 na Ásia e 1 na Oceania.

Dos 33 estudos examinados, 32 usaram ferramentas de rastreamento para detectar sintomas depressivos maternos. Ferramentas de rastreamento são muito úteis, embora não forneçam diagnósticos clínicos. A Escala de Depressão Pós-Parto de Edimburgo (EPDS), por exemplo, foi o método adotado pela maioria dos autores para detectar sintomas depressivos maternos no período pré-natal e/ou pós-parto.

Três estudos construíram trajetórias da depressão materna. No estudo de Oh et al. (2018), a Análise de Perfil Latente foi empregada para identificar três classes distintas: "sem sintomas" (escores abaixo de 10 pontos), "sintomas leves" (escores de 11 a 13 pontos) e "sintomas moderados" (escores entre 15 e 19 pontos). Rinne et al. (2019) usou a análise de crescimento de curva latente com sintomas depressivos padronizados em quatro pontos no

tempo. Vänskä et al. (2020) usou a modelagem de mistura de fatores e identificou cinco classes de trajetória: sintomas baixos estáveis, problemas pré-natais (sofrimento psicológico principalmente durante a gravidez), problemas no início do pós-parto (sofrimento psicológico principalmente 2 meses após o nascimento), problemas no final do pós-parto (sofrimento psicológico principalmente 12 meses após o nascimento) e problemas altos heterogêneos (taxas mais altas de sofrimento psicológico desde a gravidez até 12 meses após o nascimento).

Os estudos incluídos nesta revisão reportaram as funções executivas de duas formas principais: por meio de testes cognitivos e/ou questionários reportados pelos pais ou cuidadores. Vinte e seis dos 33 estudos se basearam em testes para avaliar as funções executivas. Dentre os 33 estudos incluídos nesta revisão, três diferentes formas de relatar os resultados das funções executivas foram observadas: 9 estudos relataram o resultado por domínio específico; 23 relataram escores totais incluindo múltiplos domínios; e 14 estudos apresentaram os resultados de acordo com a tarefa avaliada durante a entrevista.

A associação negativa entre a exposição aos sintomas depressivos maternos e as funções executivas das crianças foi consistente em 26 estudos, sugerindo que crianças cujas mães apresentavam níveis mais altos de sintomas depressivos maternos apresentaram pior desempenho nas funções executivas em comparação com crianças cujas mães não apresentavam síntomas depressivos ou apresentavam sintomas leves. Os estudos utilizaram uma ampla gama de variáveis de confusão, como istatus socioeconômico familiar, QI materno, idade da criança, sexo, peso ao nascer, idade gestacional e educação materna.

Em geral, os estudos apresentaram qualidade satisfatória. Viés de seleção e/ou relato foi identificado em 18 dos 33 estudos (Material Suplementar, Tabela S2). Diferentes níveis de sintomas depressivos maternos foram pouco investigados entre os estudos. A maioria deles analisou os sintomas depressivos maternos como uma variável dicotômica, e poucos estudos examinaram trajetórias de depressão materna e/ou consideraram categorias de diferentes níveis de exposição.

7.2 Resumo dos principais resultados do segundo artigo: Rodrigues et al, 2023.

Artigo 2: *Rodrigues JS, Matijasevich A, Tovo- Rodrigues L, Munhoz TN, Santos IS, Pastor-Valero M. Risk factors for executive function impairment in adolescence: an analysis of data from the 2004 Pelotas Birth Cohort study. Braz J Psychiatry. 2023;45:470-481.*

Os participantes que foram acompanhados aos 11 e 15 anos apresentaram melhores indicadores socioeconômicos do que a amostra inicial como um todo (Anexo C). A maioria das mães dos participantes acompanhados aos 11 e 15 anos de idade eram brancas, tinham entre 20 e 34 anos, possuíam pelo menos 9 anos de escolaridade e não fumaram durante a gravidez. A prevalência de meninos foi ligeiramente maior tanto no acompanhamento aos 11 quanto aos 15 anos. A maioria dos pais dos adolescentes esteve presente durante a infância. Além disso, a maioria dos adolescentes foi amamentada por pelo menos o primeiro mês de vida.

As análises ajustadas revelaram que diversos preditores perinatais e da infância estavam associados a prejuízos nas funções executivas relacionadas à atenção e à memória de trabalho. Baixa escolaridade materna foi um forte preditor de déficit nas funções executivas relacionadas à atenção (controle atencional: OR= 4,10; IC95% (1,53-10,95); flexibilidade cognitiva: OR=2,49; IC95% (0,84-7,39); atenção seletiva: OR=9,15; IC95% (3,82-21,96) e na memória de trabalho: OR=4.98; IC95% (1,41-17,62). Este resultado permaneceu consistente mesmo após a estratificação por renda familiar. Além disso, menor renda familiar foi associada a maiores chances de comprometimento do controle atencional (OR= 1,95; IC95% (1,20-3,17)). Crianças cujas mães se auto-declararam negras tiveram desempenho pior do que crianças de mães auto-declaradas brancas no controle atencional, atenção seletiva (OR=2,47; IC95% (1,86-3,27)) e memória de trabalho (OR=1.52; IC95%: (1,15-2,02)). Este resultado persistiu para o comprometimento da atenção seletiva mesmo quando a estratificação por renda familiar foi considerada.

Ter um maior número de irmãos foi associado ao comprometimento do controle atencional (OR=1,60; IC95% (1,10-2,33)) e da memória de trabalho (OR=1,89; IC95% (1,41-2,53)). Além disso, baixo peso ao nascer foi relacionado a pior atenção seletiva aos 11 anos de idade (OR=1,98; IC95% (1,40-2,79)). As trajetórias de sintomas depressivos

maternos moderada-baixa e decrescente estiveram associadas a pior memória de trabalho aos 15 anos (respectivamente: OR=1,61; IC95% (1,23-2,12); OR=1,52; IC95% (1.02-2.25)). A estratificação por renda familiar revelou que, dentro do grupo do quintil de renda mais baixa, trajetórias de sintomas depressivos maternos moderada-baixa e decrescente estiveram associadas ao comprometimento do controle atencional (respectivamente: OR=1,61; (IC95% 1,23-2,12); OR=1,52; IC95% (1.02-2.25)).

Em termos de diferenças de sexo, meninas exibiram um risco reduzido de comprometimento da atenção seletiva aos 11 anos (OR=0,54; IC95% (0,44-0,67)), enquanto apresentaram pior desempenho na memória de trabalho espacial aos 15 anos (OR=1,41; IC95% (1,11-1,78)).

A amamentação emergiu como um fator protetor, reduzindo as chances de comprometimento da flexibilidade cognitiva (OR= 0,36; IC95% (0,21-0,62)), independentemente de sua duração. Além disso, observou-se um efeito protetor no qual adolescentes cujas mães tinham 35 anos ou mais no momento do nascimento apresentaram melhor atenção seletiva em comparação com filhos cujas mães tinham 20 e 34 anos (OR=0,55; IC95% (0,37-0,82)).

7.3 Resumo dos principais resultados do terceirio artigo: Rodrigues et al, 2024.

Artigo 3: *Rodrigues, JS., Pastor-Valero, M., Maruyama, JM., Munhoz, TN., Santos, IS., Barros, AJD., Tovo-Rodrigues, L., & Matijasevich, A. (2024). Examining pathways between trajectories of maternal depressive symptoms, harsh parenting, and adolescent executive functions: Insights from the 2004 Pelotas Birth Cohort.*

A atenção sustentada, a memória episódica e a memória de trabalho estiveram correlacionadas entre si (r = 0,94; r = 0,94; r = 0,96, respectivamente) (Anexo D). O tempo médio para realizar os três subtestes foi de 39,61 (3,29) minutos. O número médio (DP) de erros totais no subteste de memória episódica foi de 10,70 (11,20), variando de 0 a 68. A atenção sustentada, avaliada pelo subteste de processamento visual rápido, apresentou uma sensibilidade média (DP) de 0,82 (0,07), com uma variação de 0,28 a 0,98. Além disso, o número médio (DP) de erros totais na memória de trabalho, avaliada pelo subteste de memória de trabalho espacial, foi de 14,21 (8,18), variando de 0 a 44.

Adolescentes cujas mães estavam na trajetória de sintomas depressivos crônica-alta exibiram menor sensibilidade média de atenção sustentada em 0,016 pontos em comparação

com aqueles cujas mães pertenciam a trajetória baixa de sintomas depressivo. Não houve evidência de um efeito direto das trajetórias dos sintomas depressivos maternos na atenção sustentada. No entanto, evidências de efeitos totais e indiretos indicam que essa associação foi parcialmente mediada pela parentalidade negativa (efeito indireto (a3*b): B=-0,003; SE=0,001; IC95% (-0,004; -0,001); efeito indireto (a4*b): B=-0,007; SE=0,002; IC95% (-0,010; -0,004)) em adolescentes de mães pertencentes às trajetória crescente de sintomas crescentes (proporção explicada: 19% (18%; 45%)) e crônica-alta (proporção explicada: 42% (34%; 186%)) em comparação com a trajetória baixa de sintomas depressivos maternos. A parentalidade negativa esteve negativamente associada à atenção sustentada (Caminho b: B=-0,003; SE=0,001; IC95% (-0,004; -0,002)).

Adolescentes cujas mães pertenciam à trajetória crónica-alta de sintomas depressivos apresentaram um maior número de erros totais na memória episódica, com uma diferença de 0,252 pontos em comparação com aqueles cujas mães pertenciam à trajetória baixa de sintomas depressivos. Nossas análises não revelaram efeitos diretos ou totais das trajetórias dos sintomas depressivos maternos na memória episódica dos adolescentes. Efeitos indiretos entre todas as trajetórias de sintomas depressivos maternos e memória episódica foram observados, sugerindo que essa associação foi mediada pela parentalidade negativa. A magnitude do efeito indireto foi maior nas trajetórias crescentes (efeito indireto (a3*b): B=0,288; SE=0,127; IC95% (0,109; 0,532)) e crónica-alta (efeito indireto (a4*b): B=0,717; SE=0,304; IC95% (0,262; 1,266)). A parentalidade negativa foi negativamente associada à memória episódica dos adolescentes (Caminho b: B=0,288; SE=0,113; IC95% (0,099; 0,473)).

Não foi encontrado efeito indireto das trajetórias dos sintomas depressivos maternos na memória episódica, indicando que essa associação não foi mediada pela parentalidade negativa (efeito indireto (a3*b): B=0,085; SE=0,090; IC95% (-0,052; 0,248); efeito indireto (a4*b): B=0,199; SE=0,206; IC95% (-0,131; 0,544)). Efeitos totais mostraram que adolescentes cujas mães estavam nas trajetórias crescente (B=1,277; SE=0,636; IC95% (0,277; 2,322)) e moderadas baixa (B=1,064; SE=0,419; IC95% (0,353; 1,751)) apresentaram pior memória de trabalho do que adolescentes cujas mães pertenciam à trajetória baixa de sintomas depressivos.

8 DISCUSSÃO

Os três artigos que compõe a presente tese contribuem para a compreensão na relação entre os sintomas depressivos maternos, examinados desde os três meses aos 11 anos de idade dos filhos, das práticas parentais negativas avaliadas aos 11 anos de idade, e de outros fatores de risco, como a baixa escolaridade materna e a renda familiar, no comprometimento das funções executivas de atenção e memória aos 11 e 15 anos. Cada artigo fornece uma perspectiva única, desde uma revisão sistemática abrangendo diversos estudos de coorte até análises específicas baseadas na Coorte de Nascimentos de Pelotas de 2004. Os achados ainda sugerem um caminho pelo qual as trajetórias dos síntomas depressivos maternos poderiam afetar as funções executivas. A seguir, discutirei os resultados de cada estudo, suas contribuições para a literatura existente e as implicações práticas para intervenções futuras.

8.1 Impacto dos sintomas depressivos maternos nas funções executivas dos filhos

O primeiro artigo desta tese (Rodrigues et al., 2024) apresenta uma revisão sistemática de 33 estudos longitudinais que investigam as consequências negativas da exposição aos sintomas depressivos maternos, desde o período perinatal até a adolescência, nas funções executivas dos filhos medidas durante a infância e a adolescência. Em 25 dos 33 estudos, observou-se uma associação negativa entre os sintomas depressivos maternos e as funções executivas dos filhos. Os resultados indicam que crianças e adolescentes expostos a níveis mais elevados de sintomas depressivos maternos apresentaram pior desempenho em funções executivas. Três estudos incluídos na revisão identificaram, ainda, que crianças cujas mães pertenciam às trajetórias crescente ou crônica-alta de sintomas depressivos durante a infância apresentavam maior comprometimentos das funções executivas em comparação a filhos cujas mães pertenciam à trajectória baixa (Oh et al., 2020; Park et al., 2018; Rinne et al., 2022). Esses achados estão em linha com estudos longitudinais que revelaram que crianças cujas mães tiveram sintomas depressivos persistentes graves na infancia apresentavam mariores problemas emocionais e comportamentais do que aquelas cujas mães tiveram sintomas persistentemente leves (Campbell et al., 2007; Flouri et al., 2017; Matijasevich et al., 2015).

Estudos anteriores investigaram a influência da depressão perinatal na programação fetal, sugerindo que a exposição à depressão materna durante a gravidez pode induzir

modificações epigenéticas que afetam a expressão gênica do sistema hipotálamo-hipófise-adrenal (HPA) (Dickens & Pawluski, 2018; Molenaar et al., 2019). Essas possíveis alterações podem predispor as crianças a uma maior vulnerabilidade ao estresse e a maiores dificuldades nas funções executivas ao longo da vida (Dhaliwal et al., 2020; Neuenschwander et al., 2018; Weikum et al., 2013). Além disso, em relação aos potenciais mecanismos que explicam a associação entre sintomas depressivos maternos e as funções executivas dos filhos na infância e adolescência, estudos exploraram aspectos da relação mãe-filho, como parentalidade, sensibilidade materna, "calor maternal" e apego (Baker, 2018; Ku & Feng, 2021). Esses fatores têm sido amplamente discutidos na literatura como possíveis mediadores entre sintomas depressivos maternos e desfechos comportamentais, como internalização e externalização (Kuckertz et al., 2018; Wolford et al., 2019). A evidência de que a parentalidade pode mediar a relação entre sintomas depressivos maternos e funções executivas foi fundamental para embasar o terceiro artigo deste estudo, que investiga especificamente o papel mediador da parentalidade negativa nas funções executivas de adolescentes.

A maioria dos estudos incluídos nesta revisão sistemática examinou populações do Norte Global, o que limita a compreensão do tema em países do Sul Global. Nessas regiões, a depressão materna é mais prevalente e frequentemente associada a adversidades familiares (J. Fisher et al., 2012). Mães com depressão severa e crônica relatam com maior frequência terem sofrido violência íntima, apresentarem pior estado de saúde e lidarem com problemas de ansiedade ou abuso de substâncias (Conlon & Lynch, 2008). Esses fatores reduzem as chances de um ambiente propício ao desenvolvimento saudável e aumentam o risco de repercussões negativas no desenvolvimento infantil dos filhos (Gelaye et al., 2016b). O acesso a um suporte social adequado, a uma renda suficiente e a um ambiente livre de estresse e conflitos propicia maiores interações positivas que promovem o desenvolvimento saudável das crianças (Deutz et al., 2020).

8.2 Fatores de risco associados às funções executivas na adolescência: implicações dos achados da coorte de pelotas de 2004

O segundo artigo que compõe esta tese (Rodrigues et al, 2023) destaca a baixa escolaridade materna como o fator de risco com o maior impacto negativo nas funções

executivas relacionadas à atenção aos 11 anos e na memória de trabalho espacial aos 15 anos. Além disso, os resultados indicaram que a amamentação (independentemente da duração) e a maternidade tardia têm um efeito protetor no desempenho das funções executivas relacionadas à atenção aos 11 anos na Coorte de Nascimentos de Pelotas de 2004.

Atualmente, muitos estudos que examinam populações de países do Norte Global se concentram na baixa renda familiar como o principal fator socioeconômico associado negativamente às funções executivas (Lawson et al., 2018). Considerando que no Brasil cerca de 42% das crianças de 0 a 14 anos vivem na pobreza, a renda familiar de fato configura um determinante social muito relevante (Junior, 2016). No entanto, nosso estudo identificou que a baixa escolaridade materna exerce um impacto ainda mais significativo sobre prejuízos as funções executivas aos 11 e 15 anos de idade. Em comparação com os países do Norte Global, os países do Sul oferecem menos proteção social para as crianças em termos de nutrição, saúde e educação, o que torna o papel das mães e cuidadores ainda mais central no processo de desenvolvimento infantil (Bedaso et al., 2021; Obradović & Willoughby, 2019). Isso configura um importante problema, ao considerar que mães cujo desenvolvimento cognitivo foi adverso ao longo da vida têm mais chances de terem filhos que também enfrentem dificuldades semelhantes (Jeong et al., 2021). Sem a intervenção adequada, é possível que a transmissão intergeracional seja algo recorrente, especialmente em países de baixa e média renda (Brieant et al., 2017). Estudos revelam que um maior nível de escolaridade das mães está diretamente relacionado a uma maior variedade de estratégias de estimulação e interação com seus filhos, bem como a um maior conhecimento sobre o desenvolvimento infantil (Fonseca et al., 2017). A maior escolaridade materna também está associada a uma diminuição do risco de sintomas depressivos, o que, por sua vez, impacta positivamente na qualidade da relação parental mãe-filho (Jeong et al., 2017).

A amamentação foi identificada como um fator protetor para a flexibilidade cognitiva aos 11 anos de idade, independentemente da sua duração. Nossos achados estão alinhados com observações longitudinais do estudo de coorte de nascimento de Pelotas de 1982 (Victora et al., 2015). Este estudo destaca a associação entre amamentação e melhor desempenho em testes de inteligência mesmo após três décadas. Importante ressaltar que, apesar do reconhecimento crescente dos efeitos positivos da amamentação no desenvolvimento cognitivo infantil, há evidências limitadas associando-a à flexibilidade

cognitiva. A duração da amamentação é um comportamento complexo influenciado por vários fatores, incluindo a duração e exclusividade do padrão de amamentação, saúde materna e outras práticas de alimentação infantil, como a idade de introdução de alimentos complementares (McGowan & Bland, 2023). Esses fatores podem variar entre os estudos que buscam descrever a relação entre a amamentação e o desenvolvimento das funções executivas, resultando em resultados inconsistentes. Os efeitos de longo prazo da amamentação na flexibilidade executiva e no desenvolvimento cognitivo não são completamente compreendidos, sendo necessário maior aprofundamento sobre os mecanismos fisiológicos e comportamentais subjacentes as associações observadas (Lopez et al., 2021).

Este estudo revela a associação entre diversas características perinatais, maternas e ambientais e o comprometimento das funções executivas na adolescência. Os achados sugerem que esse comprometimento resulta da convergência de múltiplas influências ambientais, em vez de exposições individuais isoladas. Ao considerar futuras políticas públicas que possam melhorar o desenvolvimento das funções executivas em crianças, especialmente aquelas expostas a eventos negativos ou ambientes inseguros em países de baixa e média renda, torna-se imperativo destacar o papel das influências positivas em suas experiências de vida precoce. Uma meta-análise recente de 102 estudos mostrou que intervenções parentais têm impacto significativamente maior no desenvolvimento cognitivo infantil em países de baixa e média renda comparados a países de alta renda (K. Cheung & Theule, 2019). Intervenções que priorizam sensibilidade e responsividade dos pais foram até três vezes mais eficazes nesses contextos, destacando a importância de um ambiente familiar positivo para mitigar os efeitos de ambientes inseguros no desenvolvimento das funções executivas das crianças.

8.3 Trajetórias dos sintomas depressivos maternos, parentalidade e funções executivas: relevância dos achados aos 11 e 15 anos na coorte de pelotas de 2004

As análises de caminho realizadas no terceiro artigo desta tese (Rodrigues et al., 2024b), submetido no *Journal of Affective Disorders Reports*, revelaram que as trajetórias dos sintomas depressivos maternos não têm uma associação direta com as funções executivas dos adolescentes. No entanto, ao considerar os efeitos indiretos, a parentalidade negativa

emergiu como um mecanismo explicativo. Quando a parentalidade negativa foi considerada um mediador, verificou-se que os adolescentes cujas mães estavam na trajetória "crônica-alta" apresentaram comprometimento na atenção sustentada e memória episódica aos 15 anos, em comparação com adolescentes cujas mães pertenciam à trajetória "baixa".

Nossos resultados estão alinhados com um estudo envolvendo 1.292 famílias em comunidades rurais de baixa renda nos Estados Unidos (Gueron-Sela et al., 2018), que revelou que sintomas depressivos maternos aos 15 e 24 meses não mostraram associação direta com funções executivas aos 3 anos de idade. Por outro lado, comportamentos parentais negativos, como disciplina severa, mediaram parcialmente essa relação. Comportamentos parentais severos introduzem fontes de estresse e estimulação excessiva, prejudicando a habilidade da criança em controlar efetivamente a atenção e o comportamento direcionado a metas (Berthelon et al., 2020), ambos essenciais para o desenvolvimento das funções executivas (Garon et al., 2008; Perone et al., 2018; Tovo-Rodrigues et al., 2024).

Quanto mais severos e persistentes os sintomas depressivos experimentados durante a infância, mais frequentes foram as práticas severas de criação observadas aos 11 anos de idade. Isso, por sua vez, esteve associado a uma menor atenção sustentada e memória episódica aos 15 anos de idade. Esse padrão de dose-resposta sugere que a gravidade e a duração dos sintomas depressivos maternos durante a infância podem ter um efeito acumulativo sobre os comportamentos parentais, impactando o desenvolvimento cognitivo durante a adolescência. Estudos longitudinais anteriores consistentemente evidenciam uma relação dose-resposta entre a exposição prolongada aos sintomas depressivos maternos e o comprometimento das funções executivas nos filhos (Oh et al., 2020; Park et al., 2018; Rinne et al., 2022). Contudo, essas pesquisas foram conduzidas em países de alta renda e focaram exclusivamente nas trajetórias até os três anos de idade, além de analisar as funções executivas das crianças dos três aos sete anos, sem explorar os possíveis mecanismos subjacentes. Nosso estudo expande esses achados ao identificar um mecanismo pelo qual os efeitos de longo prazo da depressão materna persistente impactam as funções executivas dos adolescentes ao longo de toda a infância. Os resultados deste estudo fornecem evidências importantes para a construção de estratégias de intervenção direcionadas a crianças e adolescentes de mães que apresentam sintomas depressivos. Além disso, o desenho

prospectivo do nosso estudo garantiu a ordem temporal entre exposição, mediador e desfechos, aumentando a confiança na inferência de caminhos causais específicos.

8.4 Limitações e ponderações

Embora a presente tese de doutorado tenha apresentado descobertas significativas sobre o tema, é importante considerar certas ponderações sobre aspectos que não foram abordados. Isso pode ser devido a limitações nos dados disponíveis e/ou à expansão além do escopo inicial do projeto.

É importante destacar a ausência de algumas variáveis essenciais tanto na análise da saúde mental materna quanto no desenvolvimento das funções executivas. Aspectos como o envolvimento, a qualidade e a frequência da relação entre o pai e a criança, bem como o nível de escolaridade paterno, poderiam influenciar ou explicar parte do impacto da depressão materna sobre as funções executivas dos filhos (Baptista et al., 2017; K. Cheung & Theule, 2019; Lucassen et al., 2015).

Utilizamos instrumentos padronizados para avaliar funções executivas como a memória de trabalho visoespacial, flexibilidade cognitiva, atenção seletiva e sustentada e memória episódica. No entanto, outras funções executivas como o auto-controle e a memória de trabalho verbal não foram avaliadas. Além disso, as tarefas foram realizadas em ambiente controlado, nos laboratórios do Centro de Pesquisas Epidemiológicas da Universidade Federal de Pelotas, o que limita a percepção holística e contextual do desempenho dessas habilidades.

O acompanhamento realizado aos 15 anos na Coorte de Nascimentos de Pelotas de 2004 sofre uma interrupçãp devido à pandemia de COVID-19, resultando em uma perda de aproximadamente 50% da coorte original. Os participantes avaliados aos 15 anos apresentavam melhores condições socioeconômicas. Portanto, não podemos descartar o viés de atrito em nossas análises. Considerando que um status socioeconômico mais elevado está associado a melhores funções executivas na prole (Hackman et al., 2015), é possível que nossos resultados tenham sido subestimados.

Outras ponderações de âmbito teórico também devem ser discutidas. Primeiramente, a frequência de práticas parentais negativas foi resportada pela mãe ou cuidador principal, o

que eventualmente pode ter introduzido viés durante a coleta de dados. O relato direto de maus-tratos pelos adolescentes seria mais preciso na determinação da prevalência dessas ocorrências, evitando o viés de desejo social das respostas dos pais (Lev-Wiesel et al., 2019). Em segundo lugar, dentro do campo da neuropsicologia, o conceito teórico das funções executivas e seus correlatos neurais não é consensual e está em constante debate (Cristofori et al., 2019; Feng et al., 2022; Zelazo, 2020). Esta complexidade ressalta a importância de interpretar os resultados desta tese dentro do enquadramento conceitual adotado. De acordo com a literatura, a definição mais amplamente aceita é aquela proposta por Diamond et al. (2014), e por isso optamos por utilizá-la para definir, conceituar e examinar as funções executivas.

Em nossas análises, utilizamos um instrumento para avaliar sintomatologia e não um instrumento diagnóstico para depressão materna. Além disso, ao considerar a depressão materna como a principal exposição, é fundamental observar que a definição de transtornos mentais, incluindo suas causas, diagnósticos e tratamentos, é objeto de controvérsia (Gagné-Julien, 2021). As discordâncias surgem porque os critérios de disfunção e normalidade são influenciados por valores socioculturais, levando ao diagnóstico de transtornos mentais em indivíduos cujas características ou comportamentos não são valorizados pela sociedade ou desviam das expectativas sociais. Além disso, na última década, a saúde mental a nível global vêm sido abordada cada vez mais por concepções que adotam uma visão individualizada, enfatizando o tratamento e a ampliação de escala, negligenciando os determinantes sociais e estruturais da saúde (Clark, 2014). Essas questões são essenciais para uma interpretação crítica desta tese.

8.5 Fortalezas e relevância

O conjunto de manuscritos desta tese utilizou os dados da Coorte de Nascimentos de Pelotas de 2004, contribuindo para preencher a lacuna de estudos em populações de países de baixa e média renda, que frequentemente são negligenciadas em comparação com países de alta renda. Cerca de 90% das crianças e adolescentes do mundo vivem em países de baixa e média renda (LMICs, do inglês *Low and Middle-Income Country*), os quais apresentam diferenças significativas em contextos socioculturais quando comparados não apenas entre si, mas especialmente com os países de alta renda (Shinde et al., 2023). As principais fontes

de dados sobre saúde dos adolescentes em países de baixa e média renda são, em geral, pesquisas realizadas em escolas, ou em visitas domiciliares (Patton et al., 2010). No Brasil, a Pesquisa Nacional de Saúde do Escolar – PeNSE realizada pelo Instituto Brasileiro de Geografia e Estatística (IBGE) tem por objetivo subsidiar o monitoramento de fatores de risco e proteção à saúde em adolescentes escolares (Oliveira et al., 2017). Embora tanto as modalidades baseadas em escolas quanto em comunidades possam fornecer dados representativos nacionalmente entre adolescentes elegíveis, existem várias limitações na medição da saúde e bem-estar dos adolescentes em LMICs (Shinde et al., 2023). Essas medidas não cobrem igualmente todos os subgrupos de adolescentes de diferentes gêneros, etnias e religiões, além daqueles fora da escola e migrantes. Além disso, os dados desagregados por idade frequentemente são escassos devido à cobertura incompleta. Vários aspectos da saúde dos adolescentes são inadequadamente abordados, incluindo saúde mental e uso de substâncias.

Os dados utilizados nesta tese foram obtidos de uma ampla população brasileira não selecionada. O desenho prospectivo de nosso estudo garante uma ordem temporal entre as exposições e desfechos, aumentando a confiança na inferência de vias causais específicas. A coleta dos dados seguiu uma metodologia rigorosa, com informações padronizadas e questionários previamente validados, permitindo o estudo de indicadores comportamentais, socioeconômicos e de capital humano. Todas as análises estatísticas conduzidas seguiram métodos pré-estabelecidos na literatura, e seguiram copiosamente as recomendações para a adequeação das análises para os dados examinados. Os sintomas depressivos maternos foram avaliados por meio de trajetórias de desenvolvimento ao longo dos primeiros 11 anos da criança, o que nos permitiu descrever os diferentes padrões e progressão dos sintomas ao longo do tempo, identificando os grupos de adolescentes mais vulneráveis. Por fim, todas as funções executivas examinadas foram avaliadas por meio de testes padronizados, evitando viés de informação.

9 RECOMENDAÇÕES E PERSPECTIVAS FUTURAS

Com base nos achados apresentados nesta tese de doutorado, enfatizamos a importância de se aprofundar o estudo sobre os mecanismos pelos quais os sintomas depressivos maternos afetam as funções executivas dos filhos. Além da parentalidade negativa, fatores como a qualidade do ambiente familiar, suporte social e aspectos culturais devem ser considerados em futuras pesquisas para melhor compreender essa relação. A inclusão de variáveis relacionadas à figura paterna, como o envolvimento e a escolaridade, é outra área de estudo recomendada, pois a literatura atual carece de informações sobre o impacto dos pais no desenvolvimento cognitivo infantil.

Além disso, é necessário que se amplie o foco das pesquisas com o intuito de incluir contextos culturais e socioeconômicos variados, especialmente em países de baixa e média renda, onde a prevalência de depressão materna e as condições de vida podem diferir significativamente dos países de alta renda. Para reduzir o viés de informação e obter uma visão mais precisa, sugere-se o uso de uma variedade de instrumentos de avaliação, incluindo diagnósticos clínicos e autorrelatos de múltiplos informantes. São fundamentais estudos longitudinais que acompanhem as crianças por maiores períodos para entender os efeitos de longo prazo dos sintomas depressivos maternos, indo além dos primeiros anos de vida e incluindo a adolescência e a idade adulta jovem.

Fortalecer redes de apoio comunitário, incluindo parceiros, familiares e profissionais de saúde, é crucial para fornecer suporte emocional e prático às mães, ajudando a reduzir o isolamento e melhorando o bem-estar materno e infantil. Por fim, é fundamental que políticas públicas reconheçam a importância da saúde mental materna para o desenvolvimento infantil, investindo em serviços de saúde mental acessíveis e eficazes, especialmente em contextos de vulnerabilidade socioeconômica. Essas recomendações buscam não apenas avançar o conhecimento acadêmico sobre a depressão materna e o desenvolvimento das funções executivas, mas também orientar a possíveis intervenções práticas e políticas públicas que possam melhorar a qualidade de vida de mães e crianças em situações de vulnerabilidade.

10 CONCLUSÃO

O conjunto de artigos apresentados nesta tese revela que o desenvolvimento das funções executivas em adolescentes é negativamente impactado pelos sintomas depressivos maternos dos 3 meses aos 11 anos e, também, por características sociodemográficas e do nascimento. Destacamos ainda que a parentalidade emerge neste estudo como um potencial alvo para intervenções e futuras políticas públicas destinadas a promover o desenvolvimento cognitivo saudável de adolescentes, especialmente aqueles em situação de vulnerabilidade. Esta pesquisa oferece uma contribuição significativa à comunidade científica ao fornecer evidências sobre o desenvolvimento das funções executivas, utilizando dados de uma coorte de nascimentos brasileira. O objetivo primordial desta tese é contribuir para o fornecimento de suporte e recursos essenciais que possibilitem a crianças e adolescentes alcançarem o máximo potencial de desenvolvimento de suas funções executivas, proporcionando-lhes, assim, um início de vida mais promissor.

10.1 Conclusões de acordo com os objetivos propostos

- A revisão sistemática constatou que a exposição aos sintomas depressivos maternos desde o perinatal até a adolescência tem um impacto negativo nas funções executivas dos filhos ao longo de seu desenvolvimento na infancia e adolescência. Embora esse achado seja consistente entre diferentes coortes, foram identificadas variações metodológicas nos estudos incluídos. Nossos resultados corroboram pesquisas anteriores sobre outros aspectos do desenvolvimento cognitivo e destacam a necessidade de atenção aos sérios efeitos da depressão materna no desenvolvimento infantil e adolescente.
- Entre diversos preditores, a baixa escolaridade materna teve o maior impacto negativo nas funções executivas relacionadas à atenção aos 11 anos e na memória de trabalho espacial aos 15 anos. Outras variáveis sociodemográficas, como a cor da pele materna (negra ou parda), baixa renda familiar, e fatores do nascimento, como baixo peso ao nascer e prematuridade, também foram identificadas como riscos para o comprometimento das funções executivas nessas idades. Por outro lado, a amamentação, independentemente da duração, surgiu como um fator protetor para a flexibilidade cognitiva aos 11 anos. Esses resultados oferecem evidências sobre o impacto de longo prazo das exposições perinatais no desenvolvimento das funções executivas e podem

orientar políticas públicas futuras visando mitigar os efeitos adversos dos fatores de risco e promover o desenvolvimento das funções executivas, especialmente em populações vulneráveis.

- Mães com sintomas depressivos elevados e persistentes durante a infância empregam práticas parentais negativas com maior frequência, o que, por sua vez, está associado ao comprometimento da atenção sustentada e memória episódica em adolescentes. Embora não tenhamos observado efeitos diretos entre as trajetórias dos sintomas depressivos maternos e as funções executivas, a parentalidade negativa aos 11 anos emergiu como um mecanismo explicativo pelo qual sintomas depressivos graves e persistentes impactam negativamente a atenção sustentada e a memória episódica dos filhos. Estes achados sublimam a necessidade de intervenções que considerem as relações parentais ao abordar o desenvolvimento cognitivo, visando mitigar resultados adversos e promover o bem-estar infantil e adolescente.

11 CONCLUSIÓN

El conjunto de artículos presentados en esta tesis revela que el desarrollo de las funciones ejecutivas en adolescentes se ve negativamente afectado por los síntomas depresivos maternos desde los 3 meses hasta los 11 años, así como por características sociodemográficas y de nacimiento. Destacamos también que la parentalidad emerge en este estudio como un objetivo potencial para intervenciones y futuras políticas públicas destinadas a promover el desarrollo cognitivo saludable de los adolescentes, especialmente aquellos en situación de vulnerabilidad. Esta investigación ofrece una contribución significativa a la comunidad científica al proporcionar evidencias sobre el desarrollo de las funciones ejecutivas, utilizando datos de una cohorte de nacimientos brasileña. El objetivo primordial de esta tesis es contribuir a proporcionar el apoyo y los recursos esenciales que permitan a los niños y adolescentes alcanzar su máximo potencial de desarrollo de sus funciones ejecutivas, ofreciéndoles así un inicio de vida más prometedor.

11.1 Conclusiones según los objetivos propuestos

- La revisión sistemática constató que la exposición a los síntomas depresivos maternos desde el periodo perinatal hasta la adolescencia tiene un impacto negativo en las funciones ejecutivas de los hijos a lo largo de su desarrollo en la infancia y la adolescencia. Aunque este hallazgo es consistente entre diferentes cohortes, se identificaron variaciones metodológicas en los estudios incluidos. Nuestros resultados corroboran investigaciones anteriores sobre otros aspectos del desarrollo cognitivo y destacan la necesidad de prestar atención a los serios efectos de la depresión materna en el desarrollo infantil y adolescente.
- Entre diversos predictores, el bajo nivel educativo materno tuvo el mayor impacto negativo en las funciones ejecutivas relacionadas con la atención a los 11 años y en la memoria de trabajo espacial a los 15 años. Otras variables sociodemográficas, como el color de piel materna (negra o mulata), la baja renta familiar, y factores del nacimiento, como bajo peso al nacer y prematuridad, también se identificaron como riesgos para el deterioro de las funciones ejecutivas a estas edades. Por otro lado, la lactancia materna, independientemente de su duración, surgió como un factor protector para la flexibilidad cognitiva a los 11 años. Estos resultados ofrecen evidencias sobre el impacto a largo plazo

de las exposiciones perinatales en el desarrollo de las funciones ejecutivas y pueden orientar futuras políticas públicas para mitigar los efectos adversos de los factores de riesgo y promover el desarrollo de las funciones ejecutivas, especialmente en poblaciones vulnerables.

- Las madres con síntomas depresivos elevados y persistentes durante la infancia emplean prácticas parentales negativas con mayor frecuencia, lo que, a su vez, se asocia con el deterioro de la atención sostenida y la memoria episódica en adolescentes. Aunque no observamos efectos directos entre las trayectorias de los síntomas depresivos maternos y las funciones ejecutivas, los malos tratos a los 11 años emergieron como un mecanismo explicativo por el cual los síntomas depresivos graves y persistentes impactan negativamente en la atención sostenida y la memoria episódica de los hijos. Estos hallazgos subrayan la necesidad de intervenciones que consideren las relaciones parentales al abordar el desarrollo cognitivo, con el objetivo de mitigar resultados adversos y promover el bienestar infantil y adolescente.

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APÊNDICES

Apêndice A. Artigo "*Impact of maternal depressive symptoms on offspring executive functions: a systematic review*."

Periódico: Brazilian Journal of Psychiatry

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DOI: 10.47626/1516-4446-2023-3387

Data de publicação: 03/04/2024

bjp
Braz J Psychiatry. 2024;46:e20233387
doi:10.47626/1516-4446-2023-3387
Brazilian Psychiatric Association

REVIEW ARTICLE

Impact of maternal depressive symptoms on offspring executive functions: a systematic review

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Objective: To conduct a thorough examination of the current understanding of the effect of maternal depression exposure on the executive functions (EFs) of offspring.
Methods: Following the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statement, a comprehensive search for peer-reviewed cohort studies was performed on the MEDLINE (via PubMed), ScienceDirect, LILACS, PsycINFO, and SciELO databases. Study quality was assessed using the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. The evidence was evaluated using the Grading of Recommendation, Assessment, Development, and Evaluation framework.
Results: Thirty-three cohort studies from different countries, enrolling a total of 38,981 participants, were analyzed. Twenty-four studies confirmed the hypothesis of a harmful effect of maternal depressive symptoms on offspring EF. However, high heterogeneity among studies was found, and meta-analysis was not feasible. Fetal programming, genetics, and parental practices have been identified as potential mechanisms that can affect the EFs of children born to mothers who have experienced depressive symptoms.
Conclusion: Our findings suggest a negative association between maternal depressive symptoms and offspring EF. Further studies on the effects of chronicity/severity of maternal symptoms and changes in EFs in different sensitive periods are needed.
Registration number: PROSPERO CRD42020221193.

Keywords: Maternal health; executive control; cohort studies

Introduction

Maternal depression refers to non-psychotic major depressive episodes occurring during pregnancy or the entire first postpartum year.[1,2] Globally, approximately 17% of women who give birth experience this condition, with rates ranging from around 15% in high-income countries to as high as 20% in low-income countries.[3] Such depressive states render mothers more vulnerable to reduced emotional involvement and diminished positive affect. These effects extend to their relationship with their children, resulting in impaired communication and affection, alongside heightened hostility and irritability.[4-7] Disruptions in the mother-child relationship during early life can have an impact on the child's brain development and may increase the child's levels of stress hormones.[8,9] Consequently, these effects have the potential to influence the child's long-term neurobehavioral development and overall well-being.[10,11] The chronic stress and emotional instability associated with maternal depression can potentially affect the neural pathways underpinning executive functions (EFs).[12]

EFs are a set of control mechanisms that module the operation of various cognitive subprocesses and regulate goal-directed behavior.[13-15] Despite variation in definitions,[16,17] EFs are broadly construed to include three subcomponents: inhibition, working memory, and cognitive flexibility.[18,19] The development of EFs is intricately linked to both neurodevelopment and social growth throughout childhood and adolescence.[20-22] Age-related improvement in measures of EF reflects individual experiences and acquisition of knowledge, beliefs, and values.[23] EFs predict a wide range of outcomes in mental, social, and physical health in early life and adulthood, with lifelong impact.[15,24,25] Adequate development of EF is associated with higher academic and professional

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Submitted Jun 06 2023, Accepted Jan 10 2024.

How to cite this article: Rodrigues JS, Pastor-Valero M, Trambaiolli LR, Bozzini AB, Matijasevich A. Impact of maternal depressive symptoms on offspring executive functions: a systematic review. Braz J Psychiatry. 2024;46:e20233387. http://doi.org/10.47626/1516-4446-2023-3387

achievement.[26,27] Conversely, inadequate EF development is associated with higher odds of engaging in high-risk behaviors, such as addiction and violence.[28-31] Exposure to highly stressful environments in childhood has been shown to be associated with deficits in EFs such as working memory, attention, and inhibitory control development.[32]

Examining the impact of maternal depressive symptoms on EF from the perspective of cohort studies not only aids in comprehending child development but also provides insights into implications for individuals' long-term well-being and success as they face challenges along the life course. Cohort studies are the most robust form of medical research after experiments such as randomized controlled trials, and the most appropriate designs to study this relationship.[33]

In a meta-analysis published in 2021, Power et al.[34] comprehensively examined the prevalence and impact of maternal depression during pregnancy and the first year postpartum. Their analysis included 26 cohort studies and found a small, statistically significant relationship between perinatal depression and child EF (effect size r = 0.07; 95%CI 0.03 to 0.10).

This systematic review aims to provide a more comprehensive and updated synthesis of the available literature and to broaden its scope by not imposing restrictions on the timing of assessment of symptoms of maternal depression. Our specific objectives include: to describe and compare the findings of cohort studies that explore the association between maternal depression symptoms and offspring EF; to assess the quality of these studies using standardized tools for cohort study evaluation; and to discuss the limitations of these studies and future perspectives.

Methods

Design

This is a systematic review of cohort studies. The protocol was registered with the University of York Centre for Reviews and Dissemination (CRD) international prospective register of systematic reviews (PROSPERO) (record CRD42020221193) and the study was carried out in accordance with the 2020 version of the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statement.[35]

Systematic search

We searched the following databases from inception to August 20, 2023: MEDLINE (via PubMed), ScienceDirect, LILACS, PsycINFO, and SciELO.

The final search query was developed for use in PubMed and then adapted for the other databases (Supplementary Table S1), as follows: maternal depression: maternal depression OR maternal depression trajectories OR maternal depression trajectory OR depression symptomatology, OR perinatal depression OR postpartum depression OR depression pregnancy; development: cognitive development OR child development OR executive function development OR adolescent development; EFs: executive functions OR executive function OR working memory OR inhibitory control OR cognitive control OR executive function attention-related OR attention-related, executive function OR cognitive flexibility OR self-regulation OR cognitive function. These search terms were combined in the following rule: 1 AND (2 OR 3).

In addition, we conducted a hand search of the reference lists of the selected articles to identify potential studies of interest missed by the original query.

Selection of articles

Eligibility criteria are described in Box 1. The selection of relevant studies, based on titles and abstracts, was carried out in the Rayyan app,[36] independently by two authors (JSR and ABB). Any disagreements were resolved by consulting a third author (AM). Duplicates identified through the electronic databases were manually checked and removed. Finally, the full articles were retrieved. Interobserver variability was calculated using Cohen's kappa coefficient (k).

Data extraction

Data extraction was carried out independently by two authors (JSR and ABB); again, any disagreement was resolved by consulting a third author (AM). To extract the most relevant information, we created a data extraction sheet including 24 items grouped into six categories: 1) study description; 2) population characteristics; 3) exposure characteristics; 4) main outcomes; 5) results, including information regarding control for potential confounding factors and mediation analysis; and 6) conclusion. The extracted data are available at <https://osf.io/32ez8/>. This checklist was applied by JSR, and information was reviewed by AM. Table 1[37-69] lists the main characteristics of the population under study; Table 2 includes information on measurement tools used to evaluate maternal depression and EFs. Supplementary Table S2 provides detailed information on statistical analyses, main outcomes, and limitations.

Box 1 Eligibility criteria

Inclusion criteria
Cohort studies
Original and peer-reviewed studies
English, Spanish, Portuguese, and other languages
Exclusion criteria
Overlapped extracted data
Books, conference papers, theses, and articles without available full text (conferences, editorials, author responses)
Non-original articles (reviews and analyses)
Articles with different exposures or outcomes
Non-compliance with study objectives

Table 1 Main characteristics of the population of the studies included in the systematic review

Authors	Country	Population description	Sample size
Comas[37]	United States	Prospective cohort of primiparous adolescent mothers, which were recruited during their last trimester of pregnancy from various community services and resources located in South Bend, Indiana, and in Aiken, South Carolina.	165
Hughes[38]	United Kingdom	Study based on data from groups residing in low-income neighborhoods and support groups for young mothers within Cambridgeshire, United Kingdom.	126
Rhoades[39]	United States	Data from the FLP, which is a large longitudinal study of children and families living in rural, lower income communities in the United States (North Carolina and Pennsylvania).	1,155
Prior[42]	United Kingdom	Birth cohort representing a large low-risk community (excluding cases of poverty, single parenthood, preterm birth, or teenage motherhood). Participants were recruited from three maternity wards. Only mothers who were healthy, completed secondary education, were older than 21 years, were married or cohabiting, earning above the poverty line, and whose infants were full-term, healthy singletons were included.	900
Lagasse[41]	United States	Data from the MLS. Participants were recruited postpartum at four participating hospital sites from 1993 to 1995.	1,388
Dhaliwal[40]	Canada	Prospective cohort whose participants were recruited either through self-referrals from the community or through referrals from the departments of reproductive psychiatry and family medicine at BC Women's Hospital, Vancouver, Canada, between 2003 and 2009.	118
Faleschini[43]	United States	Study based on Project Viva, a prospective pre-birth cohort study of mother and child pairs enrolled between 1999 and 2002 at initial prenatal visits at Atrius Harvard Vanguard Medical Associates, a multispecialty group practice in eastern Massachusetts.	1,225
Gueron-Sela[44] (sample overlapped with Rhoades[39])	United States	See Rhoades.[39]	1,037
Jensen[45]	United Kingdom	Study based on the ALSPAC. Pregnant women residing in the former Avon Health Authority in South West England, who had an estimated date of delivery between April 1, 1991 and December 31, 1992, were included in the study.	6,979
Oh[46]	Korea	Data from the PSKC. Participants were recruited in medical institutes nationwide from April to July 2008.	1,191
Rinne[47]	United States	A subset of women recruited to Community Child Health Network from three study sites (Lake County, Illinois; Washington, D.C.; Eastern North Carolina) who enrolled in a longitudinal follow-up study of the child's subsequent development.	125
Hermansen[48]	Norway	Study based on the MoBA, NIPH 2010, for which participants were recruited in the period 1999-2008.	103
Poehlmann[49]	United States	Cohort nested in a larger longitudinal study, focusing on infants born preterm or low birthweight. Participants were recruited from three NICUs in southeastern Wisconsin between 2002 and 2005.	172
Wade[50]	Canada	Birth cohort located in the cities of Toronto and Hamilton. Women were recruited between 2006 and 2008 through a program called HBHC.	501
Berthelsen[51]	Australia	Study based on the LSAC. Participants were recruited in 2004.	4,819
Vänskä[52]	Finland	Married or cohabiting Finnish Caucasians. Half of the sample included couples with history of infertility and successful assisted reproduction; the other half had conceived naturally. Couples with multiple pregnancies were excluded, and only women older than 25 years of age were included.	360
El Marroun[53]	Netherlands	Ongoing population-based cohort (the Generation R Study). Mothers with a delivery date from April 2002 until January 2006 were enrolled in the study.	5,883
Weikum[54]	Canada	Part of a longitudinal cohort study examining the effects of prenatal exposure to selective serotonin reuptake inhibitors and maternal mood disturbances. Participants were physician-referred or self-referred from the Reproductive Mental Health Clinic at BC Women's Hospital and Health Centre, community midwife clinics, or family physician practices in the greater Vancouver metropolitan area.	57
Ross[55]	Canada	Study based on a subsample of maternal-child pairs enrolled in the APrON prospective cohort recruited between 2009 and 2012 in Alberta, Canada.	525
Plamondon[56]	Canada	Study based on the Hamilton, Ontario cohort. Participants in Hamilton were referred from the SJHC Women's Health Concerns Clinic and SJHC Ultrasound Department, Hamilton, Ontario, Canada.	236
Buss[57]	United States	Study based on a prospective cohort study. Women were recruited early in pregnancy for study participation between 1998 and 2002.	89

Continued on next page

Table 1 (continued)

Authors	Country	Population description	Sample size
Neuenschwander[58]	Canada	Cohort study of middle- to high-income pregnant women from southwestern Canada.	107
Hutchison[59]	Canada	Based on a cohort study in which women were physician-referred or self-referred from the Reproductive Mental Health Program at BC Columbia Women's Hospital and Health Centre, family physician practices, and community midwife clinics in the Vancouver Metropolitan area in British Columbia, Canada.	191
Rotheram-Fuller[60]	South Africa	Based on a prospective cohort study whose participants were recruited in three peri-urban townships outside of Cape Town, South Africa, from May 2009 to September 2010.	1,119
Nolvi[61]	Finland	Data from the FinnBrain Birth Cohort Study. Participants were recruited at maternal welfare clinics of a geographically defined area, which performed pregnancy ultrasound scans for the women eventually referred to give birth at Turku University Hospital in the Southwest Finland Hospital District and the Åland Islands in Finland.	304
Hackman[62]	United States	Data from the NICHD SECCYD. Participants were recruited from designated hospitals at 10 data collection sites during the year 1991.	1,364
Yan[63] (sample overlapped with Hackman[62])	United States	See Hackman.[62]	1,364
Ku[64] (sample overlapped with Hackman[62])	United States	See Hackman.[62]	1,364
Wang[65]	United States	See Hackman.[62]	1,364
Baker[66]	United States	Based on the Head Start FACES study. FACES used children and families recruited from the 2007 to 2008 Head Start PIR, which included 2,600 Head Start programs in the 50 U.S. states and the District of Columbia.	3,349
Familiar[67]	South Africa, Malawi, Uganda, and Zimbabwe	Data from IMPAACT P1104S, an observational longitudinal study of three cohorts of children enrolled between 5 and 11 years of age conducted at six research sites: South Africa (Wits RHI Shandukani Research Centre in Johannesburg, Perinatal HIV Research Unit in Soweto, and Family Clinical Research Unit in Cape Town), Malawi (University of North Carolina Project at Kamuzu Central Hospital in Lilongwe), Uganda (Makerere University - Johns Hopkins University Clinic Mulago National Referral Hospital in Kampala), and Zimbabwe (Parirenyatwa General Hospital in Harare).	611
Feng[68]	China	Based on a prospective cohort study whose participants were recruited at birth in the Haidian Maternal and Child Health Hospital and Peking University Third Hospital from December 2012 to November 2014.	176
Yu[69]	United States	The participants consisted of 414 mothers from a secondary analysis using data from the 18-year follow-up from the New Mothers' Study in Memphis, Tennessee.	414

ALSPAC = Avon Longitudinal Study of Parents and Children; APrON = Alberta Pregnancy Outcomes and Nutrition; FACES = Family and Child Experiences Survey; FLP = Family Life Project; HBHC = Healthy Babies Healthy Children; IMPAACT = International Maternal Pediatric Adolescent AIDS Clinical Trials Network; LSAC = Longitudinal Study of Australian Children; MLS = Maternal Lifestyle Study; MoBA = Norwegian Mother and Child Cohort Study; NICHD SECCYD = National Institute of Child Health and Development Study of Early Child Care; NICUs = neonatal intensive care units; NIPH = Norwegian Institute of Public Health; PIR = Program Information Report; PSKC = Panel Study on Korean Children; SJHC = St. Joseph's Health Center.

Assessment of reporting quality

The National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used to assess the reporting quality of the studies.[70] This tool is a critical appraisal instrument designed to evaluate the quality of cohort studies, including population description/recruitment, sources of bias (e.g., attrition), confounding, study power, and strength of causality in the association between exposure and outcome. It consists of 14 items with three possible answer categories: yes, no, or cannot determine/not applicable/not reported. Studies were categorized as good if they addressed 80% or more of the required items, fair if they covered between 60 and 80% of the items, and poor if they addressed less than 60% of the required items.

Two coauthors (JSR and ABB) applied the tool and rated the articles independently. According to NHLBI recommendations, studies were evaluated comprehensively, based on the details reported and strategies adopted to minimize bias. Any disagreements between the reviewing coauthors were resolved by a third researcher (AM).

Assessment of certainty in evidence

Meta-analysis was unfeasible because of the high heterogeneity found among studies. To assess the accuracy of the evidence collected, a summary of the limitations in study design (risk of bias), inconsistency of results, indirectness of evidence, and imprecision was created using the Grading Quality of Evidence and

Table 2 Instruments used to assess maternal depression and EFs in the studies included in the systematic review

	Maternal depression		EFs	
Authors	Instruments	Time point(s) of assessment (child's age as reference)	Instruments	Time point(s) of assessment (child's age as reference)
Prenatal				
Hermansen[40]	BDI-II	3rd and 7th months of pregnancy	NEPSY-II (Statue Subtest), ANT	5 and 6 years
El Marroun[53]	BSI	20.6 weeks of pregnancy	BRIEF-P, NEPSY-II (attention and executive functioning)	4 and 7 years
Prenatal and postpartum				
Buss[57]	CES-D, BDI	2nd trimester of pregnancy, 6-9 years	Flanker task, Sequential Memory task	6-9 years
Weikum[54]	HAM-D	3rd trimester of pregnancy, 6 years	Hearts & Flowers task	6 years
Jensen[45]	EPDS	8th month of pregnancy, 2 and 8 months postpartum, 1 year and 9 months, 3 year and 9 months	TEAch	8 years
Plamondon[58]	EPDS	3rd trimester of pregnancy, 6 months postpartum	CANTAB, ECBQ	1 year and 6 months, 4 years
Vánská[52]	GHQ-36,[72] BDI	2nd trimester of pregnancy, 2 and 12 months postpartum	FTF	6 and 7 years
Neuenschwander[55]	HAM-D	3rd trimester of pregnancy, 6 years	Hearts & Flowers task	6 years
Nolvi[61]	EPDS	14th, 24th, and 34th gestational weeks, 6 months postpartum	Delayed Response task	8 months
Rotheram-Fuller[63]	EPDS	2 weeks postpartum, 6, 18, and 36 months	Executive Function Battery	3 years
Hutchinson[59]	EPDS, BDI, HAM-D	2nd and 3rd trimester of pregnancy, 6 months postpartum, 3 and 6 years	BRIEF	6 years
Faleschini[43]	EPDS	Mid-pregnancy, 6 and 12 months postpartum	BRIEF	Mid-childhood
Oh[48]	K6	9 months of pregnancy, 6 months postpartum, 1 and 2 years	EFDSQ	7 years
Dhaliwal[47]	HRSD	6th and 9th months of pregnancy, 6 years	BRIEF	6 years
Ross[62]	EPDS	2nd and 3rd trimesters of pregnancy, 3 months postpartum	BRIEF-P	2 years
Rinne[47]	EPDS, CES-D	2nd and 3rd trimesters of pregnancy, 3 months postpartum	Dimensional Change Card Sort task, Flanker Inhibitory Control-Attention task	5 years
Postpartum				
Poehlmann[49]	CES-D	At discharge, 4, 9, 16, 24, and 36 months postpartum	Snack Delay, Gift Bag Towers, Shapes Walk-a-Line Slowly Whisper	2 and 3 years
Rhoades[50]	BSI-18	1 and 7 months postpartum	Simon task, Flexible Item Selection Span-type Working Memory	3 years
Hughes[39]	BDI	2-4 and 6 years	Beads Working Memory task, Day-Night Game, Tower-of-London task	2 and 6 years
Comas[37]	BDI	3, 5, 8, 10 years	D-KEFS, TEA	18 years
Hackman[42]	CES-D	1 month postpartum	WJ Psychoeducational Battery - Revised, Tests of Cognitive Ability, Tower of Hanoi task	4 years and 6 months, 1st, 3rd, and 5th grade
Yan[51] (sample overlapped with Hackman[42])	CES-D	6 months postpartum, 1 year and 3 months, 2 and 3 years, 4 years and 6 months, 6 years	CPT, CBQ	4 years and 6 months
Lagasse[41]	BDI, BSI		Delay of Gratification task, Prohibition task, TOVA, CANTAB	5, 9, and 13 years

Continued on next page

Table 2 (continued)

	Maternal depression		EFs	
Authors	Instruments	Time point(s) of assessment (child's age as reference)	Instruments	Time point(s) of assessment (child's age as reference)
		4 and 30 months postpartum, 4 years, 5 years and 6 months, 9, 11, and 13 years		
Wang[65] (sample overlapped with Hackman[62])	CESD	6 and 15 months postpartum, 2 and 3 years, 4 years and 6 months	CPT, Memory for Sentences Subtest from the WJ Psychoeducational Battery, Tower of Hanoi task	1st grade
Berthelsen[51]	K6	4 and 5 years	Cogstate Assessment Battery	14-15 years
Wade[50]	CES-D	2 months postpartum	Bear/Dragon, DCCS	4 years
Feng[66]	EPDS	3 days postpartum, 6 months postpartum	Working memory and Inhibition task, Two-Cup task, Three-Cup task, Planning test	6 months
Gueron-Sela[44] (sample overlapped with Rhoades[39])	BSI-18, CES-D	6, 15, and 24 months postpartum	Working Memory Span, Pick-the-Picture Game, Silly Sounds Stroop, Spatial Conflict, Animal Go/No-Go, Something is the Same Game	3 and 4 years
Baker[49]	CES-D	1st year postpartum	Pencil-tapping task	5 years
Prial[40]	SCID and DSM-IV Axis I Disorders	6 and 9 months postpartum, 6 and 10 years	CANTAB	10 years
Familiar[67]	HSCL-25	At discharge, 6 months, 2 years	BRIEF	7.2 years
Ku[64] (sample overlapped with Hackman[62])	CES-D	6 months postpartum, 1 year and 3 months, 2 and 3 years, 4 years and 6 months, 1st, 3rd, and 5th grades	Tower of Hanoi task	1st, 3rd, 5th grades
Yu[59]	RAND MHI	2 years	Digital Span task, Attention Sustained Subtest of the Leiter, International Performance Scale, Gambling task	6 and 18 years

ANT = Attentional Network task; BDI = Beck Depression Inventory; BRIEF = Behavior Rating Inventory of Executive Function; BRIEF-P = Behavior Rating Inventory of Executive Function - Preschool version; BSI = Brief Symptom Inventory; CANTAB = Cambridge Neuropsychological Test Automated Battery; CBQ = Children's Behavior Questionnaire; CES-D = Center for Epidemiological Studies Depression; CPT = Continuous Performance Test; DCCS = Dimensional Change Card Sort; D-KEFS - Dalis Kaplan Executive Functioning System; ECBQ = Early Childhood Behavior Questionnaire; EFDSQ = Executive Function Difficulty Screening Questionnaire; EFs = executive functions; EPDS = Edinburgh Postpartum Depression Scale; FTF = Five to Fifteen; GHQ = General Health Questionnaire; HAM-D = Hamilton Depression Rating Scale; HRSD = Hamilton Rating Scale for Depression; HSCL-25 = Hopkins Symptom Checklist; K6 = Kessler Psychological Distress Scale; MHI = Mental Health Inventory; TEA = Test of Everyday Attention; TEAch = Test of Everyday Attention for Children; TOVA = Test of Variables of Attention; WJ = Woodcock-Johnson.

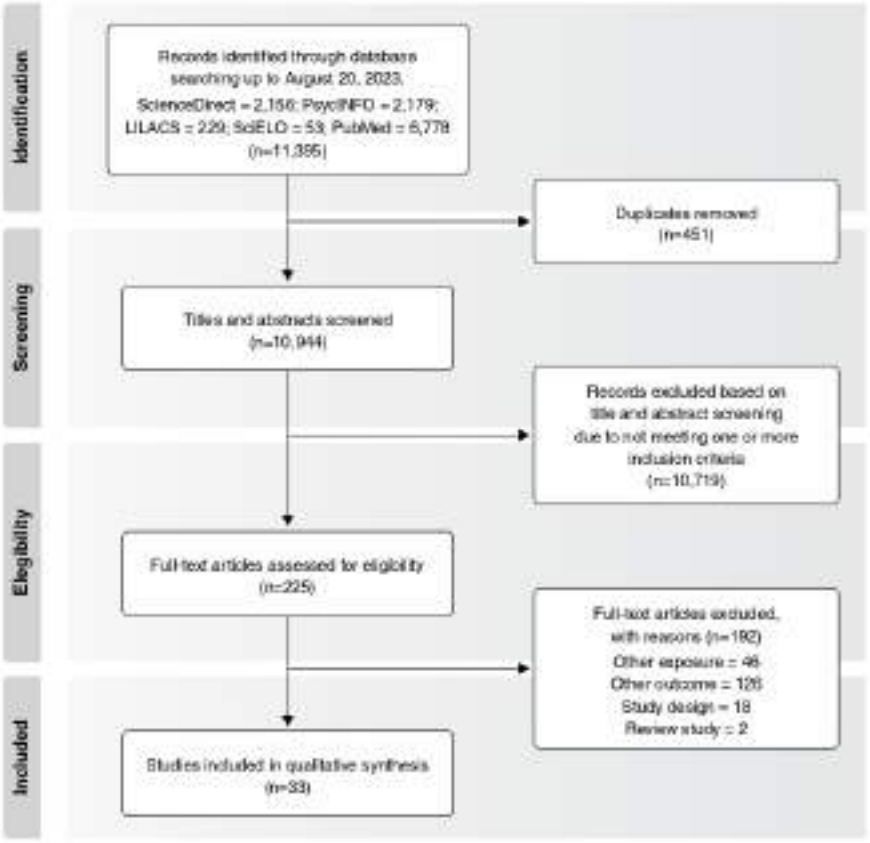

Figure 1 PRISMA flow diagram.[35]

Strength of Recommendations (GRADE) framework for systematic reviews.[71]

Results

Using the search criteria described above, 11,395 references were retrieved (2,156 from Science Direct, 2,179 from PsycINFO, 229 from LILACS, 53 from SciELO, and 6,778 from PubMed), of which 451 duplicates were removed. After evaluation of titles and abstracts, 10,719 records were discarded. We retrieved and analyzed a sample of 226 articles for full-text reading and rejected 192. Thus, 33 articles were ultimately included in this review (Figure 1). Assessment of study quality was carried out by two authors (JSR and ABB), with high interobserver agreement (k > 90%). Disagreements were resolved by a third author (AM).

The main characteristics of the study populations included in our review are shown in Table 1. All studies were published between 2010 and 2022. Sample sizes ranged from 57 to 6,979 participants. Most studies were conducted in the general population, with exception of Comas et al.,[37] Hughes et al.,[38] and Rhoades et al.[39] which used cohorts from low-income communities, and Priel et al.,[40] whose cohort that included only low-risk families, excluding cases of poverty, single parenthood, preterm birth, or teenage motherhood. Notably, with the exception of Lagasse et al.,[41] the samples under examination primarily consisted of mothers living with partners; the mean (SD) age was 30.84 (5.18) years. Only nine studies described inclusion and/or exclusion criteria.[37-39,42-47]

The study populations were geographically distributed as follows: 21 studies were conducted in North America, seven in Europe, two in Africa, two in Asia, and one in Oceania, as illustrated in the Supplementary Figure S1.

Five studies incorporated variables related to the child's father, grandmother, and teacher. For instance, two studies included paternal educational level and age as covariates.[48,49] Another study evaluated the mother's history of cumulative risk as a covariate, operationalized as the grandmother's experience of adversities during her own motherhood.[50] Berthelsen et al.[51] considered teachers' reporting on children's effortful control and self-regulation and used these variables as a level of the

hierarchical model. Comas et al.[37] considered teachers' reporting on attentional regulation and approaches to learning as mediators of the association between ecological risk factors and executive functioning.

Detecting and reporting maternal depression symptoms

Of the 33 studies examined, 32 used screening tools to detect maternal depressive symptoms (Table 2[37-61,64-69]). Screening tools are very useful, despite not providing clinical diagnoses. The Edinburgh Postpartum Depression Scale (EPDS), for instance, is a specific tool adopted by most authors to detect maternal depressive symptoms in the prenatal and/or postpartum period. In addition, general depression screening tools were used, such as the six-question short form Kessler Psychological Distress Scale (K6), the Beck Depression Inventory 13 (BDI), the Center for Epidemiological Studies Depression (CES-D) scale, the Hamilton Rating Scale for Depression (HAM-D), the Brief Symptom Inventory 18 (BSI), the General Health Questionnaire 36 (GHQ), and the Hopkins Symptom Check List-25 (HSCL-25).

Three studies constructed trajectories of maternal depression.[46,47,52] Oh et al.[46] employed latent profile analysis (LPA) to identify three distinct classes: no symptoms (scores under 10 points), mild symptoms (scores ranging from 11 to 13 points), and moderate symptoms (scores falling between 15 and 19 points). Rinne et al.[47] used latent curve growth analysis with standardized depressive symptoms at four time-points. Vänskä et al.[52] used factor mixture modeling and identified five trajectory classes: stable low symptoms, prenatal problems (psychological distress mainly during pregnancy), early postpartum problems (psychological distress mainly 2 months after birth), late postpartum problems (psychological distress mainly 12 months after birth), and heterogeneous high problems (higher rates of psychological distress from pregnancy to 12 months after birth).

Assessing and reporting executive functions

Studies included in the present review described two approaches to EF assessment: performance-based and/or reporting (Supplementary Figure S2). Performance-based measures are used to assess components of EF through a child's performance on either tests or tasks; measurements of EF through reporting are based on parents' or teachers' reports about children's skills and/or behaviors regarding EF. Of the 33 studies, 26 relied on performance-based measurements to assess EFs.

EFs were evaluated from ages 1 to 18. Eight studies conducted assessments at multiple time points, with five studies at two time points, three studies at three time points, and one study at four time points. In 29 studies, EFs were assessed between the ages of 3 and 11 (Supplementary Figure S3).

Seven studies measured EFs through maternal and/or paternal and teacher reporting. Thirty-one studies relied solely on the mother's report. However, Vänskä et al.[52] considered both mothers' and fathers' reports. The father's observations were statistically correlated with maternal observations in the EF subdomain of planning and organizing (r range: 0.52-0.71, $p < 0.01$). In this study, combined mental health status of both parents significantly predicted children's EFs, rather than the mental health of either the mother or father alone (β = 0.15, $p < 0.05$). In Faleschini et al.,[43] teachers' reports were considered a primary outcome of EFs, although mothers' reporting was assessed too.

Among the 33 studies included in this review, three different ways of reporting EF outcomes were observed: nine studies reported domain-specific outcomes (e.g., inhibition control, working memory, planning, attention-related EFs, and cognitive flexibility); 23 reported total scores including multiple domains; and 14 studies presented the results according to the task assessed during the interview. Sixteen studies used more than one method to report their outcomes.

Association between maternal depression and executive functions

The negative association between exposure to maternal depressive symptoms and children's EFs was consistent in 26 studies, suggesting that children whose mothers had higher levels of maternal depressive symptoms had poorer EF than children of mothers who had either no symptoms or only mild symptoms.

In assessing the association between maternal depression symptoms and children's EFs, control for a wide range of confounding variables was reported. Most notably, these variables included family socioeconomic status, maternal intelligence quotient (IQ), child age, sex, birth weight, gestational age, and maternal education.

Two studies assessed maternal depressive symptoms only during pregnancy. El Marroun et al.[53] found an association between maternal depressive symptoms in the second trimester and attention shift problems (β = 0.33, 95%CI 0.60 to 1.58) and emotional control problems (β = 0.26, 95%CI 0.41 to 1.45) at 4 and 7 years of age. In contrast, Hermansen et al.[48] compared children from mothers with depressive symptoms versus children from mothers without depressive symptoms during pregnancy and found no differences on attention-related ($F = 0.60$, $p = 0.55$) and inhibitory control ($F = 0.11$, $p = 0.90$) EF domains at 5 years of age.

Fourteen studies examined maternal depressive symptoms both during pregnancy and postpartum. Impaired EFs in children were associated with both exposures in six studies.[43,45-47,52,54] A negative effect of exposure to maternal depressive symptoms only in the prenatal period on children's EFs was observed in five studies,[42,55-58] while one study found an effect only with postpartum exposure.[59] Two studies found no association between prenatal or postpartum exposure to maternal depressive symptoms and children's EFs.[60,61]

The effects of postpartum maternal depressive symptoms exposure were examined in seventeen studies. Twelve studies observed a negative impact of exposure to maternal depressive symptoms during early and late

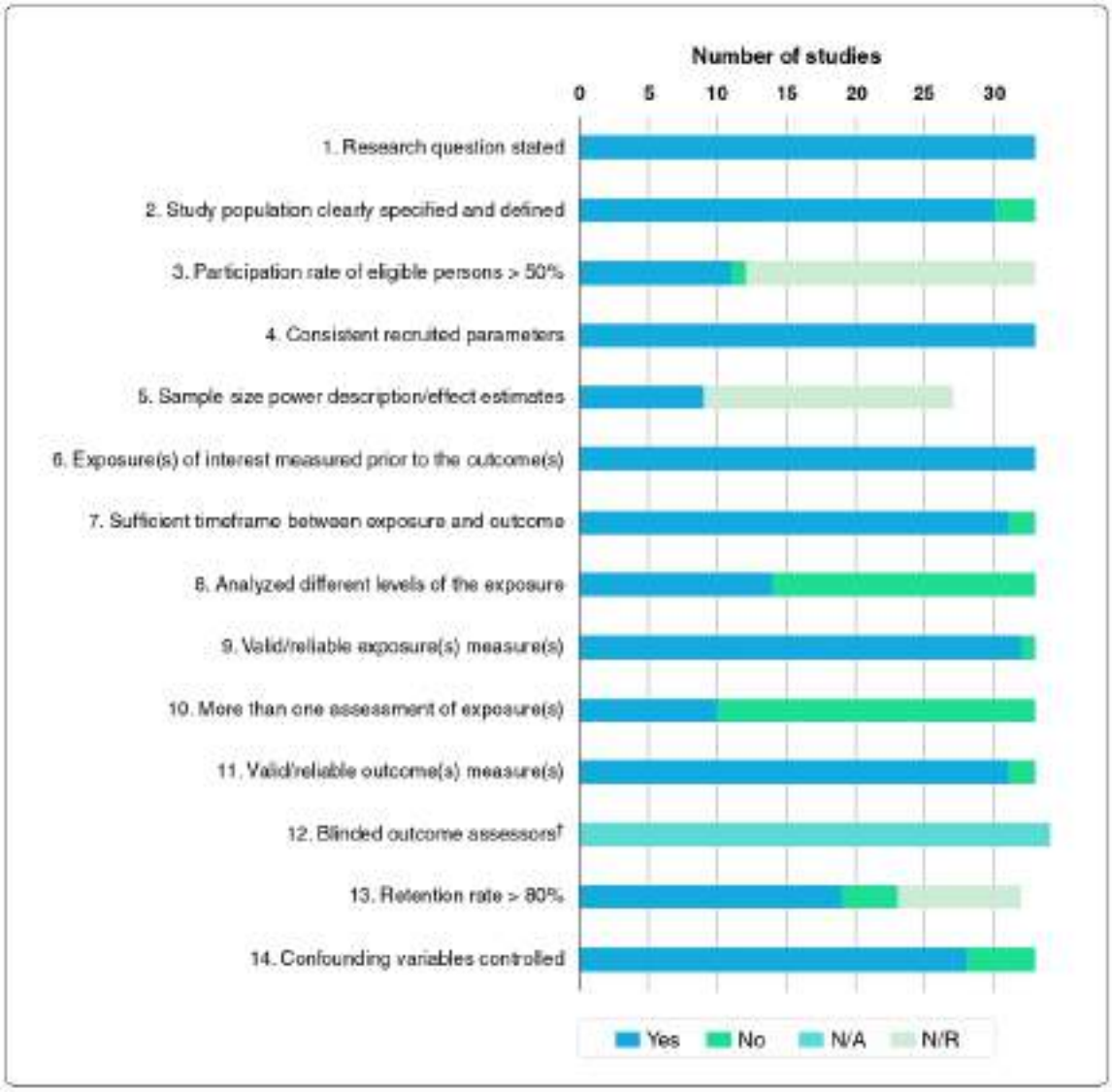

Figure 2 Risk of bias reported through the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies checklist (n=33 studies). N/A = not applicable; N/R = not reported.

childhood on children's EFs, while five studies found no association.[39,59,61,62,63]

Reporting quality

The number of studies that met each of the criteria established by the NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies[70] is shown on Figure 2. The overall quality rating for each of the included studies is summarized in Supplementary Table S3. According to the three-category scale of quality of reporting (good, fair, and poor), nine studies were classified as good, 21 as fair, and two as poor. There was complete agreement between the two independent assessors regarding these evaluations.

All 33 studies included in this review had a prospective design. Most authors stated characteristics of maternal depressive symptoms and EFs, such as their definitions, methods of measurement, and time points of assessment. However, in 20 of the 33 studies, the participation rate was below 50%, and 19 studies had a retention rate below 80%. In addition, most studies did not include a justification for sample size or description of statistical power.

Overall, the included studies yielded evidence of fair quality. Selection and/or reporting bias were identified in 18 of 33 studies (Supplementary Table S3). Different levels of maternal depressive symptoms were poorly investigated among studies. Most analyzed maternal depressive symptoms as a dichotomous variable, while

a few examined trajectories of maternal depression and/or considered categories of different levels of exposure.

Grading the evidence

All 33 studies included in this systematic review were assessed according to the GRADE criteria for narrative evidence.[71] Risk of bias was mainly due to attrition and selection bias (Supplementary Table S4). However, in most studies, both exposed and unexposed participants were from the same population and had the same risk of developing EF problems. Inconsistency and indirectness of results were not severe, although some variability between studies was noted. In general, results were not imprecise, but this aspect must be interpreted with caution because of the lack of sample size descriptions in most studies.

Discussion

Systematic review

This systematic review analyzed 33 cohort studies that examined maternal depressive symptoms during pregnancy and the postpartum phase, as well as their combined occurrence in both periods. The negative association between exposure to depressive symptoms before and after childbirth and children's executive functioning in early, mid, and late childhood – and, in some cases, adolescence – was consistent in 25 studies, even after accounting for the large variability in geographic populations. In addition, some insights were gained into possible mechanisms related to prenatal and postpartum exposures, including evidence of fetal programming, genetics, and parenting practices.

Exposure to prenatal depressive symptoms has been associated with alterations in early brain development that may impair executive functioning in childhood and adolescence, as has been observed in many studies included in this review.[43,45-47,52,54,57,58,60] This may be related to the fetal programming hypothesis that occurs during embryonic and fetal development, a critical period for neurodevelopment. Several biological systems have been hypothesized as mechanisms by which maternal depression and fetal programming influence child development.[73] The hypothesis put forth by Sohr-Preston and Scaramella[74] suggests that prenatal depression is related to alterations in the development and regulation of the hypothalamic-pituitary-adrenal (HPA) axis, which is a central component of the hormonal stress response system.[75] The HPA axis is responsible for the release of glucocorticoids, including cortisol, which warn the organism of potential threats and maintain homeostasis.[76] Disorders of the HPA axis can affect placental function, cross the placenta, and reach the fetus.[77] Therefore, maternal prenatal depression may affect the development of the HPA circuit and the brain development of offspring, as well as later risk for mental illness.[78,79] These changes may lead to altered cortisol patterns later in infancy, which has been associated with problems in EFs and behavioral changes.[58] The mediating role of cortisol reactivity on the association between prenatal depressive symptoms and EFs was reported by Neuenschwander et al.[58] Cortisol reactivity mediated the effect of prenatal maternal depression on lower EFs for boys, suggesting that there are probably different mechanisms underlying the effects of exposure to depressed/anxious prenatal maternal mood symptoms on EFs for girls.

An interesting finding from the study by Weikum et al.[54] is the significant role played by the gene *SLC6A4* in inhibition, working memory, and cognitive flexibility in children exposed to maternal depressive symptoms. This gene encodes the serotonin transporter (5-HTT), which is central to the regulation of synaptic serotonin levels and behavior, and has been observed to be a risk factor in studies of EF impairment.[80,81] Weikum et al.[54] have expanded the knowledge of the role of this gene by showing that children who have a long allele of *SLC6A4* are less resilient when exposed to maternal depressive symptoms; they performed better in EFs when not exposed to maternal major depressive symptoms and worse when exposed to them than all other groups. In the presence of a mother with more depressed mood, EFs were best preserved in children with at least one short *SLC6A4* allele.

The examined studies have contributed valuable insights into the complex relationship between postpartum depressive symptoms and children's EF impairments, employing path analysis to uncover underlying mediators.[40,44,50,64,65] The mechanisms were mainly related to parenting practices. The first year of life, when maternal depression was measured in most of the studies included in this review, is a critical period for neurodevelopment, characterized by robust gray matter growth, rapid myelination, and maturation of white matter pathway microstructure in the child's cerebral cortex.[82] During childhood and adolescence, there is a dramatic increase in brain plasticity – as a result of the dynamics between the dopaminergic and GABAergic systems – and consequent facilitation of the development and consolidation of higher-order neural networks, including those related to EFs.[83,84] These processes could be influenced by the mother-child relationship, primarily due to stimulation of the child's cognitive abilities during infancy.[44] The parenting practices of mothers with postpartum depressive symptoms are impaired, including by increased interpersonal stress and a lack of maternal sensitivity, warmth, and regulatory behaviors.[40,45,64-66] Ku et al.[64] found an interesting mediating effect of maternal sensitivity (the mother's ability to perceive and appropriately respond to her child's emotional and physical needs), suggesting that mothers with lower maternal depression symptoms are more likely to accurately detect their child's signals and respond to their child in a warm, prompt, and appropriate manner, which in turn predicts better EF. Negative parenting practices reduce cognitive stimulation in the environment and impair children's abilities to regulate attention, emotions, and stress,[84,85] which undermines the development of EFs.[32]

The negative impact of maternal depression on offspring EFs is not restricted to clinical cases of depression. Exposure to depressive symptoms can be understood as

a continuum capable of negatively influencing the neurodevelopment throughout childhood and adolescence.[89] A strategy adopted by some authors to assess the chronicity/persistence of the effects of maternal depression over time was to work with trajectories of depressive symptomatology. These studies revealed that EFs were most impacted during childhood among those children whose mothers either had increasing depression symptoms in early and mid-childhood or had chronic and severe trajectories of maternal depression.[48,54] This finding converges with results from previous studies that analyzed the impact of this exposure on offspring outcomes, such as intelligence and internalizing and externalizing behaviors.[11,87,88] This review has found that few studies employ this approach, highlighting a gap in the existing literature. Examining the trajectory of maternal depression symptoms provides more information and insight into their duration, intensity, and variability over time. Furthermore, when studies encompassed both prenatal and postpartum periods, contradictory results emerged. Specifically, five of the reviewed studies exclusively found a negative impact of prenatal exposure, while one study emphasized an exclusive postnatal influence. Interestingly, all of these studies employed multiple linear regression models to assess these associations.

The sensitive period for the typical development of EFs occurs from 3 to 5 years of age, followed by two other developmental peaks during the adolescence and early adulthood.[20,89,90] In this systematic review, the time at which EFs were measured varied considerably, ranging from 3 to 11 years in most of the studies. Thus, the impact of maternal depression between different sensitive periods could not be compared. Future investigation on sensitive periods for the development of EFs is necessary.

A great diversity of instruments used to measure EFs was identified, largely divided between instruments based on direct observation of individual performance and instruments based on third-party reports (mainly maternal). The first approach was most popular among the studies in our sample, and is more robust regarding psychometric parameters and environmental control.[91] On the other hand, measures based on third-party reports enable assessment of EFs in a more naturalistic context, including aspects of everyday life.[92,93]

Studies relying on maternal reports are susceptible to information bias, as mothers exhibiting symptoms of depression may perceive their children's behavior and development differently.[94,95] Notably, two studies, conducted by Vánská et al.[52] and Faleschini et al.,[43] compared maternal reports with those of fathers and teachers, respectively. Surprisingly, contrary to expectations based on previous research, no significant differences were found between mothers' and fathers' or between mothers' and teachers' reports. While the results did not reveal significant disparities in EF reports between mothers and fathers, it is worth noting that we did anticipate the possibility of bias, especially when mothers were experiencing depression. Additionally, both studies focused on more socioeconomically advantaged populations. Differences related to socioeconomic status could occur.

Studies that have found no association between maternal depressive symptoms and children's EF may be explained by several reasons. First, none of these have accounted for examination of the severity of maternal depression. Second, selection bias can be present in studies in which mothers with higher socioeconomic status are overrepresented.[50,51,65] In addition, shorter measurement periods between exposure and outcome may not capture the full effects.[62] Finally, limited sample sizes could also make studies underpowered to detect associations.[41]

Achieving a theoretical definition of EFs that is consensual among researchers in the field is challenging, as new theories and concepts have emerged over the past 20 years with the advancement of neuroimaging techniques.[17,96-101] For example, some studies considered attentional outcomes to be part of EFs,[41,43,46-48,50,62,68] while others understood EFs and attention as two different outcomes.[39,53,56-58,69,88] These divergences were reflected in our comparisons across studies, and is consistent with previous research.[34,102] Considering the marked heterogeneity of EF definitions used in the literature, the establishment of a common concept is needed, although this may not be an easy task because the exact neural basis involved in this theoretical construct is still unknown.

Limitations of the studies included in the review

The results of this systematic review should be interpreted with caution due to the limitations identified in the included studies. Most were classified as having fair quality, with only nine studies[39-41,44-46,55,58,64] classified as having good quality. Lack of information regarding sample power, losses to follow-up, and severity of maternal depression were the most frequent problems identified. In addition, many studies were affected by selection bias, which limited the generalization of results.

Limitations of the systematic review

The heterogeneity of the studies precluded meta-analysis. Different instruments were employed to assess maternal depressive symptoms and evaluate EF. The assessment of EFs was conducted either through maternal reports or through objective measures. Given the methodological limitations identified by the GRADE assessment and the variability of study quality detected by the NHLBI checklist, we considered that a meta-analysis would have been an inappropriate summary. A previous systematic review pooled the effect of correlation coefficients between maternal depression and EFs and found considerable heterogeneity (I^2 = 50%, p = 0.01) and a small observed effect size (r = 0.07; 95%CI 0.03 to 0.10).[34]

Application of the search query resulted in many articles that were ultimately not relevant to the study objective. This could be due to the broad search equation constructed, as different terms are currently used to refer to EFs.

Implications and future directions

This comprehensive review, based on multiple cohort studies, provides compelling evidence that both prenatal and postpartum exposure to maternal depressive symptoms can impair executive functioning in offspring, extending the knowledge of previous studies that focused only on one time period.[103,104] Additionally, this study goes further by providing a thorough examination of the mechanisms behind the relationship between exposure to maternal depressive symptoms and EFs, filling important gaps in the current literature and further advancing the understanding of the issue, as highlighted by Power et al.[34] These findings underscore the need to address maternal mental health during pregnancy and the postpartum period.

Future research should examine in greater detail the interplay of neural, environmental, and social factors in the relationship between maternal depression and the development of EFs in children. Two particularly important aspects require further investigation: the effects of chronic exposure to maternal depressive symptoms in childhood on the development of EFs and the specific effects of maternal depressive symptoms on the development of EFs during sensitive periods. Another important aspect that should be considered in future studies is the role played by pregnancy planning and a strong support network. These aspects can have a significant impact on maternal mental health, particularly in the context of maternal depression.[105,106] A support network that includes partners, family, friends, and medical professionals plays a key role in providing emotional and practical assistance to mothers. These support systems offer a safety net for mothers and reduce the isolation that can contribute to maternal depression.

In conclusion, this systematic review found that exposure to maternal depressive symptoms during and after pregnancy has a negative impact on children's EFs throughout their development. Although this finding was consistent across cohorts, methodological variability was identified among the included studies. Our findings are in line with previous research on other aspects of cognitive development and indicate that the serious effects of maternal depression on child development warrant attention. Future research is needed to further investigate the mechanisms involved in this relationship and the possibility that specific sensitive periods may have a greater impact on development.

Acknowledgements

JSR is supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP; grant no. 2020/13425-3; 2023/05522-9). AM received a postdoctoral fellowship from the Fundación Carolina and Grupo Tordesillas (Convocatória C. 2021, Programa de Movilidad de Profesorado de Universidades del Grupo Tordesillas).

Disclosure

The authors report no conflicts of interest.

Author contributions

JSR: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft.
MPV: Formal analysis, Investigation, Methodology, Project administration, Writing – original draft.
LRT: Conceptualization, Investigation, Methodology, Writing – review & editing.
ABB: Conceptualization, Formal analysis, Investigation, Writing – original draft.
AM: Conceptualization, Formal analysis, Investigation, Project administration, Supervision, Writing – review & editing.
All authors have read and approved of the final version to be published.

Handling Editor: Karen Jansen

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http://doi.org/10.47626/1516-4446-2023-3387

Supplementary Table S1 Search strategy

Database	Results	Search query
MEDLINE (via PubMed)	6,778	(Maternal depression OR Maternal depression trajectories OR Trajectories, maternal depression OR Maternal depression trajectory OR Trajectory, maternal depression OR Depression symptomatology OR Symptomatology, maternal depression OR Perinatal depression OR Postpartum depression OR Depression pregnancy OR Depression pregnancy OR Executive function risk factors OR Risk factors, executive functions) AND (Executive functions OR Executive function OR Working memory OR Inhibitory control OR Cognitive control OR Executive function attention-related OR Attention-related, executive function OR Cognitive flexibility OR Self-regulation OR Cognitive function OR Cognitive functions OR Cognitive development) *Filters applied: Full text, Humans, Exclude preprints.*
Science Direct	2,156	Maternal Depression AND Executive function *Filter: research articles*
PsycINFO	2,179	Any Field: maternal depression OR Any Field: maternal behavior OR Any Field: perinatal depression OR Any Field: postpartum depression AND Any Field: inhibitory control AND Any Field: cognitive control AND Any Field: attention AND Any Field: cognitive flexibility AND Any Field: self-regulation AND Any Field: executive function AND Any Field: working memory AND Any Field: child development AND Any Field: adolescent development AND *Publication Type: Peer Reviewed Journal AND Population Group: Human AND Methodology: Prospective Study*
LILACS	229	((maternal depression) OR (postpartum depression)) AND ((executive functions) OR (executive function) OR (working memory) OR (inhibitory control) OR (self-control) OR (attention) OR (adolescent behavior) OR (child development) OR (adolescent development))
SciELO	53	((maternal depression) OR (postpartum depression) OR (perinatal depression) OR (depression pregnancy) OR (executive function risk factors)) AND ((executive function) OR (cognitive function) OR (working memory) OR (inhibitory control) OR (cognitive control) OR (attention) OR (cognitive development))

Supplementary Table S2 Statistical analyses, main outcomes, and limitations of studies included in the systematic review

		Maternal depression and EF	
Authors	**Data analysis**	**Main findings**	**Main limitations reported by authors**
Poehlmann[49]	Bivariate correlations between continuous variables were calculated and reported. A series of SEM were constructed to assess whether EC skills at 24- or 36-months postnatally were associated with attention problems, ADHD symptoms, cognitive skills, and internalizing or externalizing behavior problems at 36 months. Maternal depression was included as a covariate. Covariates (all SEM models): neonatal health risks, infant gender, family socioeconomic status risks, maternal depression, maternal interaction (anger)	Correlations between maternal depression symptoms and EC at ages 2 and 3 were reported, respectively: r = -0.17, p < 0.05; r = 0.51, p < 0.01. Also, descriptive measures of maternal depression and EC at ages 2 and 3 were reported, respectively: M(SD) = 0.77(0.99), range [0-4]; M(SD) = -0.03(0.47), range [-1.07-1.41]; M(SD) = -0.01(0.56), range [-1.21-2.08]. Results of SEM models revealed that maternal depression was not linked with children's EC skills at 24 months (β[SE] = -0.00[0.03], p > 0.10).	1) Families that remained in the study were more socioeconomically advantaged than those who dropped out of the study or could not be located. 2) Results cannot be generalized to full-terms infants because findings were based on infants born preterm, their results are not generalizable to full-term infants. 3) Several measures relied on maternal report, and thus, shared method variance may have led to spurious positive findings. 4) Children's diagnoses of ADHD were not investigated, but instead relied on maternal report of children's symptoms.
Buss[57]	Hierarchical linear regression analyses were performed to assess the association between average pregnancy anxiety and depression and child EF. HLM growth curve analyses were performed to test whether the trajectory of change in maternal prenatal psychosocial state over the course of gestation as well as levels at specific time points during gestation were associated with children's EFs. Covariates: Hispanic ethnicity, number of obstetric risk factors, concurrent child age at assessment, maternal WAIS PRI scores	Higher maternal prenatal depression scores were associated with lower performance on the sequential memory task (β = -0.42, p = 0.01; F(8.78) = 3.7, p = 0.001). The non-significant interaction between prenatal maternal depression and child sex (β = 0.27, p = 0.51) revealed that this effect occurs both with boys and girls. When mean pregnancy-specific anxiety, mean state anxiety, and mean depression scores were entered stepwise on level 2, maternal prenatal depression did not contribute to the prediction of cognitive performance in this multivariate model.	Data on parent-child interactions were not assessed.
Rhoades[58]	Authors performed a LCA to identify and describe family ecological risk profiles. Information from the LCA model was used to assign children to risk profiles (including maternal depression symptoms, described as maternal mood problems), and the mean differences in EF scores were examined across these risk profiles. Partial eta squared was calculated to determine the effect sizes for the impact of risk profiles on EFs. Mediators: parent-child interactions, language skills	Results of LCA revealed no association between MDS and child EFs (β = -0.004, SE = .0.013, p > 0.05).	There was possible underpowering of the mediation analyses in this study due to the sample size. However, the authors reran the original models using the bootstrapping approach and found nearly identical results.
Weikum[54]	GEE modeling was used to examine moderation effects on the association SRI exposed and non-exposed children and Hearts and Flower task. GEE moderator: genotype (LL and at least one S allele) Covariates: maternal mood, child's age at test day	Results of GEE showed that accuracy on EF task was inversely related to the level of MDS (B = 0.099; 95%CI 0.035 to 0.163), and an interaction effect indicating that this was particularly true for children with the LL variant (B = -0.092; 95%CI -0.171 to -0.014).	It was not possible to infer that prenatal SRI exposure and genetic variations did indeed alter 5-HT function, because there was no direct measurement of changes in 5-HT signaling in utero and at age 6.
Hughes[38]	Bivariate correlations between continuous variables were calculated and reported. LGM was	Results of bivariate correlation between: BDI at 2 years (r = -0.02[0.80], p > 0.05), at 3 years (r = 0.00[0.99], p >	1) Too few EF tasks were included to draw conclusions with confidence.

	used to examine the predictive relations between mother's DEP and children's EF latent factor. Confounders: across-time stability in variation in EF, mother's education, mother's positive control.	0.05), at 4 years (r = -0.09[0.30], p > 0.05), at 6 years (r = -0.03[0.75], p > 0.05) and Tower of London at 6 years; BDI at 2 years (r = 0.05[0.61], p > 0.05), at 3 years (r = 0.02[0.83], p > 0.05), at 4 years (r = -0.02[0.80], p > 0.05), at 6 years (r = -0.07[0.42], p > 0.05), and Day-Night task at 6 years (r = 0.50[0.61], p < 0.05); BDI at 2 years (r = -0.23, p < 0.05), at 3 years (r = -0.16[0.08], p > 0.05), at 4 years (r = -0.26, p > 0.05), at 6 years (r = -0.18[0.05], p > 0.05), and Beads working memory at 6 years. Results of LGM revealed that the regression coefficient between the intercept of mothers' DEP and the EF latent factor was significant (95%CIs -0.049 to -0.05), indicating that lower average levels of mothers' DEP predicted better child EF 4 years later. Similarly, the regression coefficient between the slope and the EF latent factor was marginally significant (95%CIs -0.53 to 0.01), indicating that children whose mothers' DEP reduced more rapidly across time-points had higher EF scores at age 6. After adjustment for confounders, the intercept of mothers' DEP and the EF latent factor at age 6 remained significant.	2) Interactions with fathers were not assessed. 3)The analyses did not address potential mediating mechanisms, as mothers' DEP was unrelated to observational ratings of positive control, precluding any analysis of mediation effects.
Jensen[45]	Bivariate correlations between continuous variables were calculated and reported. Path models were constructed to evaluate direct and indirect links between maternal depression and EFs. One indirect pathway examined a bidirectional inter-relation between maternal depression and interpersonal stress as predictors of EFs. Mediators: interpersonal stress.	Results of bivariate correlation between maternal depression symptoms at 8 months of pregnancy and attention (r = 0.012, p > 0.05) and inhibition (r = 0.013, p > 0.05) were reported. Also, maternal depression from 0 to 2 years and attention (r = 0.017, p > 0.05) and inhibition (r = 0.018, p > 0.05) were reported. Maternal depression from 2 to 4 years and attention (r = 0.026, p < 0.05) and inhibition (r = 0.027, p < 0.05) were significantly correlated. Direct links showed that maternal depression negatively impacted children's attention and inhibition skills (standardized effect not reported). Indirect links showed a bidirectional relationship between maternal depression and interpersonal stress where maternal depression on pregnancy increased interpersonal stress (β = 0.175, p < 0.05), which, in turn, increased maternal depression at 2-4 years (β = 0.396, p < 0.05), which then impacted child performance on attention (β = 0.028, p < 0.05) and inhibition (β = 0.026, p < 0.05). Authors reported that risks that were distal to the child's social environment (i.e., contextual risks) can work to maintain risks that are more proximal to the child's social environment (i.e., maternal depression and interpersonal stress).	1) Measures of maternal depression, contextual risks, interpersonal stress, and the child's social cognitive skills were based on maternal reports, introducing the problem of shared methods variance. 2) Maternal reports on child social cognition may be affected by information bias. 3) The risk measures were collected at least 4 years prior to the cognitive assessments at age 8; therefore, unmeasured factors more proximal to the assessments may have influenced the cognitive outcomes. 4) The present study is correlational in nature and the indirect pathways should not be considered causative. 5) Fifth, attrition bias on this study meant that mothers high in DEP with co-occurring contextual risk and interpersonal stress were more likely to have children who did not complete the cognitive assessments.
Comas[37]	Bivariate correlations between continuous variables were calculated and reported. Four multiple regression models were constructed to assess the association between maternal depression and EFs. Model I and III assessed moderation effects of EC, considering maternal	Results of bivariate correlations between MDS on early childhood and youth Trail Making Test (r = -0.08, p > 0.10), Tower Test (r = -0.20, p < 0.10), TEA Dual-task (r = -0.15, p > 0.10), and EF composite score (r = -0.20, p < 0.10) were reported. Besides, correlations between MDS on middle childhood and youth Trail Making Test (r	1) Reporting for child NA was made by mothers. Therefore, child NA and MDS were not completely independent constructs. 2) Results from this study may not be generalizable to all families, especially because this study is based on sample of adolescent mothers and their children,

	depression exposure at ages 3-5, and at ages 8-10, respectively; Model II and IV assessed moderation effects of NA, considering maternal depression exposure at ages 3-5, and at ages 8-10, respectively. Moderator: EC, NA. Model I and II covariates: maternal IQ, socioeconomic status, maternal age at birth. Model III and IV covariates: Model I additionally adjusted for maternal depressive symptomatology at ages 3-5.	= -0.25, p < 0.05), Tower Test (r = -0.05, p > 0.10), TEA Dual-task (r = 0.00, p > 0.10), and EF composite score (r = -0.12, p > 0.10) were reported. Means and SD were also reported on Youth Trail Making Test (M[SD] = 9.66 [2.65]), Tower Test (M[SD] = 8.43 [2.34]), TEA Dual-task (M[SD] = 9.79 [2.62]), and EF composite score (M[SD] = 0.00 [0.71]). Results of Model I showed that both maternal depressive symptomatology at ages 3 and 5 (β[SE] = -0.463 [0.234], p < 0.05) predicted child EC/self-regulation (β[SE] = 0.303 [0.124], p < 0.05). A significant temperament × early maternal depressive symptomatology interaction was found in predicting mean EF performance (β[SE] = -0.618 [0.409], p < 0.05). Higher levels of MDS in early childhood overrode any associations between child EC and EF, whereas temperament contributed more significantly to EF at low levels of early maternal depression. Moderation analysis revealed that among children with greater EC, there was a significant negative association between early maternal depressive symptomatology and EF performance (β = 1.07, p < 0.001). However, among children with lower EC, the association between early maternal depressive symptomatology and EF performance was not significant (β = -0.10, p > 0.05). Results of Model II showed that both maternal depressive symptomatology at ages 3 and 5 (β[SE] = -0.568 [0.250], p < 0.05) and high child NA (β[SE] = 0.093 [0.056], p < 0.10) predicted low and high EF performance respectively. Higher levels of MDS in early childhood overrode any associations between child NA and EF, whereas temperament contributed significantly to EF at low levels of early maternal depression. Results of moderation analysis indicated that among children with low NA, there was a significant association between early maternal depressive symptomatology and EF performance (β = -1.2, p < 0.001). However, among children with high NA, association between early maternal depressive symptomatology and EF performance was not significant (β = 0.10, p > 0.05). Results of Model III revealed that child EC predicted EF performance. A significant temperament x middle childhood maternal depressive symptomatology interaction was found in predicting mean EF performance (β = 0.773, p < 0.05). At low levels of middle childhood MDS, there were no differences in EF between children high and low in parent- and teacher-rated EC. At high levels of middle childhood MDS, however, children with higher EC had higher EF performance scores than children with lower EC. Moderation analysis revealed that among children with greater EC, there was a significant positive association between middle childhood maternal depressive	which provides for a unique context of increased risk for maladaptive maternal and child outcomes.

		symptomatology and EF performance (β = 0.54, p < 0.05). However, among children with lower EC, the association between middle childhood maternal depressive symptomatology and EF performance was not significant (β = -0.36, p > 0.05). Model IV did not reveal a significant temperament vs. middle childhood maternal depressive symptomatology interaction (β = 0.26, p > 0.05).	
Hackman[52]	Longitudinal growth curve model was computed using hierarchical linear models. Mediation analyses employed multilevel mediation. Control variables: gender, ethnicity, maternal performance on the PPVT, when the child was 36 months old, mother's husband or partner at home. Mediators: early childhood home enrichment composite score, maternal sensitivity composite score for infant and early childhood periods, stressful life events experienced by the family, birthweight, gestational age, postpartum depression, and parent stress in infancy.	Postpartum depression mean score was measured by CES-D scale and reported (M[SD] = 11.0[8.6]). Postpartum depression was not a significant mediator on the association between income-to-needs and working memory with either adjusted (estimate of the magnitude of the mediated effect [â^b] = 0.04, proportion mediated = 0.05) or unadjusted (estimate of the magnitude of the mediated effect = 0.22, proportion mediated = 0.01) mediators. Also, regarding mediation analysis of the effect of income-to-needs and maternal education on planning efficiency, postpartum depression did not appear as a significant mediator, whether adjusted (income-to-needs [â^b] = 0.06, proportion mediated = 0.08, maternal education [â^b] = 0.02, proportion mediated = 0.05) or unadjusted in multiple mediation models (income-to-needs [â^b] = 0.05, proportion mediated = 0.08, maternal education [â^b] = 0.02, proportion mediated = 0.05).	Authors did not state study limitations clearly.
Plamondon[56]	Bivariate correlations between continuous variables were calculated and reported. Multiple linear regressions were used to predict main outcomes (attention shifting, attention focusing and spatial working memory). Covariates: child sex, birth weight and gestational age.	Results of bivariate correlation between maternal depression symptoms at third trimester of pregnancy and attention orienting (r = -0.119, p > 0.10), attention focusing (r = 0.132, p > 0.10), attention shifting (r = 0.024, p > 0.10), and spatial working memory (r = -0.156, p > 0.10) were reported. Also, correlation between maternal depression symptoms at 6 months postnatal and attention orienting (r = -0.134, p > 0.10), attention focusing (r = 0.074, p > 0.10), attention shifting (r = 0.042, p>0.10), and spatial working memory (r = -0.073, p>0.10) were reported. MDS during pregnancy were associated with the worse performance on spatial working memory (β (SE) = -0.345(0.152), p < 0.05). MDS at 6 months postpartum were not associated with worse performance on spatial working memory (β (SE) = -0.062(0.131), p = 0.64).	1) Because this study is based only on correlational data, it is not possible to infer causality between prenatal stress and the child's cognitive outcomes. 2) Most of the information was provided by the mothers.
Hermansen[48]	One-way ANOVA was performed to compare scores from the three different groups: prenatal exposure to SSRI, medically untreated DEP, and CON. For significant associations, planned contrasts were performed between SSRI- and depression-exposed, as well as between either	Performance on the NEPSY-II tasks (visual attention and Statue) was similar across groups SSRI (visual attention M[SD] = 4.52[0.58], Statue M[SD] = 3.68[1.02]), DEP (visual attention M[SD] = 4.44[0.55], Statue M[SD] = 3.66[1.22]), and CON (visual attention M[SD] = 4.58[0.50], Statue M[SD] = 3.58[1.03]),	1) Women in this study were generally highly educated, with the majority having studied at the university level; nearly all were in a relationship with the child's father; and overall they had healthy pregnancies, with little exposure to medications, nicotine, and alcohol, all of which are variables

	exposure group and controls. Control variables: gestational age, birth weight, birth length, age at testing.	indicating no effects of pre-natal exposure to depression or SSRIs upon general cognition or inhibition. Regarding the Attention Network task, the between-group analysis revealed only marginal differences between the groups in terms of either measure (reaction time, accuracy, and inverse inefficiency score), none of which reached statistical significance.	contributing to a good developmental outcome. 2) There was no clinical evaluation of the mothers' depression, only self-reports. 3) It was not possible to investigate the impact of different medications, dosages, and timings of the exposure.
Yan[25] sample overlapped with Heckman[42]	Bivariate correlations between continuous variables were calculated and reported. Two SEM were constructed to test: 1) The mediation effect of EC and others variables in the relation of children's individual and environmental characteristics (temperament, intelligence, care quality, maternal sensitivity) to their resilience in the presence of mothers' DEP; 2) the moderation effect of EC and others variables in the relation of mothers' DEP and children's resilience either by moderating the negative impact of mothers' DEP or by affecting the outcome through additive main effects. Model adjustments: child gender, ethnicity, income-to-needs ratio, maternal education, marital status, data collection site. Model I mediators: self-assertion, mastery motivation, and EC. Model II moderators: self-assertion, mastery motivation, and EC.	Bivariate correlation between MDS and EC was calculated ($r = -0.28$, $p < 0.01$). In the first model, children's EC was the strongest and most consistent predictor of resilience across domains, including academics, social skills, and internalizing and externalizing behaviors, even in the presence of maternal depression. In the second model, no interaction was detected between maternal depression and EC, suggesting that children's resilience in the presence of a depressed mother is due to the combined effects of their EC and the mother's depression, rather than an interaction between the two.	1) Findings were based on a non-clinical population and may not be generalized to clinical populations. 2) Children's agentic system (self-assertion, EC, and mastery motivation) and resiliency outcomes were assessed at only one point in time. 3) Findings generated from a North American sample could not be generalized to samples in Eastern culture.
Lagasse[41]	Bivariate correlations between continuous variables were calculated and reported. SEM was used to examine associations between caregiving stress (composite score including MDS score averaged by three follow-ups) and executive functioning.	Correlations between caregiving stress (including MDS) at age 5 and executive functioning at different ages were reported: at age 5 ($r = 0.04$, $p > 0.05$); at age 9 ($r = -0.04$, $p > 0.05$); at 13 years ($r = -0.04$, $p > 0.05$). Caregiving stress at age 9 and executive functioning at ages 9 and 13 were correlated, respectively: $r = -0.04$, $p > 0.05$; $r = -0.10$, $p < 0.01$. Correlation between caregiving stress at age 13 and executive functioning at age 13 was also reported ($r = -0.11$, $p < 0.01$). Results of SEM showed that caregiving stress at age 5 predicted poorer executive functioning at age 9 ($\beta = -0.07$, $p < 0.05$), which in turn predicted poorer executive functioning at age 13 ($\beta = -0.07$, $p < 0.05$). Caregiving stress at age 9 predicted caregiving stress at age 13 ($\beta = 0.58$, $p < 0.001$), but not executive functioning at age 13 ($p > 0.05$).	1) Due to the non-interventional nature of the study, direction of effect could not be inferred. 2) Executive functioning tasks were different at each follow-up. 3) All children in the sample were at high risk because of prenatal substance exposure and poverty.
El Marroun[43]	Linear regression analysis was used to investigate the relation of exposure to prenatal SSRI use and MDS with EFs. Model I adjustment: maternal education, maternal cognitive ability, ethnicity, smoking habits, child's age, gender, birth weight.	Model I revealed that association between children exposed prenatal DEP without the use of SSRIs was significant ($\beta = 0.21$, $B = 3.28$, 95%CI 0.97 to 5.59, $p = 0.005$). Prenatal DEP, without the use of SSRIs, were associated with maternal reporting of attention shifting problems in their children ($\beta = 0.33$, $B = 1.09$, 95%CI	It was not possible to further split the groups by individual SSRI (sertraline, paroxetine, fluoxetine, or citalopram) due to the small number of SSRI-exposed children.

	Model II adjustment: Model I adjustment + the level of DEP during pregnancy.	0.60 to 1.58, p < 0.001) and emotional control problems (β = 0.28, B = 0.93, 95%CI 0.41 to 1.45, p < 0.001). However, prenatal DEP, without the use of SSRIs, were not associated with maternal reports of inhibition problems, working memory problems, and planning/organization. There was no difference when comparing children exposed to SSRIs to children exposed to maternal depression ($\beta_{total\ score}$ = 0.89, 95%CI -0.10 to 7.88, p = 0.80).	
Wang[65] (sample overlapped with Hackman[62])	Bivariate correlations between continuous variables were calculated and reported. SEM was performed to examine if mothers' DEP during the child's infancy predicted children's poor sustained attention and EF in first school year. A second SEM analysis was used to examine the mediation of mothers' low sensitivity in this association. A third SEM analysis was carried out to determine whether poor sustained attention and EF mediated the relationship between mothers' DEP during a child's infancy and children's adjustment problems in third school year. Mediators: mothers' low sensitivity.	Correlations were reported between mother's DEP in infancy and child's inhibition (r = -0.10, p < 0.01), working memory (r = -0.15, p < 0.01), and planning (r = -0.11, p < 0.01). Similarly, but at age 3 months, DEP was correlated with inhibition (r = -0.09, p < 0.05), working memory (r = -0.13, p < 0.01), and planning (r = -0.08, p < 0.05). At age 5 months, DEP was correlated with inhibition (r = -0.12, p < 0.01), working memory (r = -0.17, p < 0.01), and planning (r = -0.10, p < 0.01). In the child's first grade, DEP was correlated with inhibition (r = -0.08, p < 0.01), working memory (r = -0.11, p < 0.01), and planning (r = -0.08, p < 0.01). Finally, DEP in the 3rd school year was correlated with inhibition (r = -0.10, p < 0.01), working memory (r = -0.16, p < 0.01), and planning (r = -0.08, p < 0.01). Results supported the hypothesis that mothers' DEP during the child's infancy, regardless of later symptoms at 36 months old, 54 months old and first grade, predicted children's EF in first grade (standardized coefficient = -0.16, p < 0.05). Results of the second SEM analysis showed a significant indirect effect of mothers' low sensitivity on the association between MDS and EFs (βind = -0.25, p < 0.001). The third SEM analysis showed two significant indirect paths: 1) Mothers' DEP during a child's infancy predicted low maternal sensitivity at 36 months, which then predicted children's poor sustained attention at 54 months; this, in turn, predicted EF at school entry. Poor EF then predicted low cognitive and academic competence in third grade (β = -0.02, p < 0.05); 2) Mothers' DEP in infancy predicted children's poor EF at school entry; poor EF then predicted low cognitive and academic competence in 3rd school year (β = -0.09, p = 0.00).	1) The results may not be generalized to non Western or clinically depressed populations. 2) Results could reflect not *only* DEP during the child's infancy, but stable characteristics of mothers associated with the likelihood that they will develop these symptoms. 3) Conclusions about the timing and developmental linkage among the variables examined in this study cannot be determined definitively. 4) Important aspects of depression not examined could have contributed to these findings, for example, its chronicity, clinical relevance, or specific configuration of symptoms. 5) One component of EF, switching flexibly between tasks, is unavailable in the NICHD data.

Vänskä[52]	One-way ANCOVA was performed to examine early parental mental health as a predictor of child EFs. Parental mental health was classified in four trajectories (healthy parents, solely maternal problems, solely paternal problems, and both maternal and paternal problems), determined in a previous study. Covariate: child's gender.	Results of ANCOVA showed that parental mental health problems predicted poor children's EFs (F-statistics = 2.58, p < 0.05). Post-hoc tests with contrasts revealed that the joint parental additive model was the only statistical predictor of EFs (diff. = 0.15, p < 0.05). The joint parental additive model represents the group including both mothers and fathers that presented mental health problems.	1) Parents assessed the child's mental health and development, which makes the assessment susceptible to bias. 2) Attrition in the final assessment was substantial among both parents, but especially among fathers, which tempered the ability to interpret and generalize our findings. 3) Mothers in this sample were older than mothers in the larger population due to our exclusion criteria in the natural conceived sample as well as the fact that half the sample had a history of infertility and some mothers included in the reproduction treatment group had taken years to achieve pregnancy.
Berthelsen[31]	Bivariate correlations between continuous variables were calculated and reported. Path analyses were used to estimate the direct and indirect effects of hypothetically casual relationships among maternal mental health and EF. Model 1 was unadjusted and examined the direct effects of ecological risk variables (including maternal mental health) when children were 4-5 years on EF, at age 14-15 years. Model 2 was fully adjusted and included paths from each covariate to the outcome variable of EF. Model 3 was fully adjusted, and all direct and indirect paths were modeled simultaneously. Mediators: child attentional regulation (at age 4-5 years) and approaches to learning (at 6-7 years). Covariates: child gender, child age in months at 14-15 years, Aboriginal or Torres Strait Islander status, language other than English at home; and child' score of the PPVT at 4-5 years of age.	Correlations between maternal mental health and both attentional regulation (r = 0.13, p < 0.01) and executive functioning r = 0.04; p < 0.05) were calculated. There were no significant either direct or indirect pathways between maternal mental health and EF (β = -0.02, p > 0.05; β = 0.00, p > 0.05).	1) Lack of fine-grained measurement of self-regulatory behaviors such as inhibitory control and working memory. 2) The components of the model of EF used in this study were somewhat different from those assessed in many other child development studies that had a strong focus on inhibitory control, including using EC as a primary theoretical model.
Wade[30]	Bivariate correlations between continuous variables were calculated and reported. A linear relationship between CCR and executive functioning was calculated. Path analysis was used to examine CCR (single parenthood, teenage motherhood, low education, had clinical levels of maternal depression, experienced high levels of marital conflict) as a predictor of EFs. Mediators: parenting capacities (reflective capacity and cognitive sensitivity).	Correlation between CCR and executive functioning was reported (r = -0.13, p < 0.05). Means and SD of child's age at each follow-up were also reported: T1 (M = 2 months, SD = 0.16); T2 (M = 1.6 years, SD = 0.27); T3 (M = 3.15 years, SD = 0.27); T4 (M = 4.79, SD = 0.28). Results of linear regression analysis showed a significant negative linear trend between the number of risks and EF, F = 5.01 (df = 310), R^2 = 0.016, p = 0.026. Path analysis showed that there were two indirect paths (z): the first predicted EF via both parenting capacities, from CCR at T1 through reflective capacity at T2 and cognitive sensitivity at T3 (z = 2.07, p = 0.039); the second indirect effect operated from CCR at T1 through cognitive sensitivity at T3 but not reflective capacity at T2 (z = 2.06, p = 0.040). More specifically, on the first path, CCR at T1 predicted worse reflective capacity at T2 (β[SE] = 0.19[0.08], p = 0.014), which predicted	1) Data generalization was limited by the relatively low-risk sample, with more than three-quarters of mothers reporting one or zero psychosocial risks. 2) Sample attrition may have introduced some systematic bias. 3) The authors relied primarily on maternal reports, which can lead to information bias. 4) The cumulative adversity scores were based on the summation of six specific risks. Some of these risks were naturally dichotomous, whereas others were based on specified cut-points. 5) Fathers' reflective functioning or cognitive sensitivity was not measured.

		worse cognitive sensitivity at T3 (β[SE] = 0.29[0.06], p = 0.001) then, in turn, predicted poor EF at T4 (β[SE] = 0.27[0.06], p = 0.001). On the second path, and CCR at T1 predicted poor cognitive sensitivity at T3 (β[SE] = 0.14[0.06], p = 0.023), which in turn predicted worse EF at T4 (β[SE] = 0.27[0.06], p = 0.001). The total indirect effect from CCR at T1 to EF at T4 was significant (z = 2.21, p = 0.027).	
Neuenschwander[69]	Bivariate correlations between continuous variables were calculated and reported. Linear regression and mediation analysis were performed to examine the relation between maternal mood (depression and/or anxiety) and EF. Two mediation models were constructed through bootstrapping to examine indirect effects of each mediation variable. Adjustments (linear regression): child age and sex, concurrent maternal mood, and prenatal SSRI antidepressant exposure. Controlled variables (mediation models): concurrent maternal mood (at 6 years of children's age), prenatal SSRI exposure, time of the day of saliva assessment where required. Mediators: children's stress regulation (cortisol reactivity and diurnal cortisol levels).	Correlation between prenatal maternal mood on two different moments and child's EF were reported: at third trimester of pregnancy (r = -0.19, p = 0.052) and at age 6 (r = 0.07, p > 0.05). Results of linear regression showed that prenatal depressed and/or anxious maternal mood was a significant predictor of child EFs at 6 years (β = -0.639, p = 0.014) after adjustment. Also, it was observed that at lower levels of depressed and/or anxious prenatal maternal mood, the association between child's EFs and maternal mood was linear. However, when prenatal mood reached a certain level of severity, this relationship plateaued and increasing mood disturbances had no further impact on EFs. The relation between prenatal maternal mood and child EFs was not moderated by sex (β = -0.020, p = 0.819). However, in this model sex was marginally related to child EFs (β = -0.158, p = 0.059), indicating that boys had somewhat better EFs than girls. The first mediation model showed that the mediation role of stress reactivity was moderated by sex: depressed and/or anxious prenatal maternal mood was linked to heightened cortisol reactivity which, in turn, predicted poorer EFs for boys (B = -0.0053, 95%CI -0.0142 to -0.0004), but not for girls (B = 0, 95%CI -0.0021 to 0.0025). Cortisol level was neither an indirect effect for boys (B = -0.0022 [0.0034] 95%CI -0.0086 to 0.0047) nor for girls, (B = 0, 95%CI -0.0014 to 0.0020). Significant negative direct effects of prenatal depressed and/or anxious mood on child's EF were observed on the two models: diurnal cortisol model (B = -0.014, p = 0.008) and the cortisol reactivity mode (B = -0.011, p = 0.022). These effects were not moderated by child's sex.	1) Due to the non-interventional nature of the study, causal effects of prenatal maternal mood on child behavior could not be inferred. 2) The time between the measurement of the mediator (HPA axis activity) and outcome (EF performance) was not optimal, because variables were measured at the same time point. 3) Measurement of EFs and cortisol has limitations by itself. It is a reaction from subjective aspects and can differ among some children.
Nolvi[42]	Bivariate Spearman correlations between continuous variables were calculated and reported in the entire sample and in girls and boys separately.	Bivariate correlation between postnatal DEP and child's EF were reported: in girls only (r = -0.15, p > 0.10), in boys only (r = -0.08, p > 0.10), and in both girls and boys (r = -0.11, p > 0.10). These results revealed that EF in the whole sample was not significantly correlated with postnatal MDS. The authors did not include postnatal DEP on the additional analysis.	1) An attrition bias was observed with regard to 6-month questionnaire data, which was related to maternal education and postnatal stress. 2) Other infant interactions were not measured, which might be a potential mediator of family risk factors. 3) The finding of a prenatal stress by sex interaction in predicting infant EF was only statistically significant when excluding the discontinued experiments (fussing/inattentive infants), which

			necessitates caution in interpretation and generalization of this finding to other populations.
Rotheram-Fuller[40]	A mixed-effect linear regression model with REML was used to assess the prediction of each category of maternal depression (having depressed mood [EPDS > 13] at all assessments, antenatally only, postnatally only, or depressed at both antenatal and at least one postnatal assessment) and child's EFs. Adjustments: mother's HIV status, alcohol use, food insecurity, baseline education, children's age.	Most of the mothers in this population sample (58%) experienced depressed mood either while pregnant or at some point over the first 3 years of their child's life. Results of REML showed that executive functioning at 36 months did not show any significant differences overall across maternal depressed mood based on the Silly Sounds ($p = 0.77$) and Something's the Same tasks ($p = 0.62$), but there were significant differences overall on the operation span score ($F = 4.0$, $p = 0.01$). Children of postnatally depressed mothers scored lower on the Operation Span task compared with children of antenatally/postnatally non depressed mothers ($p < 0.01$; ES = 0.17. The authors did not report the estimated coefficient from linear regression model.	The EPDS is only a screening measure of depressed mood and does not provide a diagnosis of depression. Furthermore, the time span for which the symptoms are reported is limited, and it is not clear how well this measure may tap executive functioning among South African children at 3 years of age.
Feng[38]	A multiple linear regression analysis was conducted to identify association between any potential factors and poor performance in the preterm infant group. Control variables: children's cognitive and motor scores.	Maternal depression was not related to the EF deficits in preterm infants. The authors did not report linear regression coefficient despite assessing the relationship between maternal depression and EFs.	High-risk infants and extremely low birth weight infants were not included in the study. Hence, a comprehensive assessment of poor EF causes in preterm infants was not possible.
Gueron-Sela[44] (sample overlapped with Rhoades[39])	Bivariate correlations between continuous variables were calculated and reported. Direct associations between maternal depression symptoms and children's EF were made estimating a path model across each time point of MDS on EF outcomes. Next, to examine the mediating role of parent-child interactions, they estimated a partial ARCL. Mediators: harsh-intrusiveness at 24 and 36 months.	Results of bivariate correlations were reported between MDS at 6 months and EF at 36 months ($r = 0.00$, $p > 0.05$); MDS at 6 months and EF at 48 months ($r = -0.04$, $p > 0.05$); MDS at 15 months and EF at 36 months ($r = -0.04$, $p > 0.05$); MDS at 15 months and EF at 48 months ($r = -0.10$, $p < 0.05$); MDS at 24 months and EF at 36 months ($r = -0.09$, $p < 0.05$); MDS at 24 months and EF at 48 months ($r = -0.15$, $p > 0.05$). Results of path analysis showed no significant direct links between MDS at 15 ($\beta = -0.06$, $p = 0.07$) and 24 months ($\beta = -0.05$, $p = 0.19$) and EF at 48 months. However, an indirect effect was observed: MDS at 15 months was significantly linked to harsh-intrusiveness at 24 months, which was associated to harsh-intrusiveness at 36 months, and poor EF at 48 months ($\beta = -0.009$; $p = 0.01$).	1) Findings are correlational in nature and could not infer a causal link between MDS, mother-child interaction, and child EF. 2) The independent effect size between MDS, harsh-intrusiveness and EF was small, limiting the ability to draw extensive conclusions based on these findings. 3) The authors focused on one domain that underlies the link between MDS and children's EF, namely mother-child interactions, and studies identified additional pathways, including genetic factors, dysfunctional neuro-regulatory systems, and exposure to stressful life events that may also be relevant for understanding this link.
Baker[46]	Bivariate correlations between continuous variables were calculated and reported. Path analysis was performed to assess the direct and indirect effects of maternal depression on Head Start children's development. Path model adjustment: child age, gender, race/ethnicity, time spent in childcare, maternal education, single-parent status, and poverty status. Mediator: maternal parenting (maternal warmth).	Bivariate correlation between maternal depression and EFs was reported ($r = -0.06$, $p < 0.01$). Mean, SD, maximum and minimum scores on EFs (M[SD] = 11.63[5.04], range [0.00-16.00]) and maternal depression (M[SD] = 4.60[5.72], range [0.00-36.00]) were also reported. Among all mothers, 20% met the clinical criteria for mild depression, 9% for moderate depression, and 7% for severe depression. Results of path analysis showed no significant direct link between maternal depression and EFs ($b = -0.04$, $SE = 0.02$, $\beta = -0.07$, $p > 0.05$). However, MDS were associated with	1) Maternal depression and parenting were assessed via maternal reports. 2) Lack of information provided in the data set about fathers. 3) The study used a single objective measure of EF that could not address every single dimension of childhood EF.

		children's EF through maternal warmth (b = -0.0004, SE = 0.02, β = -0.005, p < 0.05). The full model explained 8% of the variance in children's EF.	
Hutchison[59]	Bivariate correlations between continuous variables were calculated and reported. Correlational analyses and two hierarchical regression models were constructed. Model 1: maternal education + maternal depression variables. Model 2: maternal education, BDI at three years + SSRI exposure.	Correlations between EPDS and BRIEF GEC T scores were reported at the second trimester of pregnancy (r = 0.19, p < 0.05), at the third trimester of pregnancy (r = 0.28, p < 0.01), at 3 months postpartum (r = 0.28, p < 0.001) and at 6 months postpartum (r = 0.24, p < 0.001). Maternal education was entered as a control variable in the first step of both Models 1 and 2, and explained 4% of the variance in EF of both models. Results of Model 1 showed that all MDS variables (HAM-D, EPDS, BDI from second semester of pregnancy to 6 years) predicted 14% of unique variance in EF. However, only BDI at the age 3 emerged as a significant univariate predictor (β = 0.28, p < 0.05). Results of Model 2 showed that BDI at the age 3 explained 10% of unique variance in EF, and emerged as a significant univariate predictor (β = 0.35, p < 0.001). Prenatal SSRI exposure predicted 1% of unique variance in EF at the age 6 and did not emerge as a significant univariate predictor (β = -0.17, p > 0.05). Summarizing, higher levels of MDS, especially at 3 years, were associated with poorer maternal reports of EF skills at 6 years. Associations between prenatal SSRI exposure and EF outcomes were not significant, even when controlling for maternal education and MDS at 3 years.	1) Use of HAM-D scores in the non-exposed group. 2) Mothers in the cohort were predominantly highly educated. 3) Maternal education is only one component of socioeconomic status. 4) BRIEF measure of child EF was completed by mothers; some may argue that mothers who are depressed may have a negativity bias towards rating their children, which may explain the associations between MDS and poorer EF.
Faleschini[43]	Multivariable regression models (Model 1 crude) were constructed to evaluate associations of period-specific (mid-pregnancy, 6 months postpartum, 12 months postpartum) exposure to high MDS (EPDS score ≥13) with cognitive and behavioral outcomes in mid-childhood. Model 2 adjustment: maternal race/ethnicity, age at enrollment, education, household income, pre-pregnancy body mass index, smoking during pregnancy, child's sex. Model 3 adjustment: Model II additionally adjusted for maternal IQ. Model 4 adjustment: Model III additionally adjusted for DEP at prior periods assessed.	Exposure to high MDS in mid-pregnancy was associated with poorer scores on behavioral EF based on the three BRIEF subscales, according to both teachers' reporting (BRIEF Global Executive Composite [β = 3.83 points 95%CI 1.32 to 6.35], BRIEF Behavior Regulation Index [β = 3.93 points 95%CI 1.41 to 6.45], BRIEF Metacognition Index [β = 3.26 points 95%CI 0.75 to 5.81), and mothers' reporting (BRIEF Global Executive Composite [β = 3.83 points 95%CI 1.32 to 6.35], BRIEF Behavior Regulation Index [β = 3.93 points 95%CI 1.41 to 6.45], BRIEF Metacognition Index [β = 3.26 points 95%CI 0.72 to 5.81]). After accounting for confounders and maternal IQ, the association was attenuated, although it remained significant on the BRIEF Behavior Regulation Index with 2.44 points based on teachers' reporting (95%CI 0.00 to 4.88). High MDS at 6 months postpartum was associated with higher scores (worse performance) on the BRIEF Global Executive Composite score (β = 2.78 points 95%CI 0.18 to 5.39) and on the BRIEF Metacognition Index, according to teachers' disclosure (β = 2.86 points 95%CI 0.21 to 5.50). After adjusting for confounders, the associations were greatly attenuated, especially after accounting for prenatal DEP.	1) The EPDS is an instrument used to assess DEP but is not equivalent to clinical diagnosis. 2) The authors did not measure maternal EF or behavior problems, which may be part of the confounding structure. 3) The authors cannot exclude that effects found on prenatal exposure could include influences from postnatal symptoms, but they chose not to control for postnatal symptoms in the statistical model as they could be part of the pathways. 4) Mothers' reports of child development may be biased, especially in the case of depressed mothers, so all results derived therefrom should be interpreted with caution.

		BRIEF Global Executive Composite (β = 0.62 points 95%CI -2.08 to 3.32), BRIEF Metacognition Index (β = 0.91 points 95%CI -1.83 to 3.65). Exposure to MDS at 12 months postpartum was associated with poorer behavioral EF on the three BRIEF subscales according to teachers' reporting in the unadjusted models: BRIEF Global Executive Composite (β = 4.39 points 95%CI 1.48 to 7.30]), BRIEF Behavior Regulation Index (β = 4.45 points 95%CI 1.49 to 7.42) with a mean of 4.22 points higher.	
Oh[46]	Authors identified maternal depression trajectories from pregnancy until 2 years after childbirth using LPA. ANOVA was performed comparing child EF by maternal depression trajectory group. A generalized linear mixed-effect model was used to estimate the effect of maternal depression trajectories on child EFs at ages 7, 8, and 9 years.	Three classes of maternal depression were identified: class 1, the "no symptom" group (42.23%); class 2, the "mild symptom" group (46.85%); and class 3, the "moderate symptom" group (10.92%). Among the EF scales evaluated in the 7th year, subscales of plan-organization difficulty (classes 1, 2, and 3, respectively: M[SD] = 16.39[4.15], M[SD] = 17.53[4.27], M[SD] = 18.83[4.66], ANOVA p < 0.001), behavioral regulation difficulty (classes 1, 2, and 3, respectively: M[SD] = 13.62[3.17], M[SD] = 14.38[3.60], M[SD] = 15.49[3.67], ANOVA p < 0.001), and emotional regulation difficulty (classes 1, 2, and 3, respectively: M[SD] = 10.49[2.87], M[SD] = 11.54[3.37], M[SD] = 12.76[3.42], ANOVA p < 0.001) had the highest scores in the "moderate symptom" group followed in order by "mild symptom" and "no symptom" groups. These significant differences between the groups were maintained in the 8th and 9th years of evaluations. The attention-concentration difficulty subscale showed significantly higher scores in classes 3 and 2 than in class 1 in the 7th year (classes 1, 2, and 3, respectively: M[SD] = 14.36[3.86], M[SD] = 15.26[4.32], M[SD] = 15.71[4.23], p < 0.001). These significant differences between the groups were maintained in the 8th and 9th years of evaluations. The mixed-effect model revealed that the overall group effect was significant, confirming a significant EF difference according to maternal depression trajectory with "no symptom" group as the reference: Plan-organization difficulty – "mild symptoms" group (β[SE] = 1.08[0.34], 95%CI 0.41 to 1.76, p = 0.002), "moderate symptoms" group (β[SE] = 2.40[0.56], 95%CI 1.31 to 3.49, p < 0.001); Behavioral regulation difficulties – "mild symptoms" group (β[SE] = 0.82[0.26], 95%CI 0.31 to 1.33, p = 0.002), "moderate symptoms" group (β[SE] = 2.07[0.41], 95%CI 1.20 to 2.84, p < 0.001); Emotional regulation difficulties – "mild symptoms" group, (β[SE] = 1.09[0.27] 95%CI 0.56 to 1.63, p < 0.001), "moderate symptoms" group (β[SE] = 2.28[0.44], 95%CI 1.42 to 3.14, p < 0.001); Inattention – "mild symptoms" group (β[SE] = 0.94[0.33], 95%CI 0.30 to 1.59, p = 0.004), "moderate symptoms" group (β[SE] = 1.18[0.53], 95%CI	1) Lack of investigation of the history of maternal depression before pregnancy. 2) Measurement of EF was performed using only a parental self-report questionnaire, rather than an objective test. 3) The authors did not control for environmental factors which may have occurred in the large time gap from early maternal depression to child outcome measurement.

		0.13 to 2.21, p = 0.027). The time effect was significant, except in cases of behavioral regulation difficulty scores, indicating that all EF subscales other than behavioral regulation significantly increased over time. Executive function exhibited a nonsignificant group × time interaction (p > 0.01).	
Priel[43]	A *t* test was performed to compare CANTAB mean scores between children of depressed and non-depressed mothers. The authors conducted a path analysis for a comprehensive model on the direct and mediated paths leading from maternal MDD to children's EF. Mediators: child disorder and maternal regulate behaviors.	*t*-test results showed no significant differences in EF between children of depressed and non-depressed mothers (t = 0.45, p > 0.05, Cohen's d = 0.08). Path analysis showed that maternal depression was linked with lower maternal regulatory behavior at the age 6, and maternal regulatory behavior was linked with greater EF skills (95%CI -0.181 to -0.016). Besides, maternal depression appeared linked with lower maternal regulatory behavior at the age of 9 months, which led to child psychiatric disorder, and those children had lower EF (95%CI -0.026 to -0.001). Similarly, maternal depression appeared linked with lower maternal regulatory behavior at the ages 6 and 10, which led to child psychiatric disorder, and those children had lower EF (at 6 years 95%CI -0.058 to -0.002), (EF at 10 years 95%CI -0.038 to -0.001). No direct effect was found between maternal depression and children's EF.	1) As they focused on the long-term effects of maternal depression apart from other comorbidities, findings need replication in higher risk samples. 2) Omission of fathers as reporters of children's well-being and regulatory outcomes. 3) Additional EF tasks are needed. 4) The sample size did not enable separating children exposed to maternal depression symptoms at 6 and at 10 years. 5) The sample included only married/cohabiting couples with medium-to-high socioeconomic status.
Dhaliwal[42]	Regression modeling was used to examine relationships between pre- and postnatal maternal depression (HRSD) scores and child BRIEF Global Executive Composite T-scores. Initially, prenatal maternal depression was used as a continuous variable, then, to examine additive interactions, a dichotomous measure of prenatal maternal depression was used (coded as 1 when HRSD ≥ 8 and 0 otherwise). Confounder: maternal mood at child's age 6.	Results of regression models showed that exposure to prenatal depression symptoms (HRSD ≥ 8) was associated with poorer BRIEF scores (50.76 vs. 56.63; p < 0.001). A two-way interaction emerged between SSRI exposure and prenatal depression, suggesting that, for mothers who took antidepressants prenatally, the more depressed they were prenatally (i.e., they did not benefit from pharmacotherapy), the higher their children's BRIEF scores (β = 2.70, 95%CI 1.02 to 4.38). Postnatal maternal depression was not significantly associated with BRIEF scores (β = 0.20, p > 0.10). Results of regression models using maternal depression as a dichotomous variable showed no association between maternal depression symptoms at 6 years and BRIEF scores (β = -0.03, 95%CI -0.31 to 0.26). A two-way interaction was also apparent between SSRI exposure and prenatal maternal mood, suggesting that mothers who took SSRI medication and were prenatally depressed had children with poorer EFs (higher BRIEF scores) (β = 43.18, 95%CI 21.00 to 65.36). Executive functions among children whose mothers were at least mildly symptomatically depressed during pregnancy (i.e., HRSD > 8) remained relatively stable even with increasing levels of household CHAOS scores, regardless of their prenatal SSRI exposure status: SSRI-exposed (β = −0.67, 95%CI -1.53 to 0.18, p = 0.12); non-exposed (β = 1.01, 95%CI -0.53 to 2.55, p = 0.20).	1) The available sample may have constrained the power needed to test two- and three-way interactions. 3) The study lacked information about the effect of fathers, maternal partners, or significant others in shaping household chaos. 4) The use of dichotomized maternal mood measures could misclassify mood status and may not reflect the impact of patterns of mood trajectories across pre and postnatal periods. 5) Due to the cohort design, exposures could not be randomized nor could the impact of variations in the severity of maternal mood be controlled for introducing possible "confounding by indication".

Ross[69]	Bivariate correlations between continuous variables were calculated and reported. Linear regression models were constructed to predict children's EF from prenatal anxiety and DEP. Model 1 used maternal prenatal and postpartum anxiety only as predictors. Model 2 used maternal prenatal and postpartum DEP only. Model 3 used both prenatal and postpartum anxiety and DEP as predictors. Covariates: maternal ethnicity, marital status, maternal age at study entry, education, household income, and country of origin, report of any alcohol use during pregnancy, parity, history of maternal anxiety or depression disorder, gestational age at birth, and birth weight (g). Moderator: postnatal maternal distress.	Prenatal and postnatal DEP were significantly correlated with EF (respectively, r = 0.198, p < 0.05; r = 0.178, p < 0.05). The "Maternal anxiety or depression diagnosis" (history of maternal anxiety or depression disorder) covariable was not independently associated with poor EF at 2 years of age (β[SE] = -0.211[0.722], p = 0.770). Results of Model 2 showed that pregnancy depression was associated with poor EF (β[SE] = 1.280[0.473], p = 0.007), but not postpartum depression (β[SE] = 0.976[0.462], p = 0.035). Similarly, on Model 3 neither pregnancy depression nor postpartum depression were associated with poor EF: respectively, β(SE) = 0.745(0.601), p = 0.215; β(S.E) = 0.509(0.550), p = 0.355. On both models, depression interaction term was not statistically significant: Model 2, β(SE) = -0.220(0.316), p = 0.486; Model 3, β(SE) = -0.284(0.340), p = 0.404.	1) All measures were maternal self-reports, which can lead to information report bias. 2) Many associations were tested, and not all were maintained after multiple test corrections. 3) Specific pathways were proposed by the fetal programming hypothesis and interpersonal model of stress transmission by which perinatal distress could affect child outcomes, but these mechanisms were not directly tested.
Familiar[67]	Unadjusted and adjusted linear regression models were performed with GEE models to separately assess associations between caregiver depression (as continuous and dichotomous measure) and BRIEF scores. Adjustments: cohort, site, gender, age at baseline, caregiver relationship to child, residential zone, WHO height for age z score, and socio-economic index.	Higher BRIEF scores represent worse performance on EF. Results of unadjusted and adjusted models showed that all EF domains (e.g., BRIEF scores) were significantly associated with caregiver's depression symptoms: unadjusted model BRIEF BRI (β[SE] = 7.29[0.76], p < 0.001), BRIEF MI (β[SE] = 5.12[0.77], p < 0.001), BRIEF GEC (β[SE] = 6.66[0.77], p < 0.001); Adjusted model BRIEF BRI (β[SE] = 7.08[0.81], p < 0.001), BRIEF MI (β[SE] = 6.02[0.84], p < 0.001), BRIEF GEC (β[SE] = 6.98[0.84], p < 0.001).	1) Findings do not represent causal relationships. 2) The relatively large sample size may have resulted in significant but perhaps small and not clinically meaningful effects. 3) A small proportion of caregivers in this study were men.
Ku[61]	Bivariate correlations between continuous variables were calculated and reported. LGM for MDS, maternal sensitivity, and child planning skills were estimated, separately. The bootstrapping method was used to calculate a longitudinal mediation in the latent growth curve modeling framework, with the intercept and the slope of MDS as the predictors, the intercept and the slope of maternal sensitivity as the mediators, and the intercept and the slope of child planning skills as the outcomes. Covariates: child gender and child early cognitive skills at 15 months, maternal education at 1 month, and family income-to-needs ratio at 1 month. Mediator: maternal sensitivity.	MDS across multiple time points showed moderate levels of negative correlations with child's EFs at school grades 1 (G1), 3 (G3), and 5 (G5): DEP 6M and EF G1 = -0.04, p > 0.05; DEP 15M and CEF G1 = -0.06, p > 0.05; DEP 24M and EF G1 = -0.016, p < 0.01; DEP 36M and EF G1 = -0.08, p < 0.05; DEP 54M and EF G1 = -0.010, p < 0.01; DEP 6M and EF G2 = -0.09, p < 0.01; DEP 15M and EF G2 = -0.13, p < 0.01; DEP 24M and EF G1 = -0.20, p < 0.01; DEP 36M and EF G1 = -0.14, p < 0.01; DEP 54M and EF G1 = -0.016, p < 0.01; DEP 6M and EF G5 = -0.11, p < 0.01; DEP 15M and EF G5 = -0.10, p < 0.01; DEP 24M and EF G5 = -0.15, p < 0.01; DEP 36M and EF G5 = -0.10, p < 0.01; DEP 54M and EF G5 = -0.016, p < 0.01. Lower MDS at 36 months predicted higher maternal sensitivity at 54 months (B[SE] = -0.081[0.015], 95%CI -0.112 to -0.052), which in turn predicted both higher levels of child planning skills in Grade 1 and a greater increase in planning skills from Grade 1 to 5 (B[SE] = 0.625[0.219], 95%CI 0.201 to 1.038; B[SE] = 0.561[0.277], 95%CI 0.047 to 1.027, respectively). The results suggest that early MDS may have long-term effects on the development of EF,	1) The three assessments of planning skills did not allow the authors to estimate nonlinear change, such as quadratic change. 2) Other family members' behavior, such fathers' autonomy support, may influence child EF and were not addressed on this study.

		especially planning skills, during middle childhood, and that one important pathway through which MDS affect child EF outcomes is maternal sensitivity.	
Yu[69]	Linear regression models were used to evaluate the effects of maternal depression with offspring EF. Model I adjustment: gestational age at delivery, pre-pregnancy BMI, offspring sex, household income, maternal education, maternal employment, and marital status at 2-year assessment. Model II adjustment: Model 1 + maternal IQ.	In model 1 (without adjusting for maternal IQ), maternal emotionality (higher levels of DEP and emotional instability) was associated with worse 6-year working memory (β = -1.87, 95%CI -3.15 to -0.60) and 6-year response inhibition (β = 0.37, 95%CI 0.02 to 0.72) and marginally associated with 18-year working memory (β = -0.26, 95%CI -0.56 to 0.03). In model 2 (adjusting for maternal IQ), the association between maternal emotionality and 6-year working memory was attenuated but remained significant (β = -1.79, 95%CI -3.05 to -0.52). However, the significant association with 6-year response inhibition became marginally significant (β = 0.33, 95%CI -0.03 to 0.68), and the borderline association with 18-year working memory disappeared (β = -0.22, 95%CI -0.52 to 0.08).	1) Observational study design did not allow a causal relationship to be established. 2) The analysis could not fully adjust for the multitude of confounding variables, including genetic predisposition, postnatal environment, and offspring lifestyle behaviors (e.g., diet, sleep). 3) Maternal measurements were limited to the postnatal period. 4) Lack of examination of maternal anxiety and stress. 5) The study did not examine possible mediators between maternal psychological factors and offspring EF. 6) There was a large time gap between maternal and offspring assessments.
Rinne[47]	Multivariate linear regression models were constructed to examine associations between trajectories of MDS and child performance on EF tasks at age 5. Covariates: child's sex, age, and race/ethnicity; and maternal education.	After adjustment for covariates, children of women with decreasing MDS at age 5 years performed significantly worse on the inhibitory control task than children of women with few stable symptoms (β = 0.35; B = -10.74, 95%CI -17.04 to -4.43, p = 0.001). Children of women with increasing symptoms also scored significantly lower on the inhibitory control task at age 5 compared to women with low-stable symptoms (β = -0.21; B = -8.10, 95%CI -15.70 to -0.50, p = 0.04). There were no significant associations between MDS trajectories and child performance on the cognitive flexibility task.	1) Small sample size. 2) Selection bias. Although the full cohort and follow-up cohort were both racially and ethnically diverse and mostly low-income, there may have been bias in the women who opted to participate in the longitudinal follow up study. 3) MDS was not assessed in the first trimester of pregnancy nor between postpartum and early childhood.

ADHD = attention-deficit/hyperactivity disorder; ANCOVA = analysis of covariance; ANOVA = analysis of variance; ARCL = autoregressive cross-lagged; BDI = Back Depression Inventory; BMI = body mass index; BRI = Behavioral Regulation Index; BRIEF = Behavior Rating Inventory of Executive Function; CANTAB = Cambridge Neuropsychological Test Automated Battery; EF = executive function; CCR = current cumulative risk; CES-D = Center for Epidemiologic Studies Depression Scale; CON = comparison group; DEP = depressive symptoms; df = degrees of freedom; EC = effortful control; EF = executive function; EPDS = Edinburgh Postnatal Depression Scale; GEC = Global Executive Composite; GEE = general estimating equation; GEE = generalized estimating equation; HAMD = Hamilton Rating Scale for Depression; HIV = human immunodeficiency virus; HLM = hierarchical linear modeling; HPA = hypothalamic-pituitary-adrenal; HRSD = Hamilton Rating Scale for Depression; IQ = intelligence quotient; LCA = latent class analysis; LGM = Latent growth model; LPA = latent profile analysis; MDD = major depressive disorder; MDS = maternal EP; MI = Metacognition Index; NA = negative affectivity; NICHD = National Institute of Child Health and Development; PPVT = Peabody Picture Vocabulary Test; PRI = Perceptual Reasoning Index; REML = restricted maximum likelihood estimation; SE = standard error; SEM = structural equation model; SRI = serotonin reuptake inhibitor; SSRI = selective SRI; TEA = Test of Everyday Attention; WAIS = Wechsler Adult Intelligence Scale; WHO = World Health Organization.

Supplementary Table S3 Detailed scores for the NHBLI checklist

Study (year)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	YES	NO	N/R	Classification
Poehlmann[49]	1	1	N/R	1	N/R	1	1	0	1	1	1	N/A	1	1	10	1	2	Fair
Buss[57]	1	0	N/R	1	N/R	1	1	1	1	1	1	N/A	N/R	1	9	1	3	Fair
Rhoades[39]	1	1	1	1	1	1	1	1	1	1	0	N/A	1	1	12	1	0	Good
Weikum[54]	1	1	N/R	1	N/R	1	1	0	1	0	1	N/A	1	1	9	2	2	Fair
Hughes[38]	1	1	N/R	1	1	1	1	0	1	1	1	N/A	1	1	11	1	1	Good
Jensen[45]	1	1	N/R	1	1	1	1	0	1	0	1	N/A	1	1	10	2	1	Fair
Comas[37]	1	1	1	1	1	1	1	0	1	0	1	N/A	1	1	11	2	0	Good
Hackman[52]	1	1	1	1	N/R	1	1	0	1	1	1	N/A	1	1	11	1	1	Good
Piamondon[56]	1	1	1	1	N/R	1	1	0	1	0	1	N/A	N/R	1	9	2	0	Good
Hermansen[48]	1	1	N/R	1	N/R	1	1	1	1	0	1	N/A	N/R	0	8	2	2	Fair
Yan[63]	1	1	N/R	1	N/R	1	1	0	1	0	1	N/A	N/R	1	8	2	3	Fair
Lagasse[41]	1	1	1	1	N/R	1	1	0	1	1	1	N/A	N/R	1	10	1	2	Fair
El Marroun[53]	1	0	1	1	N/R	1	1	1	1	1	1	N/A	1	1	11	1	0	Good
Wang[65]	1	1	N/R	1	N/R	1	1	0	1	0	1	N/A	N/R	1	8	2	2	Fair
Vänskä[62]	1	0	N/R	1	N/R	1	1	1	1	0	1	N/A	1	0	8	3	1	Fair
Berthelsen[51]	1	1	1	1	N/R	1	1	0	1	0	1	N/A	N/R	1	9	2	2	Fair
Wade[60]	1	1	N/R	1	N/R	1	1	0	1	0	1	N/A	1	1	9	2	2	Fair
Neuenschwander[58]	1	1	N/R	1	N/R	1	1	1	1	0	1	N/A	1	1	10	1	2	Fair
Nolvi[61]	1	1	1	1	N/R	1	0	0	1	0	1	N/A	1	1	9	3	1	Fair
Rotheram-Fuller[50]	1	1	N/R	1	N/R	1	1	1	1	0	1	N/A	1	0	9	2	2	Fair
Feng[64]	1	1	N/R	1	N/R	1	0	1	1	0	1	N/A	N/R	0	7	3	3	Poor
Gueron-Sela[44]	1	1	1	1	1	1	1	0	1	1	1	N/A	1	1	12	1	0	Good
Baker[66]	1	1	N/R	1	N/R	1	1	0	1	0	0	N/A	N/R	1	7	3	2	Poor
Hutchison[59]	1	1	N/R	1	N/R	1	1	0	1	0	1	N/A	1	1	9	2	2	Fair
Faleschini[43]	1	1	1	1	1	1	1	1	1	0	1	N/A	1	1	12	1	0	Good
Oh[46]	1	1	N/R	1	1	1	1	1	1	0	1	N/A	1	0	10	2	1	Fair
Priel[49]	1	1	N/R	1	N/R	1	1	0	1	0	1	N/A	0	1	8	3	2	Fair
Dhaliwal[42]	1	1	1	1	1	1	1	1	1	0	1	N/A	1	1	12	1	0	Good
Ross[55]	1	1	N/R	1	N/R	1	1	1	1	0	1	N/A	1	1	10	1	2	Fair
Familiar[67]	1	1	N/R	1	N/R	1	1	1	1	0	1	N/A	1	1	10	1	2	Fair

Ku[54]	1	1	0	1	N/R	1	1	1	0	0	1	N/A	0	1	8	4	1	Fair
Yu[69]	1	1	N/R	1	N/R	1	1	0	1	1	1	N/A	N/R	1	9	1	3	Fair
Rinne[47]	1	1	N/R	1	N/R	1	1	0	1	1	1	N/A	0	1	9	2	2	Fair
Poehlmann[49]	1	1	N/R	1	1	1	1	1	1	0	1	N/A	0	1	10	2	1	Fair

References cited according to the reference list on the main article.

1 = yes; 0 = no; N/R: not reported; N/A: not applicable.

List of questions:
1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

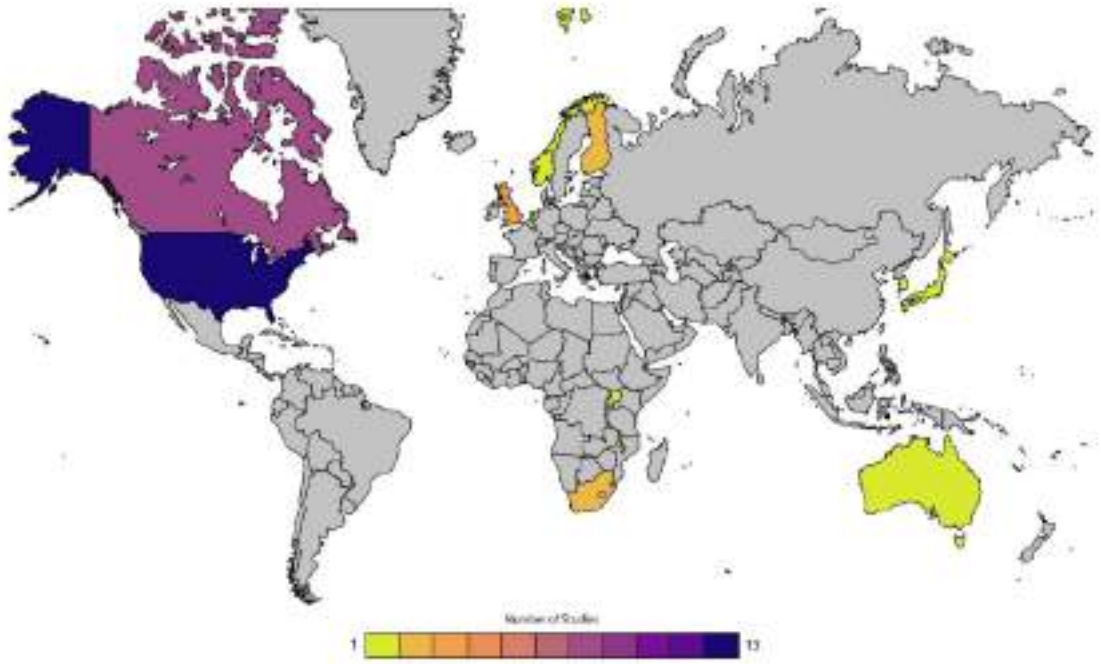
Table S4 Overall quality assessment using an adapted version of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework

GRADE domain	Rating with reasoning
No. of studies	33
Study design	Prospective cohort studies
Methodological limitations of the studies (risk of bias)	Five studies reported attrition bias.[45,49,50,52,61] Nine studies used maternal reporting as a measure of executive function, which can be considered an source of information bias.[42,43,46,53,55,56,59,63,67] However, four of these studies also assessed executive functions through other methods, such as paternal reports,[52] teacher reports,[43] and tasks.[53,63] Selection bias was reported in six studies.[40,41,47,48,63,65] However, in most articles, both exposed and unexposed participants were from the same population and had the same risk of developing executive function problems. Therefore, we generally judged the studies to have no serious methodologic limitations.
Inconsistency of results	Twenty-four studies confirmed the hypothesis of negative effects of maternal depressive symptoms on children's executive functions, and 10 studies did not detect a direct association between maternal depressive symptoms and executive functions.[37-39,45,48,49,54,56,57,62] Of these, four reported an indirect association mediated by variables related to both mother and child (e.g., child mental health disorders, negative parenting characteristics, and low maternal sensitivity).[37,49,54,56] We rated the evidence as not severely inconsistent despite some variability in the results.
Indirectness of evidence	The main exposures and outcomes in the selected studies provided direct evidence to the clinical question at hand. The population ranged from 8 months to 18 years, and most studies measured outcome between 3 and 11 years, which is the optimal range for assessing executive function. The instruments used to assess maternal depressive symptoms (exposure) varied across studies. The same variability was found for the assessment of executive functions. However, all studies measured both exposure and outcome with standardized instruments. We judged the evidence as not severely indirect but noted reasonable variability in exposure and outcome measurement.
Imprecision	The total number of participants included in all studies was 38,893. One study had methodologic limitations due to a small sample size.[67] The sample size power description was poorly reported by the studies, making it difficult to adequately assess the imprecision criteria. Five studies reported "non-significant results" but did not report standard error or confidence intervals.[51,61-63,66] However, most studies reported precision measures (mainly standard error and confidence intervals) and did not present wide intervals or high standard error. We judged the evidence to have no severe imprecision, although this aspect should be interpreted with caution due to the lack of sample size power description in 25 studies.
Publication bias	We did not strongly suspect publication bias because the search for studies was comprehensive and included published studies that reported both an association and no association between exposure and outcome.

References cited according to the reference list on the main article.

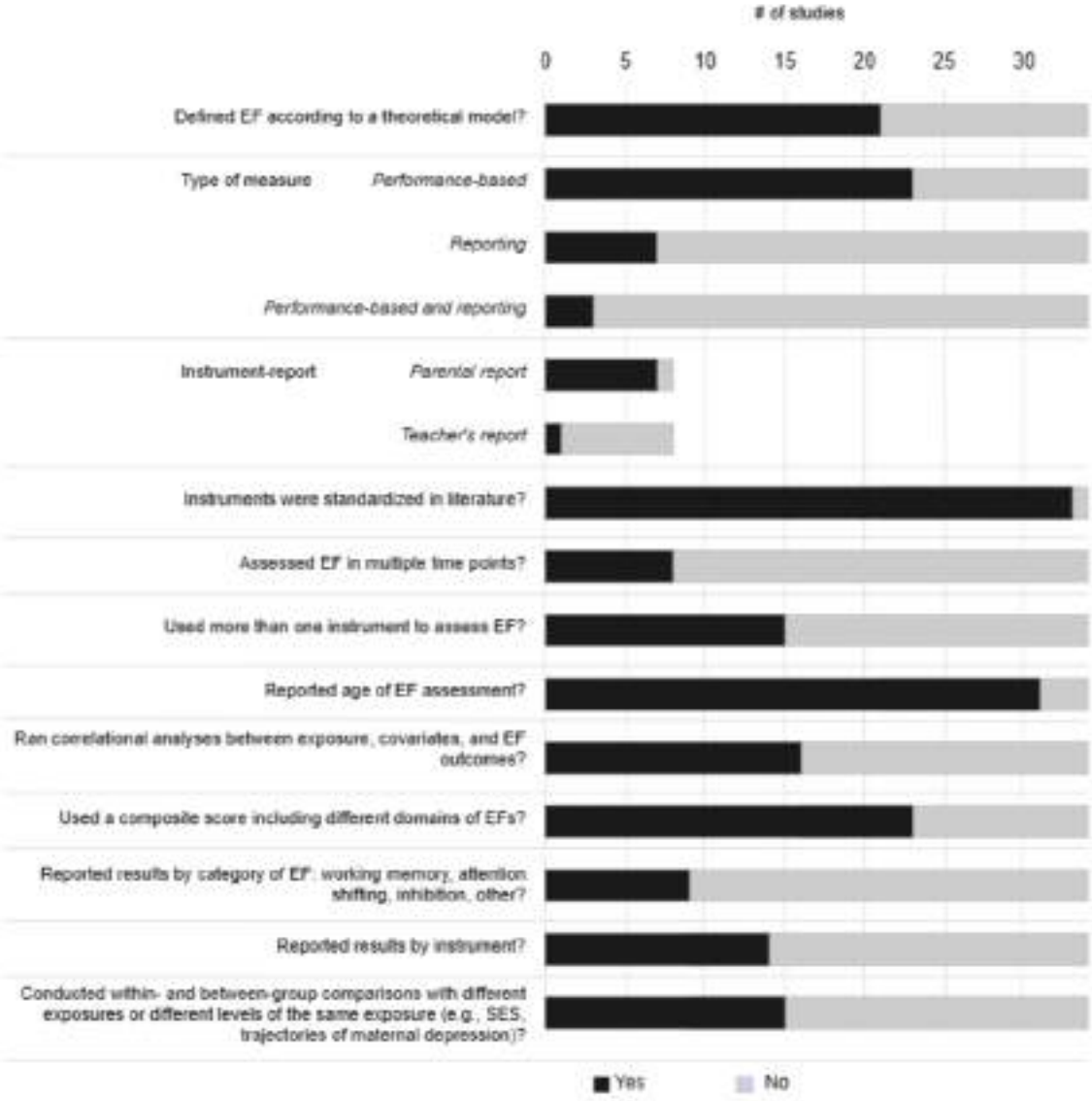
http://doi.org/10.47626/1516-4446-2023-3387

Supplementary Figure S1 Country of origin of population data from the studies included in this systematic review



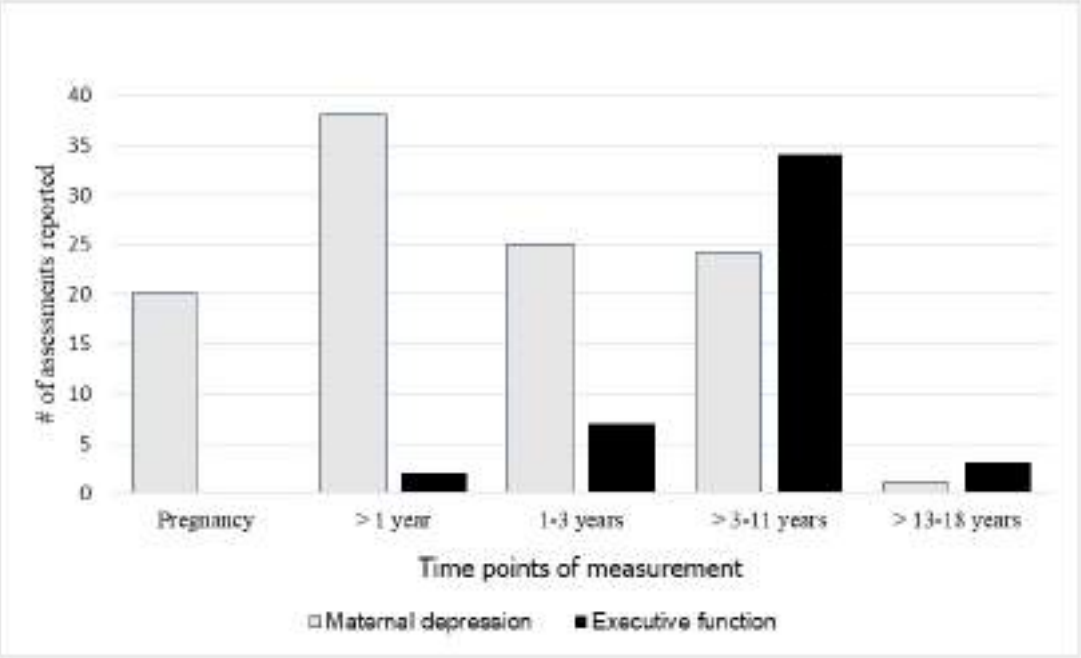
http://doi.org/10.47626/1516-4446-2023-3387

Supplementary Figure S2 Frequency of reporting information on assessment of executive functions (n=33 studies)



http://doi.org/10.47626/1516-4446-2023-3387

Supplementary Figure S3 Frequency of reporting maternal depressive and executive functions assessments per time point (n=33)



Apêndice B. Artigo "*Risk factors for executive function impairment in adolescence: 2004 Pelotas Birth Cohort study*."

Periódico: *Brazilian Journal of Psychiatry*

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DOI: 10.47626/1516-4446-2023-3277

Data de publicação: Nov/2023

Brazilian Journal of Psychiatry
bjp
Revista Brasileira de Psiquiatria

Braz J Psychiatry. 2023 Nov-Dec;45(6):470-481
doi:10.47626/1516-4446-2023-3277
Brazilian Psychiatric Association
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ORIGINAL ARTICLE

Risk factors for executive function impairment in adolescence: an analysis of data from the 2004 Pelotas Birth Cohort study

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Objective: To investigate risk factors associated with impaired attention-related executive functions (EFs) at age 11 and working memory at age 15.

Methods: Data from participants of the population-based 2004 Pelotas Birth Cohort at ages 11 (n=3,582) and 15 (n=1,960) were analyzed. The study measured attentional control, cognitive flexibility, and selective attention using the Test of Everyday Attention for Children (TEA-Ch). Spatial working memory was assessed by the Cambridge Neuropsychological Test Automated Battery (CANTAB). Logistic regression was employed to explore the relationship between perinatal and childhood exposures and EF impairment.

Results: Low maternal education had a significant negative impact on EFs. At age 11, it was associated with decreased attentional control (OR = 3.04; 95%CI 2.09-4.43), and at age 15, it was linked to impaired spatial working memory (OR = 2.21; 95%CI 1.58-3.09). Additional risk factors included low household income, black or brown maternal skin color, high parity, prematurity, low birth weight, and multiple siblings. Breastfeeding, regardless of duration, was found to be a protective factor against impaired cognitive flexibility (OR = 0.38; 95%CI 0.22-0.65).

Conclusion: This study underscores the lasting impact of perinatal exposures on EF development. Policies that mitigate the negative effects of risk factors and promote EF development, especially among vulnerable populations, are needed.

Keywords: Birth cohort; attention; memory; adolescent

Introduction

Cognitive development in childhood and adolescence is influenced by several factors, including socioeconomic and birth conditions, family characteristics, and parenting practices.[1] Executive functions (EF)s play a critical role in healthy cognitive development, as they are responsible for controlling and executing mental, attentional, behavioral, and emotional processes in situations of conflict or distraction. According to Diamond,[2] EFs are a set of higher-order cognitive abilities consisting of at least three subcomponents: inhibition, working memory, and cognitive flexibility. Other cognitive processes, such as attentional functions, act as underlying factors that support engagement of the main EFs.[3]

Previous research has shown that healthy EF development is a hugely important predictor for later life outcomes such as subjective and physical well-being.[4] Children who experience adversity during childhood and adolescence are more likely to have impaired EFs, which affects both their quality of life and development over time.[5] In the medium and long term, EF deficits are associated with high-risk behaviors such as crime and violence, obesity, overeating, substance abuse, and marital problems.[6] Attention deficits and internalizing/externalizing problems are also associated with EF development disorders.[7]

The development of EFs involves several factors and is closely linked to the sensitive periods of brain maturation and the formation of neural circuits, particularly in the prefrontal cortex and limbic regions.[8] Some of these factors are inherent to individual neurobiological development, while others are environmental. It has been argued that adolescence constitute a sensitive period for a range of cognitive functions, including affect regulation and EFs.[9]

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Submitted Jul 06 2023, accepted Sep 24 2023.

How to cite this article: Rodrigues JS, Matijasevich A, Tovo-Rodrigues L, Munhoz TN, Santos IS, Pastor-Valero M. Risk factors for executive function impairment in adolescence: an analysis of data from the 2004 Pelotas Birth Cohort study. Braz J Psychiatry. 2023;45:470-481. http://doi.org/10.47626/1516-4446-2023-3277

Studies have described multiple risk factors associated with impaired executive functioning in adolescence, including prematurity, perinatal complications, childhood abuse and neglect, low socioeconomic status, and prolonged exposure to maternal depression.[10-13] These risk factors can disrupt the normal development of brain regions involved in EFs, such as the prefrontal cortex, leading to compromised cognitive abilities.[14] Additionally, they may contribute to increased stress levels and altered neurobiological processes, further impairing the functioning of executive processes in adolescence.

Research on risk factors associated with EF impairment has increased in the literature over the past 20 years.[15,16] However, studies have mainly focused on cohorts from high-income countries (HICs), leaving a significant gap in understanding the impact of risk factors on EF development in low- and middle-income countries (LMICs).[17] Generalization of results from HICs may lead to underestimation of the harmful effects of risk factors on populations in LMICs, including countries such as Brazil. This discrepancy arises from substantial disparities in the quality of life and socioeconomic conditions experienced by these populations. In LMICs, issues such as child poverty, low birth weight, and inadequate nutrition are more prevalent than in wealthier nations. As a consequence, the impact of these risk factors is expected to be significantly more pronounced in LMICs.[18] To address this knowledge gap, the present study aims to examine the factors associated with impaired EFs related to attentional control, selective attention, and cognitive flexibility (at age 11) and working memory (at age 15) among children and adolescents from the 2004 Pelotas Birth Cohort.

Methods

Participants

The 2004 Pelotas Birth Cohort is a population-based study that included children born in Pelotas, state of Rio Grande do Sul, Brazil, between January 1 and December 31, 2004. The original cohort comprised 4,231 newborns (99.2% of all births; 51.2% boys), who were followed throughout childhood and adolescence. The data included 3,491 participants who were followed up at 11 years old and 1,950 who were followed up at 15 years old. The sixth follow-up wave (at 11 years of age) was conducted between May and October 2015, with a follow-up rate of 87%. The seventh follow-up occurred between November 2019 and March 2020; however, only 46.1% of the original cohort was followed up before the start of the coronavirus disease 2019 (COVID-19) pandemic, which disrupted further data collection. The timeline of follow-up waves is described in Figure S1 (available as online-only supplementary material). Additional information about the methodology of the 2004 Cohort and the collected data can be found in previous studies.[19,20]

Measures

Executive functions

Attention-related EFs at age 11 were assessed by performing tasks contained in the Test of Everyday Attention for Children (TEA-Ch),[21] a neuropsychological test developed to assess the multidimensional nature of attention and related EFs in children and adolescents. The three attention-related EFs assessed were attentional control, cognitive flexibility, and selective attention. At the age of 15, spatial working memory was examined using a subtest of the Cambridge Neuropsychological Test Automated Battery (CANTAB).[22] The tasks are described in Table S1 (available as online-only supplementary material).

In the present study, attention-related EFs and spatial working memory were dichotomized to define a low-performance group. Categorization of attention-related EFs was done using a cutoff point of $<$ 10th percentile, indicating those children who took the longest to complete the task. Meanwhile, categorization of spatial working memory was based on the cutoff point for the 3rd tertile, identifying those with a greater number of errors.

Perinatal exposures

Maternal, socioeconomic and pregnancy characteristics. Variables were collected in the perinatal interview and included household income (measured as a continuous variable and categorized into quintiles), maternal education (categorized into 0, 1-4, 5-8 and $\geq$ 9 years of formal education), self-reported maternal skin color (white, black, brown, yellow/indigenous), living arrangement (alone or with a partner), maternal age ($<$ 20, 20-34, and $\geq$ 35 years), and parity (defined as the number of previously born children and categorized as 1, 2, and $\geq$ 3). Smoking during pregnancy was assessed retrospectively at birth by maternal reporting; regular smokers were defined as women who smoked at least one cigarette per day in any trimester of pregnancy.

Birth characteristics and breastfeeding. The variables of the child at birth assessed were low birth weight ($<$ 2,500 g) and prematurity (gestational age $<$ 37 weeks). Duration of breastfeeding was assessed by maternal reporting at 24 months and categorized as $<$ 1, 1-3, 3-6, 6-12 or $\geq$ 12 months.

Childhood exposures

Environmental characteristics. Absence of father (social or biological father) was measured in the first 48 months of life (never absent, absent at 24 months, absent at 48 months, always absent). The number of older siblings (none, 1, $\geq$ 2) was reported by the mother in the perinatal interview.

Maternal depressive symptoms. The Edinburgh Postnatal Depression Scale (EPDS) was originally designed for the identification of postpartum depression disorders in clinical and research settings.[23] The EPDS is a self-administered scale consisting of 10 items evaluated on a 4-point scale (0-3), with a total minimum score of 0 and a maximum score of 30. The scale indicates the intensity of depressive symptoms in the 7 days preceding the interview. The validated version of the questionnaire was administered to the mothers of the 2004 Pelotas Cohort.[24] EPDS scores from the 3-month to the 11-year

follow-ups were used to construct trajectories of maternal depressive symptoms through a semiparametric group-based modeling approach, a specialized form of finite mixture modeling.[25,26] Details of the steps and methods used to identify the trajectories of maternal depressive symptoms have been reported in previous studies.[27,28] Groups 1 (low depressive symptomatology trajectory, n=1,161) and 2 (moderately low trajectory, n=1,361) represented 75.7% of mothers, who had EPDS scores < 10 points in all follow-ups. Group 3 (increasing depressive symptomatology trajectory) included 9% (n=300) of the women monitored, who had a consistent increase in depressive symptoms throughout the study period. Group 4 (descending trajectory) included 9.9% (n=329) of women and, unlike the previous group, these mothers had high EPDS scores during the first 2 years postpartum and a sharp decrease thereafter. Finally, group 5 (chronic-high trajectory) represented 5.4% of the population (n=181), and included mothers who had high EPDS scores throughout the study period.

Maltreatment. Adolescent maltreatment was evaluated at the 11-year follow-up. Caregivers, most of whom were mothers, were asked about parenting strategies using the Parent-Child Conflict Tactics Scale (CTSPC).[29] The Portuguese version of the CTSPC was adapted and validated cross-culturally for use in Brazil.[30-32] The CTSPC is a 22-item questionnaire that measures parental behavior toward the child in the preceding 12 months. The CTSPC evaluates behaviors related to nonviolent discipline (four items), psychological aggression (five items), and physical aggression, including corporal punishment (five items), physical abuse (four items), and severe physical abuse (four items; not administered in this study). All items were scored on a 3-point scale (0-2; never, once, or more than once), yielding a total score of 0 to 28. Higher scores indicate higher exposure to maltreatment. In this study, the total score on the CTSPC scale was categorized into tertiles.

Statistical analysis

Comparisons between socioeconomic, maternal, and birth characteristics among the participants of the 11-year (n=3,582) and 15-year (n=1,950) follow-ups in relation to the total number of participants at baseline (n=4,231) were performed using the chi-square test. The descriptive analysis was performed by calculating the absolute and relative frequencies of the variables of interest. Bivariate statistical analysis between each exposure and the study outcomes was performed by means of the chi-square test. To study the potential risk factors for impaired performance in EFs related to attentional control, cognitive flexibility, selective attention, and spatial working memory, logistic regression models were constructed for each EF analyzed and adjustment was performed using a hierarchical conceptual model for determining risk factors (Figure 1) with four levels: 1) level 1: adjustment for maternal, socioeconomic, and gestational characteristics; 2) level 2: adjustment for level 1 variables and environmental characteristics; 3) level 3: adjustment for level 2 variables and characteristics of birth and breastfeeding; 4) level 4: adjustment for level 3 variables and maltreatment in childhood. Odds ratios (OR) were used to assess the associations between variables. If the significance level was below 0.20, the variable remained in the model as a potential confounder for the next level.[33] An alpha level of 0.05 was considered to indicate an association. All analyses were conducted

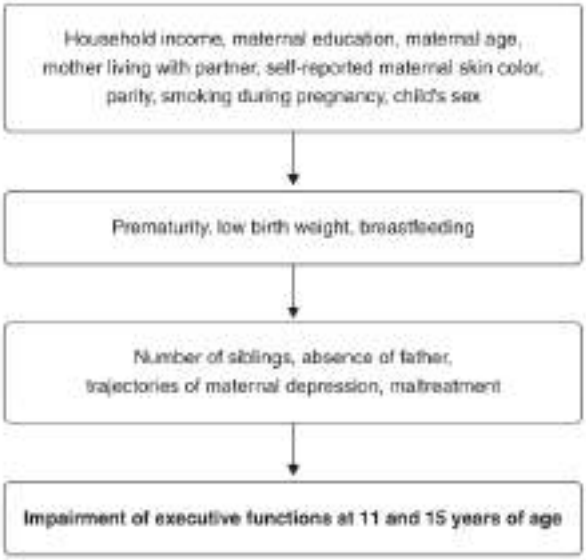

Figure 1 Conceptual model for determining risk factors associated with executive functions at 11 and 15 years of age in adolescents from the 2004 Pelotas Birth Cohort.

using Stata software, version 16.1. An additional analysis was conducted in which potential risk factors were modeled for two distinct groups: participants belonging to the lowest income quintile, representing the economically disadvantaged group; and the other participants belonging to the second to fifth income quintiles.

Ethics statement

This study was approved by the Ethics Committee for the Analysis of Research Projects (CAPPESq) of Universidade de São Paulo and by the research ethics committee of Universidade Federal de Pelotas. At the sixth follow-up (at age 11), the study was also approved by CAPPESq. Written informed consent was obtained from the adolescents' mothers or guardians. At the sixth and seventh follow-up visits (at ages 11 and 15 years), the adolescents themselves signed an assent form.

Results

Attrition analysis

Participants who were followed up at 11 and 15 years had better socioeconomic indicators than the baseline sample as a whole, as shown in Table 1. Additionally, there were fewer cases of preterm birth and low birth weight among those followed up at 11 and 15 years compared to the baseline sample. At the 11-year follow-up, a higher proportion of mothers reported living with their partner, while at the 15-year follow-up, more participants had been born to mothers aged 35 or older. There were no differences in maternal skin color or child's sex between those reached at the 11- and 15-year follow-ups and the baseline sample.

Sample description

The majority of mothers of participants followed up at 11 and 15 years of age were white, aged 20 to 34, had at least 9 years of schooling, and had not smoked during pregnancy. The prevalence of boys was slightly higher at both the 11- and 15-year follow-ups. Most adolescents' fathers had been present during childhood. In addition, the majority of adolescents were breastfed for at least the 1st month of life. For more details on participant characteristics, see supplementary material (Table S2, available as online-only supplementary material).

Bivariate analysis

Lower household income, lower levels of maternal education, and greater number of siblings were associated with attention-related EFs at age 11 and spatial working memory impairment at age 15 (Table 2). Children of single mothers and of mothers who smoked during pregnancy performed comparatively poorly in attentional control. Other factors associated with lower performance in attentional control, selective attention, and spatial working memory were black or brown maternal skin color, parity of three or more children, and absence of father at 24 and 48 months. Additionally, prematurity and low birth weight were associated with lower performance of attention-related EFs at 11 years of age. Male adolescents presented lower performance in selective attention, while girls showed lower performance in spatial working memory more frequently. Furthermore, adolescents whose mothers had chronic and severe depressive symptoms when they were aged 3 months to 11 years had lower performance in attentional control, selective attention, and spatial working memory. Higher levels of maltreatment were associated with lower performance in cognitive flexibility. Lower performance in cognitive flexibility was also observed among children who were never breastfed.

Adjusted analysis

Several perinatal and childhood predictors were associated with impaired attention-related EFs and spatial working memory (Table 3). Low maternal education was a strong predictor of deficit in attention-related EFs and spatial working memory. This observation remained consistent even after stratifying by household income (Tables S3 and S4, available as online-only supplementary material). Moreover, lower household income was associated with higher odds of attentional control impairment. Notably, children of mothers who described their skin color as black performed worse than children of white mothers on attentional control, selective attention, and spatial working memory. This result persisted for selective attention impairment even when household income stratification was taken into account.

A greater number of siblings was associated with impaired attentional control and spatial working memory. Additionally, low birth weight was found to be related to poorer selective attention at 11 years of age. Moderate-low and decreasing maternal depression symptoms were linked to poorer spatial working memory at age 15. Stratification by household income revealed that within the lowest income quintile group, moderate-low and increasing maternal depression symptoms were associated with impaired attentional control.

In terms of sex differences, girls exhibited a reduced risk of selective attention impairment at the age of 11, while presenting poorer performance in spatial working memory at age 15.

Interestingly, breastfeeding reduced the odds of impaired cognitive flexibility, regardless of duration. In addition, a protective effect was observed in which children of mothers older than 35 years showed higher cognitive flexibility. Potential risk factors such as maternal age, whether the mother lived with a partner, absence of father, smoking during pregnancy, and maltreatment were not found to have any significant association with EFs.

Discussion

Using data from a population-based cohort study, the present study examined the impacts of socioeconomic, parental, and adolescent variables on the performance of attention-related EFs at the age of 11 and spatial working

Table 1 Maternal and adolescent characteristics among participants at follow-ups conducted at 11 and 15 years of age in relation to the baseline (perinatal) sample

Variables	Perinatal (n=4,231)	Follow-ups	
		11 years (n=3,582)	15 years (n=1,950)
Household income (quintiles)		p < 0.001	p = 0.001
5th (wealthiest)	830 (19.6)	693 (19.4)	362 (18.6)
4th	856 (20.3)	754 (21.1)	432 (22.2)
3rd	816 (19.3)	709 (19.9)	407 (20.9)
2nd	854 (20.2)	716 (20.1)	383 (19.7)
1st (poorest)	871 (20.6)	696 (19.5)	365 (18.7)
Maternal education (years)		p = 0.001	p = 0.021
⩾ 9	1,801 (43.0)	1,542 (43.7)	868 (44.9)
5-8	1,731 (41.4)	1,465 (41.5)	790 (40.8)
1-4	611 (14.6)	497 (14.1)	264 (13.6)
0	43 (1.0)	29 (0.8)	13 (0.7)
Self-reported maternal skin color		p = 0.142	p = 0.057
White	2,581 (61.7)	2,197 (62.3)	1,220 (63.4)
Black	689 (16.5)	584 (16.6)	316 (16.4)
Brown	868 (20.8)	711 (20.2)	375 (19.5)
Yellow/Indigenous	43 (1.0)	35 (1.00)	14 (0.7)
Maternal age at birth (years)		p = 0.079	p < 0.001
20-34	2,865 (67.8)	2,404 (67.4)	1,296 (66.5)
< 20	799 (18.9)	669 (18.8)	350 (18.0)
⩾ 35	563 (13.3)	493 (13.8)	303 (15.6)
Mother living with partner		p = 0.001	p = 0.062
Yes	3,536 (83.6)	3,013 (84.5)	1,652 (84.8)
No	693 (16.4)	565 (15.6)	297 (15.3)
Child's sex		p = 0.348	p = 0.360
Male	2,194 (51.8)	1,840 (51.6)	996 (51.1)
Female	2,035 (48.1)	1,728 (48.4)	953 (48.9)
Low birth weight		p < 0.001	p = 0.024
No	3,803 (90.0)	3,247 (91.0)	175 (91.1)
Yes	423 (10.0)	320 (9.0)	173 (8.9)
Preterm birth		p = 0.007	p = 0.025
No	3,603 (85.5)	3,068 (86.1)	1,689 (86.8)
Yes	612 (14.5)	495 (13.9)	257 (13.2)

Data presented as n (%).

memory at the age of 15 years. Among the perinatal exposures investigated, low maternal education was the risk factor that presented the greatest negative impact on attention-related EFs at 11 years and spatial working memory at 15 years. The results also indicated that breastfeeding (regardless of duration) and late maternity had a protective effect on the performance of attention-related EFs at age 11.

Low maternal education and low household income have been consistently identified as risk factors for EFs development, as shown in a meta-analysis by Lawson et al.[15] with 18 independent populations. Our results add to this literature by showing that the negative association of low family income is particularly strong in countries such as Brazil, where about 42% of children aged 0-14 years live in poverty.[34] Furthermore, our study revealed that low maternal education had a greater negative impact on EFs at 11 and 15 years of age than household income. Maternal education plays a critical role in child development, reflecting maternal characteristics that may influence the parent-child relationship, while income has a greater impact on children's exposure to environmental stressors.[35] Compared to countries in the Global North, countries in the South offer less social protection for children in terms of nutrition, health, and education. Thus, mothers and caregivers have a more central role in the child's development process. Mothers with higher levels of education have the potential to create healthier and more stimulating home environments for child development. This includes providing greater economic resources, enhanced information processing capacity, and increased access to better educational environments.[36] Higher levels of maternal education are associated with a decreased risk of maternal depressive symptoms, which in turn can have a great impact on the quality of the mother-child relationship.[37] Interestingly, the study also found that older maternal age served as a protective factor for executive functioning impairment, possibly due to greater maternal experience and stability.

The results of this study showed negative consequences of maternal characteristics on the development of executive functioning in late childhood and

Table 2 Frequency of impairment of EFs related to attention and spatial working memory according to maternal and adolescent characteristics

Variables	EF impairment			
	Attentional control (p10) at 11 years n=3,452	Cognitive flexibility (p10) at 11 years n=3,413	Selective attention (p10) at 11 years n=3,392	Spatial working memory (p3) at 15 years n=1,910
Household income (quintiles)	p < 0.001	p = 0.001	p = 0.001	p < 0.001
5th (wealthiest)	2 (0.3)	49 (7.4)	30 (4.6)	55 (18.3)
4th	45 (6.1)	54 (7.4)	57 (7.8)	92 (21.7)
3rd	71 (10.3)	77 (11.3)	74 (10.8)	108 (27.1)
2nd	91 (13.0)	9 (1.3)	92 (13.5)	110 (29.5)
1st (poorest)	110 (16.7)	82 (12.6)	86 (13.5)	132 (36.9)
Maternal education (years)	p < 0.001	p < 0.001	p < 0.001	p < 0.001
≥ 9	72 (4.8)	106 (7.1)	85 (5.7)	162 (16.9)
5-8	159 (11.3)	166 (11.9)	158 (11.5)	235 (30.6)
1-4	105 (22.0)	64 (13.6)	87 (16.7)	100 (36.6)
0	7 (25.9)	4 (16.0)	9 (33.3)	7 (53.6)
Maternal age at birth (years)	p = 0.009	p = 0.108	p = 0.006	p = 0.065
20-34	221 (9.5)	219 (9.6)	239 (10.5)	332 (26.1)
< 20	84 (12.9)	79 (12.2)	66 (10.3)	106 (31.1)
≥ 35	37 (7.8)	43 (9.1)	33 (7.0)	69 (23.2)
Mother living with partner	p = 0.041	p = 0.907	p = 0.589	p = 0.167
Yes	277 (9.5)	287 (10.0)	284 (9.9)	421 (26.0)
No	67 (12.4)	54 (10.1)	55 (10.5)	86 (29.9)
Self-reported maternal skin color	p < 0.001	p = 0.169	p < 0.001	p < 0.001
White	142 (6.7)	19 (0.9)	151 (7.2)	279 (23.3)
Black	96 (16.1)	69 (12.3)	99 (16.1)	113 (36.6)
Brown	93 (13.6)	67 (9.9)	80 (11.9)	106 (29.0)
Yellow/Indigenous	4 (11.8)	2 (5.9)	2 (5.9)	4 (28.4)
Parity	p < 0.001	p = 0.063	p < 0.001	p = 0.009
1	105 (7.7)	131 (9.7)	109 (8.1)	183 (25.1)
2	71 (7.6)	79 (8.5)	81 (8.8)	127 (23.4)
3+	166 (14.6)	131 (11.8)	149 (13.3)	197 (30.8)
Smoking during pregnancy	p = 0.004	p = 0.788	p = 0.099	p = 0.470
No	230 (9.1)	248 (9.9)	236 (9.5)	342 (24.2)
Yes	114 (12.4)	93 (10.2)	103 (11.4)	165 (33.3)
Absence of father	p = 0.019	p = 0.841	p = 0.006	p < 0.001
Never absent	176 (8.6)	196 (9.7)	173 (8.6)	302 (25.3)
Absent at 24 months	22 (10.1)	22 (10.1)	22 (10.4)	27 (26.5)
Absent at 48 months	47 (13.0)	37 (10.3)	51 (14.4)	50 (28.2)
Always absent	52 (12.1)	36 (8.6)	47 (11.4)	66 (30.0)
Low birth weight	p = 0.004	p = 0.046	p < 0.001	p = 0.032
No	300 (9.5)	309 (9.9)	290 (9.4)	1,292 (74.1)
Yes	44 (14.7)	32 (10.8)	49 (16.8)	111 (66.5)
Preterm birth	p < 0.001	p = 0.046	p < 0.001	p = 0.334
No	275 (9.2)	282 (9.6)	271 (9.2)	434 (26.2)
Yes	69 (14.7)	58 (12.6)	67 (14.6)	73 (29.1)
Child's sex	p = 0.202	p = 0.710	p = 0.007	p < 0.001
Male	186 (10.6)	178 (10.2)	197 (11.3)	201 (20.7)
Female	158 (9.3)	163 (9.8)	142 (8.6)	306 (32.7)
Maltreatment (CTSPC score) (tertile)	p = 0.878	p = 0.022	p = 0.139	p = 0.435
1st (lower)	113 (9.6)	120 (10.3)	107 (9.2)	156 (25.0)
2nd	131 (10.1)	107 (8.4)	117 (9.2)	177 (25.8)
3rd (highest)	95 (10.2)	110 (11.9)	106 (11.5)	152 (28.8)

Continued on next page

Table 2 (continued)

Variables	EF impairment			
	Attentional control (p10) at 11 years n=3,452	Cognitive flexibility (p10) at 11 years n=3,413	Selective attention (p10) at 11 years n=3,392	Spatial working memory (p3) at 15 years n=1,910
Number of siblings	p < 0.001	p = 0.009	p < 0.001	p < 0.001
0	60 (7.2)	94 (8.5)	83 (7.5)	133 (22.5)
1	92 (7.4)	120 (9.7)	118 (9.6)	177 (24.9)
⩾ 2	158 (16.3)	119 (12.6)	125 (13.4)	176 (34.2)
Trajectories of maternal depressive symptoms	p = 0.001	p = 0.218	p = 0.040	p < 0.001
Low	84 (7.7)	95 (8.7)	84 (7.7)	115 (19.6)
Moderate-low	137 (9.6)	144 (10.2)	141 (10.0)	223 (27.5)
Decreasing	48 (12.7)	43 (11.5)	46 (12.5)	65 (32.0)
Increasing	47 (15.3)	35 (11.6)	34 (11.4)	52 (31.0)
Chronic-high	17 (10.7)	21 (13.4)	19 (12.1)	33 (35.1)
Breastfeeding duration (months)	p = 0.009	p = 0.000	p = 0.253	p = 0.047
0	11 (12.1)	19 (21.6)	15 (16.7)	16 (27.6)
< 1	27 (10.3)	21 (8.1)	25 (9.8)	40 (30.8)
1-3	71 (13.9)	67 (13.4)	53 (10.7)	93 (33.2)
3-12	105 (8.32)	116 (9.3)	120 (9.6)	175 (25.1)
⩾ 12	128 (9.7)	11 (9.0)	122 (9.5)	182 (24.7)

Data presented as n (%).
p-values from a chi-square test.
CTSPC = Parent-Child Conflict Tactics Scale; EFs = executive functions; p10 = worst decile (adolescents who took the longest to complete the task); p3 = worst tertile (adolescents who made the highest number of mistakes in the task).

adolescence. Maternal skin color (black or brown) has been identified as a risk factor insofar as it reflects disparities in access to resources and opportunities, potentially influencing the development of offspring EF.[38] Multiparity, or having multiple children, has been linked to potential challenges in parenting practices that may negatively affect children's EFs. This association is particularly notable in families of low socioeconomic status, where the presence of multiple siblings can lead to competition for parents' time and attention.[39]

Exposures to maternal depressive symptoms and a high number of siblings in the 1st years of age were identified as potential risk factors for impairment of attention-related EFs and spatial working memory at ages 11 and 15. According to the theory of ecological development, stressors in the environment and the absence of complex stimuli can impair the development and regulation of cognitive processes linked to EFs.[40] Having a higher number of siblings can impair EFs due to factors such as reduced parental monitoring, limited practice in negotiation and conflict resolution, and increased social complexity.[39] This can result in reduced opportunities for one-on-one interactions and cognitive stimulation, which are important for the development of EFs. Meanwhile, maternal depressive symptoms have a persistent negative impact on executive functioning throughout child development due to a lack of essential environmental stimuli important for cognitive growth, including cognitive stimulation, communication, and positive emotions.[41]

In addition to maternal characteristics, birth characteristics such as prematurity and low birth weight were identified as risk factors for impaired EFs at age 11. Prematurity was associated with impaired attentional control, while low birth weight was associated with impaired selective attention. These results are in line with previous research that points to prematurity and low birth weight as risk factors for several long-term cognitive outcomes, including EFs impairment.[13,42] Although positive parenting and good parental mental health can minimize the negative effects of premature birth and positively influence neurodevelopment,[43] adverse effects of prematurity and complications related to the development of brain regions such as the prefrontal cortex may be associated with cognitive deficits throughout childhood, adolescence, and adulthood.[13]

In our study, we found sex differences in selective attention at age 11 and in spatial working memory at age 15. However, this result should be interpreted with caution. A recent literature review indicates that gender is not the main factor in individual differences in EF and cognitive performance.[44] The literature suggests that these differences are often due to minor changes in task design, suggesting that variations in strategic approaches and outcome preferences contribute to the observed effects on EF, rather than being due to inherent differences in ability between the sexes.

Furthermore, breastfeeding was identified as a protective factor for cognitive flexibility at age 11 years, regardless of its duration. Our findings not only emphasize the influence of breastfeeding on children's cognitive development but also align with longitudinal observations from the 1982 Pelotas Birth Cohort study.[45] This study highlights the association between breastfeeding and improved performance on intelligence tests even after 3 decades. Importantly, despite growing recognition of breastfeeding's positive effects on child cognitive development, there is limited evidence associating it to EF,

Table 3 Logistic regression models for impairment in performance of attentional control, cognitive flexibility, and selective attention at age 11 and spatial working memory at age 15

Variables	Attentional control		Cognitive flexibility		Selective attention		Spatial working memory	
	Crude	Adjusted[1]	Crude	Adjusted[1]	Crude	Adjusted[1]	Crude	Adjusted[1]
Household income (quintiles)	p < 0.001	p = 0.029	p = 0.001	p = 0.247	p < 0.001	p = 0.241	p < 0.001	p = 0.064
5th (wealthiest)	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	-	1 (ref)	1 (ref)
4th	1.55 (0.94-2.52)	1.14 (0.69-1.89)	1.00 (0.67-1.49)	-	1.78 (1.13-2.80)	-	1.24 (0.87-1.77)	1.08 (0.75-1.57)
3rd	2.72 (1.72-4.30)	1.60 (0.98-2.60)	1.59 (1.10-2.32)	-	2.54 (1.64-3.94)	-	1.66 (1.17-2.35)	1.24 (0.85-1.80)
2nd	3.55 (2.28-5.54)	1.60 (0.98-2.60)	1.62 (1.12-2.35)	-	3.27 (2.13-5.01)	-	1.87 (1.32-2.65)	1.20 (0.81-1.78)
1st (poorest)	4.76 (3.08-7.36)	1.95 (1.20-3.17)	1.81 (1.25-2.62)	-	3.27 (2.12-5.03)	-	2.61 (1.85-3.69)	1.66 (1.13-2.45)
Maternal education (years)	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001
⩾ 9	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
5-8	2.53 (1.90-3.38)	1.55 (1.12-2.15)	1.77 (1.37 -2.28)	1.77 (1.37 -2.28)	2.14 (1.63-2.82)	1.80 (1.33-2.42)	1.89 (1.51-2.38)	1.51 (1.17-1.95)
1-4	5.60 (4.07-7.72)	3.04 (2.09-4.43)	2.06 (1.48-2.86)	2.06 (1.48-2.86)	3.81 (2.77-5.24)	3.06 (2.15-4.36)	2.70 (2.00-3.66)	2.21 (1.58-3.09)
0	8.97 (2.85-17.01)	4.10 (1.53-10.95)	2.49 (0.84-7.39)	2.49 (0.84-7.39)	8.27 (3.61-18.96)	9.15 (3.82-21.96)	7.52 (2.17-25.99)	4.98 (1.41-17.62)
Maternal age at birth (years)	p = 0.010	p = 0.003	p = 0.109	p = 0.218	p = 0.069	p = 0.014	p = 0.066	p = 0.338
20-34	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	1 (ref)	1 (ref)	-
< 20	1.41 (1.07-1.84)	1.56 (1.11-2.19)	1.31 (1.00-1.73)	-	0.98 (0.74-1.31)	1.00 (0.70-1.41)	1.28 (0.98-1.66)	-
⩾ 35	0.80 (0.56-1.15)	0.67 (0.45-0.99)	0.96 (0.6-1.33)	-	0.64 (0.44-0.94)	0.55 (0.37-0.82)	0.85 (0.63-1.15)	-
Self-reported maternal skin color	p < 0.001	p < 0.001	p = 0.173	p = 0.430	p < 0.001	p < 0.001	p < 0.001	p = 0.036
White	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Black	2.83 (2.15-3.74)	2.14 (1.60-2.87)	1.36 (1.02-1.83)	-	2.66 (2.18-3.76)	2.47 (1.86-3.27)	1.90 (1.45-2.48)	1.52 (1.15-2.02)
Brown	2.19 (1.66-2.89)	1.66 (1.24-2.22)	1.06 (0.79-1.42)	-	1.74 (1.31-2.32)	1.45 (1.08-1.95)	1.34 (1.03-1.75)	1.11 (0.85-1.47)
Yellow/Indigenous	1.86 (0.65-5.36)	1.87 (0.64-5.46)	0.61 (0.14-2.54)	-	0.81 (0.19-3.40)	0.83 (0.20-3.53)	1.32 (0.41-4.23)	1.07 (0.33-3.51)
Parity	p < 0.001	p < 0.001	p = 0.064	p = 0.287	p < 0.001	p = 0.116	p = 0.100	p = 0.251
1	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	1 (ref)	1 (ref)	-
2	0.99 (0.72-1.35)	1.13 (0.80-1.61)	0.87 (0.65-1.17)	-	1.10 (0.82-1.49)	1.03 (0.74-1.44)	0.91 (0.70-1.18)	-
⩾ 3	2.05 (1.59-2.66)	1.93 (1.36-2.74)	1.23 (0.95-1.58)	-	1.74 (1.34-2.27)	1.36 (0.98-1.90)	1.32 (1.04-1.68)	-
Smoking during pregnancy	p = 0.004	p = 0.738	p = 0.788	p = 0.264	p = 0.099	p = 0.471	p < 0.001	p = 0.063
No	1 (ref)	-	1 (ref)	-	1 (ref)	-	1 (ref)	1 (ref)
Yes	1.41 (1.11-1.80)	-	1.04 (0.80-1.33)	-	1.23 (0.96-1.57)	-	1.57 (1.26-1.96)	1.26 (0.99-1.60)
Mother living with partner	p = 0.041	p = 0.309	p = 0.907	p = 0.608	p = 0.689	p = 0.699	p = 0.167	p = 0.684
Yes	1 (ref)	-	1 (ref)	-	1 (ref)	-	1 (ref)	-
No	1.34 (1.01-1.79)	-	1.02 (0.74-1.38)	-	1.06 (0.78-1.44)	-	1.21 (0.92-1.60)	-
Child's sex	p = 0.203	p = 0.085	p = 0.710	p = 0.689	p = 0.007	p = 0.005	p < 0.001	p < 0.001
Female	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Male	1.16 (0.92-1.45)	1.23 (0.97-1.56)	1.04 (0.83-1.31)	-	1.36 (1.08-1.71)	1.41 (1.11-1.78)	0.54 (0.43-0.66)	0.54 (0.44-0.67)
Preterm birth	p < 0.001	p = 0.026	p = 0.047	p = 0.162	p = 0.047	p = 0.249	p = 0.334	p = 0.597
No	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	-
Yes	1.69 (1.27-2.25)	1.42 (1.04-1.93)	1.36 (1.00-1.84)	1.24 (0.92-1.69)	1.36 (1.00-1.84)	-	1.16 (0.86-1.55)	-

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Table 3 (*continued*)

Variables	Attentional control		Cognitive flexibility		Selective attention		Spatial working memory	
	Crude	Adjusted*	Crude	Adjusted*	Crude	Adjusted*	Crude	Adjusted*
Low birth weight	p = 0.005	p = 0.258	p = 0.623	p = 0.516	p = 0.623	p < 0.001	p = 0.033	p = 0.136
No	1 (ref)	-	1 (ref)	-	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Yes	1.63 (1.16-2.29)	-	1.10 (0.75-1.62)	-	1.10 (0.75-1.62)	1.98 (1.40-2.79)	1.45 (1.03-2.03)	1.31 (0.92-1.88)
Breastfeeding duration (months)	p = 0.010	p = 0.160	p < 0.001	p = 0.001	p = 0.267	p = 0.618	p = 0.048	p = 0.135
0	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	1 (ref)
< 1	0.84 (0.40-1.77)	1.02 (0.46-2.27)	0.32 (0.16-0.63)	0.32 (0.16-0.64)	0.32 (0.16-0.63)	-	0.15 (-0.53-0.84)	1.41 (0.68-2.91)
1-3	1.18 (0.60-2.32)	1.33 (0.65-2.75)	0.56 (0.32-0.99)	0.56 (0.31-0.99)	0.56 (0.32-0.99)	-	0.27 (-0.36-0.89)	1.42 (0.73-2.75)
3-12	0.66 (0.34-1.28)	0.87 (0.43-1.75)	0.37 (0.22-0.64)	0.40 (0.23-0.70)	0.37 (0.22-0.64)	-	-0.13 (-0.73-0.47)	1.05 (0.56-1.99)
⩾ 12	0.78 (0.40-1.51)	0.94 (0.47-1.90)	0.36 (0.21-0.62)	0.38 (0.22-0.65)	0.36 (0.21-0.62)	-	-0.15 (-0.75-0.45)	0.98 (0.52-1.85)
Number of siblings	p < 0.001	p = 0.015	p = 0.009	p = 0.358	p < 0.001	p = 0.294	p < 0.001	p = 0.042
0	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	-	1 (ref)	1 (ref)
1	1.04 (0.76-1.41)	1.05 (0.73-1.48)	1.15 (0.87-1.53)	-	1.30 (0.97-1.74)	-	1.15 (0.89-1.48)	0.96 (0.72-1.27)
⩾ 2	1.53 (1.90-3.36)	1.60 (1.10-2.33)	1.53 (1.15-2.04)	-	1.89 (1.41-2.53)	-	1.79 (1.37-2.34)	1.34 (1.00-1.81)
Absence of father	p = 0.020	p = 0.394	p = 0.842	p = 0.717	p = 0.005	p = 0.074	p = 0.471	p = 0.986
Never absent	1 (ref)	-	1 (ref)	-	1 (ref)	1 (ref)	1 (ref)	-
Absent at 24 months	1.19 (0.74-1.89)	-	1.05 (0.66-1.66)	-	1.04 (0.66-1.66)	0.93 (0.57-1.53)	1.06 (0.67-1.68)	-
Absent at 48 months	1.58 (1.12-2.23)	-	1.07 (0.74-1.54)	-	1.07 (0.74-1.54)	1.58 (1.11-2.24)	1.16 (0.82-1.65)	-
Always absent	1.46 (1.05-2.02)	-	0.87 (0.60-1.26)	-	0.87 (0.60-1.26)	1.09 (0.76-1.56)	1.27 (0.92-1.74)	-
Trajectories of maternal depressive symptoms (3 months to 11 years)	p = 0.001	p = 0.209	p = 0.221	p = 0.819	p = 0.042	p = 0.995	p < 0.001	p = 0.013
Low	1 (ref)	-	1 (ref)	-	1 (ref)	-	1 (ref)	1 (ref)
Moderate-low	1.28 (0.96-1.70)	-	1.19 (0.91-1.56)	-	1.19 (0.91-1.56)	-	1.65 (1.29-2.14)	1.61 (1.23-2.12)
Decreasing	1.76 (1.21-2.56)	-	1.36 (0.93-1.99)	-	1.36 (0.93-1.99)	-	1.93 (1.35-2.77)	1.52 (1.02-2.25)
Increasing	2.18 (1.49-3.20)	-	1.38 (0.92-2.06)	-	1.38 (0.92-2.06)	-	1.84 (1.25-2.70)	1.44 (0.95-2.20)
Chronic-high	1.45 (0.83-2.50)	-	1.62 (0.98-2.69)	-	1.62 (0.98-2.69)	-	2.22 (1.39-3.55)	1.69 (1.00-2.83)
Maltreatment (CTSPC score) (tertile)	p = 0.878	p = 0.964	p = 0.023	p = 0.051	p = 0.140	p = 0.517	p = 0.574	p = 0.753
3rd (highest)	1 (ref)	-	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	-
2nd	1.06 (0.81-1.38)	-	0.80 (0.61-1.05)	0.82 (0.62-1.08)	0.80 (0.61-1.05)	-	0.99 (0.77-1.27)	-
1st (lower)	1.07 (0.80-1.43)	-	1.19 (0.89-1.55)	1.16 (0.88-1.54)	1.18 (0.89-1.55)	-	1.15 (0.89-1.50)	-

Data presented as odds ratio (95%CI).
CTSPC = Parent-Child Conflict Tactics Scale.
* For attentional control, smoking during pregnancy (p = 0.738), low birth weight (p = 0.258), absence of father (p = 0.394), trajectories of maternal depression (p = 0.209), and maltreatment (p = 0.964) were excluded from the final model. For cognitive flexibility, household income (p = 0.247), maternal age at birth (p = 0.218), self-reported maternal skin color (p = 0.430), parity (p = 0.287), smoking during pregnancy (p = 0.264), child's sex (p = 0.689), mother living with partner (p = 0.608), low birth weight (p = 0.516), number of siblings (p = 0.358), trajectories of maternal depression symptoms (p = 0.819), and absence of father (p = 0.717) were excluded from the final model. For selective attention, income (p = 0.241), mother living with partner (p = 0.699), smoking during pregnancy (p = 0.471), preterm birth (p = 0.249), number of siblings (p = 0.294), trajectories of maternal depression symptoms (p = 0.995), breastfeeding duration (p = 0.618), and maltreatment (p = 0.517) were excluded from the final model. For working memory, maternal age at birth (p = 0.338), parity (p = 0.251), mother living with partner (p = 0.684), preterm birth (p = 0.597), absence of father (p = 0.986), and maltreatment (p = 0.753) were excluded from the final model.

as emphasized by a recent review.[46] In addition to the scarcity of studies in this field, breastfeeding duration is a complex behavior that is influenced by several factors, including the duration and exclusivity of breastfeeding pattern, maternal health, and other infant feeding practices, such as age at introduction of complementary feeding. These factors may vary across studies, leading to inconsistent results. Lastly, the long-term effects of breastfeeding on EF and cognitive development are not fully understood, and further research is needed to investigate the underlying physiological and behavioral mechanisms that may explain the observed associations.

Our study highlights the association between several perinatal, maternal, and environmental characteristics and impaired executive functioning in late childhood and adolescence. This multifaceted nature suggests that impaired EF results from the convergence of multiple environmental influences, rather than single exposures. One plausible mechanism for these impairments is toxic stress, a manifestation of chronic, uncontrollable exposure to stressors. When experienced without the support of caring adults, these stressors tend to trigger toxic stress responses in children.[47] Children exposed to prolonged adverse poverty and a buildup of unfavorable conditions (such as maternal depression, overcrowding, substandard housing, and family turbulence) often display elevated stress hormone levels.[48] Children with toxic stress exhibit higher cortisol levels, which could potentially mediate the link between these environmental factors and EF impairment. Toxic stress impacts brain architecture, particularly in regions rich in glucocorticoid receptors such as the amygdala, hippocampus, and prefrontal cortex. This leads to discernible differences in learning, memory, and EFs.[49] Caregivers, whether parents or providers, play a critical role in modulating stress hormone production during a child's formative years. Their empathetic and attentive support acts as a protective barrier against exposure to stress hormones. These practices hold special significance for vulnerable children by preventing activation of the stress system. Inappropriate parenting practices could potentially mediate the connection between risk factors and EF impairments.

When considering future public policies that could improve the development of EFs in children, particularly those exposed to negative events or insecure environments in LMICs, it becomes imperative to underscore the role of positive influences in their early life experiences. A recent meta-analysis of 102 randomized controlled trials demonstrated the impact of parenting interventions in this context, revealing more pronounced effects on child cognitive development in LMICs when compared to HICs.[50] Notably, this meta-analysis highlighted the effectiveness of interventions that prioritize parental sensitivity and responsiveness, and showed that their impact on cognitive development was three times greater in LMICs. Interventions which included parenting practices, child cognitive development, parental knowledge, and parent-child interactions were more effective than interventions lacking such content. This suggests that fostering a supportive and nurturing caregiving environment through targeted interventions can play an important role in mitigating the impact of negative events or insecure surroundings on children's EF development in LMICs.

The present study broadens our understanding of the risk factors associated with impaired EFs in adolescence. The data used were obtained from a large, unselected Brazilian population and acquired through the use of standardized instruments applied by trained field workers. However, it is important to consider some limitations. Disruption of the 15-year follow-up by the COVID-19 pandemic resulted in the loss of approximately 50% of the original cohort. Analysis of these losses to follow-up revealed that participants evaluated at age 15 had more favorable socioeconomic conditions in relation to the original (perinatal) sample. Thus, our analyses may be subjected to selection bias. If the sample had not suffered losses, the association found between maternal education and EF impairment might have been even stronger than that found in the present study. Finally, regarding the generalizability of our findings, it is important to note that our sample has particular demographic characteristics which should be considered when extending our results to other populations from different LMICs.

This study examined risk and protective factors related to impaired EFs in adolescence. The findings highlighted several significant predictors, with low maternal education showing the most detrimental effect on attention-related EFs at age 11 and spatial working memory at age 15. Perinatal exposures associated with maternal and birth characteristics, such as maternal black or brown skin color, low birth weight, and prematurity, were also identified as relevant risk factors. On the other hand, breastfeeding emerged as a protective factor for cognitive flexibility. These results provide evidence regarding the long-term impact of perinatal exposures on the development of EFs and can inform future public policies aiming to mitigate the negative effects of risk factors and enhance EF development, particularly among vulnerable populations.

Acknowledgements

This work was supported by Associação Brasileira de Saúde Coletiva (ABRASCO), Pastoral da Criança, the World Health Organization (WHO; grant 03014HNI), Programa de Apoio aos Núcleos de Excelência (PRONEX; grant 04/0882.7), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; filing 481012-2009-5, 484077-2010-4, 470965-2010-0, 481141-2007-3, 426024/2016-8), the Brazilian Ministry of Health (grant 25000.105293/2004-83), and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP; grant 2014/13864-6, 2020/07730-8). JSR is supported by FAPESP (grant 2020/13425-3, 2023/05522-9). AM received support from Fundación Carolina and Grupo Tordesillas (Call C. 2021, Tordesillas Group universities professorship mobility program). AM, LT-R, TNM, and ISS are CNPq research productivity fellows.

Disclosure

The authors report no conflicts of interest.

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Supplementary material

Risk factors for executive function impairment in adolescence: 2004 Pelotas Birth Cohort study, by Rodrigues et al.

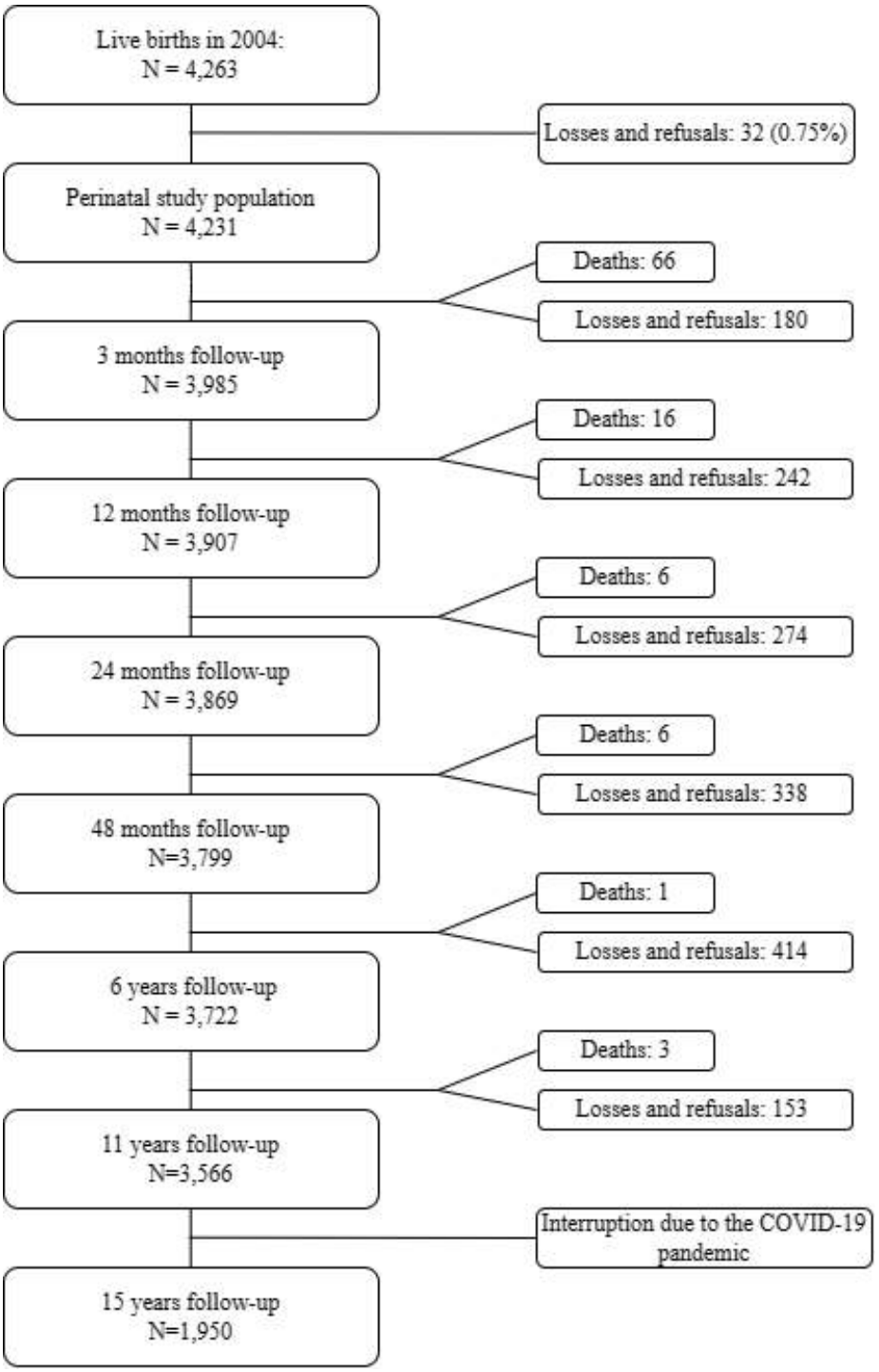

Figure S1: Flowchart illustrating the participation of subjects in the 2004 Pelotas Birth Cohort Study

Table S1: Description of executive functions tasks

Instrument	Executive function assessed	Task description and scoring
Test-of-Everyday-Attention-for-Children (TEA-Ch)	Attentional control	The child was shown to a row of 24 elements, which were composed by the numbers "1" and "2". At first, the child was instructed to read the numbers as quickly as possible while the instructor kept his finger close to each number in the row until the child read it correctly. This task was named "*Same World"*. In a second moment, the child was instructed to read the row of numbers as quickly as possible, but this time saying "one" when the number seen was "2" and saying "two" when the number seen was "1" This task was called *"Opposite World"* The average time required to complete the "*Opposite World*" task was defined as the measure of attentional control outcome. Higher reaction times indicate more impaired ability (considering verbal processing speed).
(TEA-Ch)	Cognitive flexibility	The cognitive flexibility assessment instrument was the latency time on a double attention task of the *Sky-Search subtest*. Initially, the child was instructed to select matching pairs of spacecrafts from matching and non-matching crafts contained in the test sheet. Then the same task was repeated with the addition of another task: the child was also asked to count the number of noises (beats) emitted by a recording while performing the task. The difference in speed and accuracy when completing the task with and without the addition of noises was taken as an indication of switching. A higher score indicates more impaired dual attention.
(TEA-Ch)	Selective attention	This ability was assessed by the latency time on the *"Sky-Search task"*. Initially, the child was instructed to select pairs of spacecrafts from matching and non-matching spacecrafts. On the test sheet, 50% of the spacecraft pairs were matched. The total time in seconds to perform the task (circle all pairs of spacecrafts) and the number of hits (corresponding pairs of crafts) were recorded. At another time, the child was instructed to perform the same procedure on a workout sheet that contained only matching pairs. The total time to perform this task and the number of correct answers were recorded. For each participant, motor-processing reaction time was subtracted from the ability score to provide the final measure of selective attention. The higher the score, the more impaired the child´s selective attention.
Cambridge Neuropsychological Testing Automated Battery (CANTAB)	Spatial working memory	During the test, the child was presented with a series of colored squares displayed on a tablet screen. The goal was to locate a yellow 'token' within each box by systematically selecting and eliminating boxes. With each round, an empty column on the right side of the screen would be filled, increasing the difficulty level. The number of boxes gradually increased, with a maximum of 12 boxes for participants to search through. To discourage the use of repetitive strategies, the color and position of the boxes were changed with each attempt. The total number of errors was used as an indicator of spatial working memory. Higher scores reflected greater impairment in spatial working memory.

Table S2: Frequency of participants characteristics at 11 and 15 years follow-ups

	Follow-ups	
Variables	**11 years (N=3582)**	**15 years (N=1950)**
	N (%)	N (%)
Family income (quintiles)		
5th quintile (wealthiest)	693 (19.4)	362 (18.6)
4th quintile	754 (21.1)	432 (22.2)
3rd quintile	709 (19.9)	407 (20.9)
2nd quintile	716 (20.1)	383 (19.7)
1st quintile (poorest)	696 (19.5)	365 (18.7)
Maternal education (years)		
≥ 9	1542 (43.7)	868 (44.9)
5-8	1465 (41.5)	790 (40.8)
1-4	497 (14.1)	264 (13.6)
0	29 (0.8)	13 (0.7)
Maternal age at birth (years)		
20-34	2404 (67.4)	1296 (66.5)
< 20	669 (18.8)	350 (18.0)
≥ 35	493 (13.8)	303 (15.6)
Self-reported maternal skin color		
White	2197 (62.3)	1220 (63.4)
Black	584 (16.6)	316 (16.4)
Brown	711 (20.2)	375 (19.5)
Yellow/Indigenous	35 (1.00)	14 (0.7)
Parity		
1	1,407 (39.44)	744 (38.17)
2	958 (26.86)	546 (28.01)
≥ 3	1,202 (33.70)	659 (33.81)
Smoking during pregnancy		
No	2,616 (73.32)	1,440 (73.88)
Yes	952 (26.68)	509 (26.12)
Mother living with partner		
Yes	3013 (84.5)	1652 (84.8)
No	555 (15.6)	297 (15.3)
Child sex		
Male	1840 (51.6)	996 (51.1)
Female	1728 (48.4)	953 (48.9)
Preterm birth		
Não	3068 (86.1)	1689 (86.8)
Sim	495 (13.9)	257 (13.2)
Low birth weight		
No	3247 (91.0)	175 (91.1)
Yes	320 (9.0)	173 (8.9)
Breastfeeding duration (months)		
0 months	97 (2.73)	63 (3.25)
< 1 month	273 (7.69)	133 (6.85)
1 - 3 months	539 (15.17)	287 (14.79)
3 - 12 months	1,296 (36.49)	710 (36.58)
≥ 12 months	1,347 (37.92)	748 (38.54)
Number of siblings		
0	1,150 (33.61)	603 (32.52)
1	1,285 (37.55)	726 (39.16)
≥ 2	987 (28.84)	525 (28.32)
Father absence		

Never absent	2,099 (66.76)	1,220 (70.68)
Absent at 24 months	225 (7.16)	102 (5.91)
Absent at 48 months	370 (11.77)	179 (10.37)
Always absent	450 (14.31)	225 (13.04)
Trajectories of maternal depressive symptoms (3 months to 11 years)		
Low	1,136 (32.58)	593 (31.23)
Moderate low	1,475 (42.30)	831 (43.76)
Decreasing	387 (11.10)	206 (10.85)
Increasing	319 (9.15)	171 (9.00)
Chronic high	170 (4.88)	98 (5.16)
Maltreatment (CTSPC score)		
3rd tercile (highest)	1,221 (34.70)	616 (33.30)
2nd tercile	1,350 (38.36)	698 (37.73)
1st tercile (lower)	948 (26.94)	573 (28.97)
Attention control impairment		
No	3,108 (90.03)	1,666 (91.19)
Yes	344 (9.97)	161 (8.81)
Cognitive flexibility impairment		
No	3,072 (90.01)	1,625 (89.98)
Yes	341 (9.99)	181 (10.02)
Selective attention impairment		
No	3,053 (90.01)	1,641 (91.42)
Yes	339 (9.99)	154 (8.58)
Spatial working memory impairment		
No	1,344 (73.36)	1,403 (73.46)
Yes	488 (26.64)	50 (26.54)

Table S3: Logistic regression models for impairment in attentional control, cognitive flexibility and selective attention at age 11 and spatial working memory at age 15 in adolescents in the first income quintile.

Variables	Attentional control		Cognitive flexibility		Selective attention		Spatial working memory	
	Crude OR (CI95%)	Adjusted* OR (CI95%)	Crude OR (CI95%)	Adjusted* OR (CI95%)	Crude OR (CI95%)	Adjusted* OR (CI95%)	Crude OR (CI95%)	Adjusted* OR (CI95%)
Maternal education (years)	p=0.003	p=0.005	p=0.014	p=0.008	p=0.008	p=0.002	p=0.004	p=0.004
≥ 9	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
5-8	1.95 (0.78 – 4.86)	1.66 (0.65 – 4.26)	2.44 (1.28 – 4.62)	2.72 (1.38 – 5.38)	1.65 (0.68 – 4.01)	2.01 (0.78 – 5.18)	2.77 (1.46 – 5.24)	3.00 (1.53 – 5.86)
1-4	10.31 (2.54 – 41.75)	10.79 (2.57 – 45.33)	3.08 (0.64 – 14.66)	3.56 (0.71 – 17.76)	8.54 (2.14 – 34.12)	14.56 (3.25 – 65.21)	3.89 (0.63 – 23.98)	3.27 (0.49 – 21.83)
0	Empty	Empty	Empty	Empty	Empty	Empty	Empty	Empty
Maternal age at birth (years)	p=0.525	p=0.476	p=0.056	p=0.851	p=0.102	p=0.076	p=0.739	p=0.803
20-34	1 (ref)	-	1 (ref)	-	1 (ref)	1 (ref)	1 (ref)	-
< 20	1.19 (0.34 – 4.13)	-	2.54 (1.15 – 5.64)	-	0.29 (0.04 – 2.17)	0.15 (0.02 – 1.26)	1.43 (0.54 – 3.75)	-
≥ 35	0.51 (0.15 – 1.76)	-	0.92 (0.41 – 2.04)	-	0.26 (0.06 – 1.11)	0.31 (0.07 – 1.38)	1.15 (0.60 – 2.20)	-
Self-reported maternal skin color	p=0.073	p=0.097	p=0.030	p=0.091	p=0.018	p=0.040	p=0.808	p=0.687
White	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	-
Black	1.83 (0.52 – 6.44)	1.93 (0.54 – 6.98)	2.86 (1.24 – 6.58)	2.51 (1.07 – 5.90)	3.92 (1.48 – 10.36)	3.74 (1.35 – 10.37)	1.20 (0.46 – 3.10)	-
Brown	1.61 (0.53 – 4.91)	1.30 (0.40 – 4.21)	1.79 (0.79 – 4.04)	1.47 (0.64 – 3.41)	1.91 (0.69 – 5.29)	1.34 (0.42 – 4.28)	0.67 (0.25 – 1.79)	-
Yellow/Indigenous	8.19 (1.59 – 42.23)	7.95 (1.48 – 42.64)	Empty	Empty	Empty	Empty	1.47 (0.15 – 14.37)	-
Parity	p=0.291	p=0.469	p=0.349	p=0.400	p=0.726	p=0.807	p=0.502	p=0.297
1	1 (ref)	-	1 (ref)	-	1 (ref)	-	1 (ref)	-
2	0.60 (0.21 – 1.70)	-	0.65 (0.65 – 1.17)	-	1.31 (0.56 – 3.10)	-	0.69 (0.36 – 1.31)	-
≥ 3	1.45 (0.61 – 3.48)	-	0.64 (0.30 – 1.40)	-	1.40 (0.56 – 3.50)	-	0.96 (0.49 – 1.88)	-
Smoking during pregnancy	p=0.638	p=0.222	p=0.408	p=0.117	p=0.681	p=0.308	p=0.197	p=0.486
No	1 (ref)	-	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	-
Yes	0.75 (0.22 – 2.53)	-	0.67 (0.26 – 1.73)	0.45 (0.16 – 1.22)	1.22 (0.46 – 3.30)	-	1.60 (0.78 – 3.29)	-
Mother living with partner	p=0.492	p=0.774	p=0.193	p=0.805	p=0.910	p=0.977	p=0.974	p=0.495
Yes	1 (ref)	-	1 (ref)	-	1 (ref)	-	1 (ref)	-
No	1.47 (0.49 – 4.36)	-	1.70 (0.76 – 3.79)	-	0.93 (0.28 – 3.15)	-	0.88 (0.35 – 2.22)	-
Child sex	p=0.903	p= 0.981	p=0.745	p= 0.602	p=0.121	p=0.103	p=0.004	p=0.011
Female	1 (ref)	-	1 (ref)	-	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Male	0.95 (0.44 – 2.06)	-	1.10 (0.61 – 1.98)	-	1.85 (0.85 – 4.01)	1.97 (0.87 – 4.44)	0.45 (0.26 – 0.78)	0.47 (0.27 – 0.84)
Preterm birth	p=0.258	p=0.419	p=0.286	p=0.285	p=0.625	p=0.463	p=0.329	p=0.583

Não	1 (ref)	-	1 (ref)	-	1 (ref)	-	1 (ref)	-
Sim	0.31 (0.04 – 2.34)	-	0.52 (0.16 - 1.72)	-	1.31 (0.44 – 3.87)	-	1.47 (0.68 – 3.16)	-
Low birth weight	p=0.470	empty	p=0.365	p=0.724	p=0.408	p=0.304	p=0.796	p=0.911
No	1 (ref)	-	1 (ref)	-	1 (ref)	-	1 (ref)	-
Yes	0.48 (0.06 – 3.58)	-	0.51 (0.12 – 2.18)	-	0.43 (0.06 – 3.20)	-	1.13 (0.44 - 2.89)	-
Breastfeeding duration (months)	p=0.197	p=0.546	p=0.860	p=0.673	p=0.840	p=0.834	p=0.791	p=0.619
0 months	1 (ref)	-	1 (ref)	-	1 (ref)	-	1 (ref)	-
< 1 month	2.30 (0.74 – 7.16)	-	0.38 (0.06 – 2.48)	-	0.82 (0.08 – 8.54)	-	1.18 (0.18 – 7.43)	-
1 - 3 months	1.32 (0.43 – 4.06)	-	0.63 (0.12 – 3.28)	-	0.99 (0.11 – 8.84)	-	0.90 (0.16 – 4.98)	-
3 - 12 months	0.66 (0.25 – 1.75)	-	0.50 (0.11 – 2.37)	-	0.57 (0.07 – 4.75)	-	0.73 (0.15 – 3.66)	-
≥ 12 months	Empty	-	0.52 (0.11 – 2.51)	-	0.61 (0.07 – 5.20)	-	1.06 (0.21 – 5.30)	-
Number of siblings	p=0.093	p=0.326	p=0.619	p=0.624	p=0.409	p=0.315	p=0.184	p=0.335
0	1 (ref)	-	1 (ref)	-	1 (ref)	-	1 (ref)	-
1	0.63 (0.25 – 1.59)	-	1.28 (0.66 – 2.48)	-	1.79 (0.75 – 4.26)	-	1.31 (0.70 – 2.42)	-
≥ 2	1.91 (0.75 – 4.92)	-	1.49 (0.63 – 3.49)	-	1.65 (0.53 – 5.17)	-	2.08 (0.95 – 4.54)	-
Father absence	p=0.932	p=0.732	p=0.413	p=0.145	p=0.853	p=0.783	p=0.754	p=0.644
Never absent	1 (ref)	-	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	-
Absent at 24 months	0.89 (0.11 – 6.93)	-	0.72 (0.17 – 3.11)	0.56 (0.12 – 2.61)	1.54 (0.34 – 6.90)	-	0.93 (0.19 – 4.42)	-
Absent at 48 months	1.31 (0.29 – 5.85)	-	0.51 (0.12 – 2.17)	0.17 (0.02 – 1.34)	1.12 (0.25 – 4.94)	-	0.44 (0.10 – 1.95)	-
Always absent	Empty	-	0.24 (0.03 – 1.76)	0.20 (0.03 – 1.55)	0.52 (0.07 – 3.96)	-	1.04 (0.33 – 3.25)	-
Trajectories of maternal depressive symptoms (3 months to 11 years)	p=0.004	p=0.014	p=0.721	p=0.937	p=0.891	p=0.651	p=0.122	p=0.699
Low	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	-	1 (ref)	-
Moderate low	3.71 (1.20 – 11.54)	3.38 (1.06 – 10.76)	1.38 (0.72 – 2.63)	-	1.33 (0.57 – 3.14)	-	1.42 (0.76 - 2.65)	-
Decreasing	5.27 (1.14 – 24.39)	3.71 (0.75 – 18.47)	1.99 (0.70 – 5.67)	-	1.40 (0.29 – 6.60)	-	3.48 (1.31 – 9.21)	-

Increasing	12.86 (3.26 – 50.64)	11.19 (2.62 – 47.90)	1.51 (0.42 – 5.43)	-	1.86 (0.38 – 8.89)	-	1.43 (0.44 – 4.64)	-
Chronic high	Empty	Empty	1.16 (0.14 – 9.39)	-	1.15 (0.26 – 18.05)	-	2.61 (1.63 – 10.82)	-
Maltreatment (CTSPC score)	p=0.294	p=0.658	p=0.349	p=0.113	p=0.559	p=0.725	p=0.063	p=0.301
3rd tercile (highest)	1 (ref)	-	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	-
2nd tercile	2.08 (0.82 – 5.24)	-	0.65 (0.32 – 1.31)	0.67 (0.31 – 1.45)	1.13 (0.47 – 2.71)	-	1.19 (0.62 – 2.29)	-
1st tercile (lower)	1.76 (0.58 – 5.35)	-	0.64 (0.30 – 1.40)	1.61 (0.73 – 3.53)	1.67 (0.64 – 4.33)	-	2.25 (1.11 – 4.58)	-

***** For attentional control: smoking during pregnancy (p=0.222), mother living with partner (p=0.774), child sex (p=0.981), parity (p=0.469) and maternal age at birth (p=0.476), preterm birth (p=0.419), breastfeeding duration (p=0.546), number of siblings (p=0.326), father absence (p=0.732), maltreatment (p=0.658) were excluded from the final model. For cognitive flexibility: mother living with partner (p=0.389), child sex (0.602), maternal age at birth (p=0.851), parity (p=0.400), mother living with partner (p=0.805), preterm birth (p=0.285), low birth weight (p=0.724), breastfeeding duration (p=0.673), number of siblings (p=0.624) and trajectories of maternal depression symptoms (p=0.937) were excluded from the final model. For selective attention: mother living with partner (p=0.977), parity (p=0.807), smoking during pregnancy (p=0.308), preterm birth (p=0.463), low birth weight (p=0.304), breastfeeding duration (p=0.834), number of siblings (p=0.315), father absence (p=0.783), trajectories of maternal depression symptoms (p=0.651), maltreatment (p=0.725) were excluded from the final model. For working memory: maternal age at birth (p=0.803), mother living with partner (p=0.495), smoking during pregnancy (p=0.486), selreported maternal skin color (p=0.687), preterm birth (p=0.583), low birth weight (p=0.911), breastfeeding (p=0.619), number of siblings (p=0.335), father absence (p=0.644), trajectories of maternal depression symptoms (p=0.699), maltreatment (p=0.301) were excluded from the final model.

Table S4: Logistic regression models for impairment in attentional control, cognitive flexibility and selective attention at age 11 and spatial working memory at age 15 in adolescents in the second, third, fourth and fifth income quintiles.

Variables	Attentional control		Cognitive flexibility		Selective attention		Spatial working memory	
	Crude OR (CI95%)	Adjusted* OR (CI95%)	Crude OR (CI95%)	Adjusted* OR (CI95%)	Crude OR (CI95%)	Adjusted* OR (CI95%)	Crude OR (CI95%)	Adjusted* OR (CI95%)
Maternal education (years)	p<0.001	p<0.001	p=0.008	p=0.001	p<0.001	p<0.001	p<0.001	p<0.001
≥ 9	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
5-8	2.23 (1.62 – 3.07)	1.66 (1.18 – 2.33)	1.90 (1.27 -2.84)	1.61 (1.21 – 2.16)	1.77 (1.15 – 2.73)	1.63 (1.18 – 2.25)	1.65 (1.28 – 2.14)	1.46 (1.16 – 1.91)
1-4	4.69 (3.31 – 6.65)	3.26 (2.23 – 4.77)	2.10 (1.28 – 3.45)	1.89 (1.33 – 2.70)	2.50 (1.50 – 4.18)	2.64 (1.81 – 3.85)	2.37 (1.72 – 3.28)	2.29 (1.63 – 3.21)
0	6.17 (2.49 – 15.29)	4.48 (1.66 – 12.06)	1.68 (0.20 – 13.79)	2.42 (0.81 – 7.28)	12.58 (3.23 – 49.07)	7.09 (2.84 – 17.67)	6.61 (1.90 – 22.95)	5.02 (1.43 – 17.65)
Maternal age at birth (years)	p=0.111	p=0.001	p=0.199	p=0.350	p=0.883	p=0.058	p=0.180	p=0.194
20-34	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	1 (ref)	1 (ref)	1 (ref)
< 20	1.30 (0.99 – 1.71)	1.73 (1.21 – 2.47)	1.44 (0.97 – 2.14)	-	0.95 (0.61 - 1.50)	1.06 (0.74 – 1.52)	1.18 (0.90 – 1.55)	1.09 (0.81 – 1.45)
≥ 35	0.89 (0.61 – 1.31)	0.67 (0.45 – 1.01)	1.08 (0.66 – 1.76)	-	0.88 (0.52 – 1.49)	0.60 (0.40 – 0.92)	0.82 (0.59 – 1.15)	0.76 (0.53 – 1.07)
Self-reported maternal skin color	p<0.001	p<0.001	p=0.982	p=0.629	p<0.001	p<0.001	p<0.001	p=0.009
White	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Black	2.58 (1.93 – 3.45)	2.23 (1.65 – 3.02)	1.05 (0.67 – 1.64)	-	2.46 (1.60 - 3.77)	2.33 (1.73 – 3.12)	1.87 (1.41 - 2.48)	1.65 (1.23 – 2.22)
Brown	2.02 (1.51 – 2.70)	1.74 (1.29 – 2.34)	1.09 (0.72 – 1.66)	-	1.50 (0.95 – 2.37)	1.41 (1.04 – 1.92)	1.35 (1.02 - 1.78)	1.23 (0.92 – 1.65)
Yellow/Indigenous	1.03 (0.24 – 4.41)	1.08 (0.25 – 4.69)	0.97 (0.12 – 7.76)	-	1.47 (0.18 – 11.83)	1.05 (0.24 – 4.56)	1.30 (0.33 – 5.07)	1.16 (0.29 – 4.60)
Parity	p<0.001	p<0.001	p=0.327	p=0.219	p=0.039	p=0.114	p=0.032	p=0.259
1	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	1 (ref)	1 (ref)	-
2	0.99 (0.72 – 1.35)	1.24 (0.85 – 1.81)	0.87 (0.56 – 1.35)	-	1.07 (0.67 – 1.73)	1.02 (0.72 – 1.46)	0.96 (0.72 – 1.28)	-
≥ 3	2.05 (1.59 – 2.66)	2.08 (1.43 – 3.02)	1.20 (0.82 – 1.77)	-	1.64 (1.08 – 2.48)	1.38 (0.97 – 1.96)	1.32 (1.03 – 1.72)	-
Smoking during pregnancy	p=0.026	p=0.889	p=0.337	p=0.564	p=0.337	p=0.553	p=0.001	p=0.059
No	1 (ref)	-	1 (ref)	-	1 (ref)	-	1 (ref)	1 (ref)
Yes	1.32 (1.03 – 1.69)	-	1.19 (0.83 – 1.71)	-	1.19 (0.83 – 1.71)	-	1.47 (1.16 - 1.87)	1.27 (0.99 – 1.64)
Mother living with partner	p=0.127	p=0.193	p=0.801	p=0.616	p=0.801	p=0.832	p=0.205	p=0.912
Yes	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	-	1 (ref)	-
No	1.26 (0.94 – 1.69)	1.24 (0.90 – 1.70)	1.06 (0.68 – 1.66)	-	1.06 (0.68 – 1.66)	-	1.21 (0.90 – 1.62)	-
Child sex	p=0.142	p=0.070	p=0.756	p=0.703	p=0.016	p=0.013	p<0.001	p<0.001
Female	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Male	1.19 (0.94 – 1.51)	1.26 (0.98 – 1.61)	1.04 (0.82 – 1.32)	-	1.34 (1.06 – 1.70)	1.37 (1.07 – 1.75)	0.56 (0.44 – 0.70)	0.55 (0.44 – 0.69)
Preterm birth	p<0.001	p=0.065	p=0.256	p=0.052	p=0.119	p=0.325	p=0.562	p=0.333
Não	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	-

Sim	1.76 (1.32 – 2.36)	1.40 (0.98 – 1.99)	1.30 (0.82 – 2.06)	1.37 (1.00 – 1.89)	1.45 (0.91 – 2.32)	-	1.10 (0.80 – 1.51)	-
Low birth weight	p=0.003	p=0.135	p=0.496	p=0.633	p<0.001	p<0.001	p=0.030	p=0.112
No	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Yes	1.70 (1.20 – 2.42)	1.38 (0.90 – 2.12)	1.21 (0.70 – 2.10)	-	2.67 (1.65 – 4.31)	2.17 (1.52 – 3.09)	1.50 (1.04 - 2.17)	1.37 (0.93 – 2.01)
Breastfeeding duration (months)	p=0.024	p=0.146	p<0.001	p=0.002	p=0.308	p=0.654	p=0.030	p=0.051
0 months	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	1 (ref)
< 1 month	0.71 (0.32 – 1.54)	0.86 (0.37 – 1.97)	0.27 (0.10 – 0.69)	0.34 (0.16 – 0.71)	0.35 (0.12 – 1.03)	-	1.16 (0.55 – 2.44)	1.39 (0.64 – 3.04)
1 - 3 months	1.11 (0.55 – 2.22)	1.31 (0.63 – 2.73)	0.50 (0.24 – 1.07)	0.57 (0.31 – 1.06)	0.55 (0.23 – 1.33)	-	1.39 (0.70 – 2.73)	1.44 (0.71 – 2.95)
3 - 12 months	0.65 (0.33 – 1.28)	0.83 (0.41 – 1.69)	0.28 (0.14 – 0.58)	0.39 (0.22 – 0.71)	0.50 (0.22 – 1.13)	-	0.93 (0.49 – 1.79)	1.03 (0.52 – 2.05)
≥ 12 months	0.72 (0.37 – 1.40)	0.91 (0.45 – 1.85)	0.27 (0.13 – 0.56)	0.37 (0.20 – 0.66)	0.45 (0.20 – 1.01)	-	0.83 (0.43 – 1.58)	0.89 (0.45 – 1.76)
Number of siblings	p<0.001	p=0.022	p=0.100	p=0.370	p=0.141	p=0.233	p<0.001	p=0.257
0	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	-	1 (ref)	-
1	1.11 (0.79 – 1.55)	1.12 (0.77 – 1.63)	1.14 (0.74 – 1.75)	-	1.41 (0.89 – 2.23)	-	1.12 (0.84 - 1.49)	-
≥ 2	2.41 (1.78 – 3.26)	1.65 (1.11 – 2.46)	1.55 (1.01 – 2.38)	-	1.59 (1.00 – 2.54)	-	1.67 (1.25 – 2.21)	-
Father absence	p=0.092	p=0.356	p=0.324	p=0.902	p=0.042	p=0.072	p=0.588	p=0.873
Never absent	1 (ref)	-	1 (ref)	-	1 (ref)	1 (ref)	1 (ref)	-
Absent at 24 months	1.12 (0.69 – 1.81)	-	0.50 (0.20 – 1.26)	-	1.04 (0.46 - 2.34)	0.93 (0.55 - 1.57)	1.02 (0.63 – 1.66)	-
Absent at 48 months	1.46 (1.02 – 2.08)	-	1.04 (0.60 – 1.79)	-	1.96 (1.17 – 3.28)	1.61 (1.12 – 2.31)	1.20 (0.83 – 1.74)	-
Always absent	1.38 (0.99 – 1.93)	-	0.71 (0.40 – 1.25)	-	1.57 (0.95 – 2.62)	1.10 (0.76 - 1.60)	1.21 (0.87 – 1.69)	-
Trajectories of maternal depressive symptoms (3 months to 11 years)	p=0.092	p=0.423	p=0.303	p=0.928	p=0.186	p=0.983	p=0.005	p=0.203
Low	1 (ref)	-	1 (ref)	-	1 (ref)	-	1 (ref)	-
Moderate low	1.08 (0.80 – 1.45)	-	0.93 (0.62 – 1.41)	-	1.25 (0.79 – 2.00)	-	1.59 (1.19 - 2.11)	-
Decreasing	1.41 (0.96 – 2.09)	-	1.11 (0.62 – 1.97)	-	1.94 (1.08 – 3.49)	-	1.66 (1.12 - 2.45)	-
Increasing	1.64 (1.10 – 2.45)	-	1.45 (0.81 – 2.60)	-	1.72 (0.90 – 3.28)	-	1.75 (1.16 - 2.65)	-
Chronic high	1.20 (0.69 – 2.10)	-	1.69 (0.84 – 3.38)	-	1.13 (0.45 – 2.82)	-	2.00 (1.21 – 3.31)	-
Maltreatment (CTSPC score)	p=0.949	p=0.954	p=0.879	p=0.152	p=0.907	p=0.680	p=0.924	p=0.695

3rd tercile (highest)	1 (ref)	-	1 (ref)	1 (ref)	1 (ref)	-	1 (ref)	-
2nd tercile	0.97 (0.73 – 1.28)	-	1.11 (0.74 – 1.67)	0.74 (0.53 – 1.03)	1.10 (0.71 – 1.70)	-	0.95 (0.72 – 1.25)	-
1st tercile (lower)	0.95 (0.71 – 1.29)	-	1.05 (0.69 – 1.62)	0.97 (0.69 – 1.36)	1.08 (0.69 – 1.70)	-	1.00 (0.75 – 1.32)	-

* For attentional control: smoking during pregnancy (p=0.889), father absence (p=0.356), trajectories of maternal depression (p=0.423) and maltreatment (p=0.954) were excluded from the final model. For cognitive flexibility: mother living with partner (p=0.616), smoking during pregnancy (p=0.564), self-reported maternal skin color (p=0.629), parity (p=0.219), child sex (p=0.703), maternal age at birth (p=0.350), low birth weight (p=0.633), number of siblings (p=0.370), father absence (p=0.902), trajectories of maternal depression symptoms (p=0.928) were excluded from the final model. For selective attention: mother living with partner (p=0.832), smoking during pregnancy (p=0.553), preterm birth (p=0.325), breastfeeding duration (p=0.654), number of siblings (p=0.233), trajectories of maternal depression symptoms (p=0.983), maltreatment (p=0.680) were excluded from the final model. For working memory: parity (p=0.259), mother living with partner (p=0.912), preterm birth (p=0.333), number of siblings (p=0.257), father absence (p=0.873), trajectories of maternal depression symptoms (p=0.203), maltreatment (p=0.695) were excluded from the final model

Apêndice C. Artigo "*Examining pathways between trajectories of maternal depressive symptoms, harsh parenting, and adolescent executive functions: insights from the 2004 Pelotas Birth Cohort*."

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Submetido em: *Journal of Affective Disorders Reports*

Examining pathways between trajectories of maternal depressive symptoms, harsh parenting, and adolescent executive functions: insights from the 2004 Pelotas Birth Cohort

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Abstract

Background: Continuous exposure to maternal depressive symptoms during childhood has been consistently associated with lower executive functions in offspring. However, the pathways linking this association remain poorly examined, with limited research on long-term effects in adolescence and scarce evidence from low- and middle-income countries.

Objective: This study aim to investigate the effects of maternal depressive symptom trajectories on adolescents' executive functions, exploring the potential mediating role of negative parenting.

Methods: We utilized data from the 2004 Pelotas Birth Cohort, including 1,949 adolescents followed from birth to 15 years of age. Maternal depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale from 3 months to 11 years. Harsh parenting was measured using the Parent-Child Conflict Tactics Scale at 11 years. Executive functions (sustained attention, working and episodic memory) were evaluated at 15 years using the Cambridge Automated Neuropsychological Test Battery. Path analyses were conducted in MPlus software using structural equation modeling.

Results: Of the mothers assessed, 75% belonged to the “moderate-low” or “low” depressive symptom trajectories, while 10.8% to the “decreasing,” 9.0% to the “increasing,” and 5.2% to the “chronic-high” trajectories. Mothers with elevated depressive symptoms during childhood exhibited more harsh parenting behaviors (B(SE)=2.428(0.323), 95% CI [1.881;2.952]), which, in turn, were associated with poorer executive functions (sustained attention: B(SE)=-0.003(0.001), 95% CI [-0.004;-0.002]; episodic memory (B = 0.241; 95%CI [0.030; 0.452]). No direct association was observed between maternal depressive symptoms and executive functions. When considering harsh parenting as a mediator, it was found that adolescents whose mothers had elevated depressive symptoms throughout childhood exhibited poorer sustained attention (indirect effect: B(SE)=-0.007(0.002), 95% CI [-0.010;-0.004]) and poorer episodic memory (indirect effect: B(SE)=0.717(0.304), 95% CI [0.262;1.266]).

Conclusions: Severe and persistent maternal depressive symptoms are associated with a higher frequency of harsh parenting behaviors, which in turn affect adolescents' executive functions.

Keywords: Executive functions; Maternal depression; Harsh parenting; Adolescent; Path analysis; Cohort study.

Introduction

Postpartum depression is a psychological condition that can persist for several years after childbirth. It has emerged as a global public health issue that affects the health and well-being of mothers and their children. Globally, rates of maternal depression vary by country income level, with prevalence estimated at 17.2% (95% CI: 16.0–18.5) of women worldwide, and at 20.51% (95% CI: 18.53%–22.65%) in Brazil (Wang et al., 2021). Maternal depression among Brazilian women commonly occurs in the context of social and family risk factors involving lower socioeconomic position, non-white skin color, prior history of mental disorders, unplanned pregnancy, multiparity, and poor health care during birth (Faisal-Cury et al., 2021; Theme Filha et al., 2016).

Longitudinal studies have focused on how continued exposure to patterns of maternal depression affects offspring cognitive development, examining effects related to the severity, chronicity and timing of mothers' depressive symptoms (Ahmed et al., 2019; Campbell et al., 2007; Cents et al., 2013; Ku et al., 2024). Children whose mothers had severe and chronic depressive symptoms were found to have more emotional and behavior problems when compared to those whose mothers had persistently low symptomatology (Campbell et al., 2007; Flouri et al., 2017; Matijasevich et al., 2015). This relationship was maintained after controlling for sociodemographic variables and sex of the child (Cents et al., 2013; Maruyama et al., 2023).

Continuous exposure to maternal depressive symptoms also has been consistently associated with lower executive functions in children (Oh et al., 2020; Park et al., 2018; Rinne et al., 2022). Executive functions refers to a set of higher-order cognitive abilities necessary to self-regulation and control of goal-directed behavior (Zelazo, 2020). It is widely accepted that there are three core executive functions: inhibitory control, working memory and cognitive flexibility (Diamond, 2013). These functions play an important role in storing and recovering autobiographical memories and attention (A. V. Fisher, 2019; Ricker et al., 2018). They are responsible for regulate focus, filtering distractions, and facilitating the encoding of memories. Research suggests that executive functions begin to emerge early in infancy, with basic skills needed for executive functions emerging before three years of age, and more specific skills developing into early childhood (Best & Miller, 2010). Throughout childhood and adolescence, executive functions continue to improve (Zelazo, 2020). Persistent maternal depression during early childhood, regardless of severity, is linked to impaired executive functions in children such as planning, organization, attention, and self-regulation at ages 7, 8, and 9 years (Oh et al., 2020). Additionally, studies found that an increasing trend in mothers' depressive symptoms during early childhood is especially problematic for children's inhibitory control in middle childhood (Park et al., 2018; Rinne et al., 2022).

While previous studies support the detrimental effect of maternal depression on offspring executive functions, the pathways linking this association remain poorly examined (Power et al., 2021). The family stress model emphasizes the negative effect of parental stress on parent–child relationships and child development in economically disadvantaged households (Conger et al., 2010). In this model, parents in lower socioeconomic households experience more financial and social stressors, which lead to increased psychological stress and depression. Consequently, depressed mothers are more likely to adopt negative parenting strategies when managing conflicts with their children (Newland et al., 2013). In a review of previous research by Fay-

Stammbach et al. (2014), four dimensions of parenting were identified that may impact on the development of executive functions: parental scaffolding; parental stimulation; parental sensitivity; and parental behavioral control/discipline (including harsh parenting). Harsh parenting is characterized by high levels of control, involving demands on the child, and low levels of warmth, leading the child to feel less accepted (Chang et al., 2003). This includes behaviors such as anger, coercion, aggression, and unplanned harsh emotional reactions toward the child. Maternal negative control and power assertive strategies were related to lower offspring's metacognition and inhibitory self-control (Lucassen et al., 2015). Negative maternal-child interaction and intrusiveness, including negative control, negative affection, corporal punishment, and conflict, also had detrimental effects on children's executive function (Blair et al., 2011; Hughes & Devine, 2019).

Studies that have examined the continued effects of mothers' depressive symptoms and harsh parenting strategies on offspring executive functioning have mainly focused on outcomes in childhood (Fay-Stammbach et al., 2014; Power et al., 2021). Executive functions related to attentional and memory skills continue to mature throughout adolescence, as more complex skills develop that enable performance monitoring, feedback learning, and relational reasoning (Berthelsen et al., 2017; Crone & Dahl, 2012). The lack of research on the long-term effects of maternal depressive symptoms and harsh parenting on this important period of offspring development limits the understanding of their effect on executive functioning in adolescence.

Another aspect that requires deeper investigation is the association between maternal depressive symptoms and the executive functions of children from low- and middle-income countries (LMIC). Longitudinal studies have predominantly investigated this association in high-income countries (HICs) (Power et al., 2021). However, maternal depression and cognitive development challenges are more prevalent in low- and middle-income countries (LMICs) (Gelaye et al., 2016). This gap demands specific attention, especially given the significant differences in quality of life and socioeconomic circumstances experienced in LMICs (Silveira et al., 2019).

To address these gaps in the literature, this study sought to examine the effects of trajectories of maternal depressive symptoms on adolescent outcomes, using a Brazilian population-based birth cohort study. We focused on adolescents' sustained attention (the ability to maintain attentional focus on relevant stimuli with repeated presentations over extended periods), episodic memory (the ability to learn, store, and retrieve information about unique personal experiences that occur in daily life), and working memory (holding and updating information for current processing). The main objectives of the present study were: (i) to examine the effects of maternal depressive symptoms trajectories from 3 months to 11 years on the adolescent's executive functions at age 15 years in a LMIC context; (ii) to explore the mediating role of harsh parenting at age 11 years.

Methodology

Participants

The 2004 Pelotas Birth Cohort is a large population-based study of all live newborns from 1 January to 31 December 2004 to women living in the urban area of the city of Pelotas, Brazil. All hospitals with maternity wards were visited daily by research team members, and all live births (N=4263) were eligible for enrolment in the cohort. A total of 4231 newborns, 99.2% of all births in the city that year, were included in the study. Following an initial assessment at birth by an interdisciplinary research team, participants were evaluated at home at ages 3, 12, 24, and 48 months, with respective follow-up rates of 95.7%, 94.3%, 93.5%, and 92.0%. Participants underwent evaluations at ages 6, 11 and 15, with interviews conducted at the research clinic of the Epidemiologic Research Centre at Federal University of Pelotas. The 11-year follow-up occurred in 2015 and included 3566 participants (86.6% of the cohort). The 15-year follow-up, initiated in November 2019 had to be interrupted due to the COVID-19 pandemic. 1949 participants (48.5% of the cohort) were assessed at the research clinic before the onset of the pandemic. Both at the 11- and 15-year follow-ups, participants engaged in face-to-face interviews without maternal assistance. Further details on the 2004 Pelotas Birth Cohort methodology can be found elsewhere (I. S. Santos et al., 2011, 2014).

Measures

Main exposure: trajectories of maternal depressive symptoms

Maternal depressive symptoms were evaluated using the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987) at the offspring's ages of 3, 12, 24, and 48 months, as well as at 6 and 11 years. The EPDS was originally designed for identifying postpartum depression disorders in clinical and research settings. The EPDS is a self-report, 10-item scale (score range: 0–30, with higher scores indicating more severe depressive symptoms) that measures the intensity of depressive symptoms over the preceding seven days. We used a Brazilian version of the questionnaire, validated in a previous study (Santos et al., 2007).

Trajectories of maternal depression were constructed using a semiparametric, group-based modeling approach proposed by Nagin and Tremblay (1999). Details of the steps and methods used to identify the trajectories of maternal depressive symptoms were reported in previous studies (Azeredo et al., 2017; Matijasevich et al., 2015). Briefly, 90% of the cohort with data from at least three follow-ups was included in the analyses. Individuals with missing information were not excluded from the model due to the ability of group-based trajectory modeling to handle missing data using maximum likelihood estimation (Nagin, 2005). The number and shape of trajectories were based on the best fit of the model (maximum Bayesian information criteria, BIC) and on the interpretability of the trajectories obtained (Nagin, 2005). Posterior probability scores (i.e., the individual's probability of belonging to each of the trajectory groups) were used to select the appropriate model. According to Nagin (2005), an average probability score should be higher than 0.70 for all groups. In order to model trajectories of maternal EPDS scores, analyses were conducted specifying three-, four-, five-, and six-group models. BIC improved as more groups were added. Among the models considered, a five-group model emerged as the most suitable and parsimonious, characterized by average posterior probabilities ranging from 0.78 to 0.87 across Groups 1 to 5. Inspection of parameter estimates for the five-

group model revealed that three trajectories were best represented by a cubic term, one trajectory was linear, and another quadratic. Group 1, named “low,” and Group 2, named “moderate low,” represented mothers who had EPDS scores lower than 10 across all time points, suggesting low depressive symptomatology. Group 3, named “increasing,” represented women who showed a consistent increase in depressive symptoms during the study period. The fourth group, named “decreasing,” included mothers who had high EPDS scores in the first two years postpartum and a marked decrease afterward. Finally, the fifth group, named “high-chronic,” included women who consistently exhibited high EPDS scores throughout the study period.

In our current study, we adopt these predefined trajectories of maternal depressive symptoms as the primary exposure. These trajectories are summarized in a categorical dummy variable comprising five different categories, each representing a unique trajectory.

Outcomes: executive functions at age 15 years

Executive functions were evaluated through three subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Sahakian & Owen, 1992). The assessment took place during the 15-year follow-up by a trained team of psychologists at the research clinic. Participants engaged with the tests displayed on a tablet screen, and the sessions were supervised to ensure active participation in the tasks.

Sustained attention was assessed through the Rapid Visual Processing (RVP) subtest. A white box was shown in the center of the screen, inside which digits from 2 to 9 appeared in a pseudo-random order at a rate of 100 digits per minute. Participants were asked to detect target sequences of digits (for example, 2-4-6, 3-5-7, 4-6-8). When the participant saw a target sequence, they had to respond by selecting the button in the center of the screen as quickly as possible. The level of difficulty varied, with either one or three target sequences that the participant had to watch for simultaneously. The outcome was a continuous variable, ranging from 0.00 to 1.00, reflecting the subject's sensitivity in detecting target sequences (highest values indicating greater sensitivity).

Episodic memory was assessed through the Paired Associate Learning (PAL) subtest. Boxes were displayed on the screen and opened in a randomized order, with one or more containing a pattern. The patterns were then displayed in the middle of the screen, one at a time, and the participant had to select the box in which the pattern was originally located. If the participant made an error, the boxes were opened in sequence again to remind the participant of the locations of the patterns. Increased difficulty levels were used to test high-functioning, healthy individuals. The outcome was a continuous variable representing the frequency of incorrect box selections for patterns by the participants (higher values indicating poorer performance).

Working memory was assessed using the Spatial Working Memory (SWM) subtest. The test began with a number of colored squares (boxes) shown on the screen. The aim of the test was for the participant to find one yellow 'token' in each of the boxes by selecting them and using a process of elimination, then use the tokens to fill up an empty column on the right-hand side of the screen. Depending on the difficulty level used, the number of boxes gradually increased until a maximum of 12 boxes were shown for the participants to search. The color and position of the boxes were changed from trial to trial to discourage the use of stereotyped search

strategies. The outcome was a continuous variable indicating the frequency of revisits to boxes where a token had previously been found incorrectly (higher values indicating poorer performance).

For each outcome, mean, standard deviation, percentiles, and the range of measured values were computed. Variables from CANTAB were generated automatically by the system, The total time taken to complete the three subtests was calculated in minutes by subtracting the initial time from the final time at the end of the battery subtest.

Mediating variable: harsh parenting at age 11 years

Caregivers, predominantly mothers at age 11 (92.5%), were asked about harsh parenting strategies using the parent-to-child version of the Conflict Tactics Scale (CTSPC) (Straus et al., 1998). Cross-cultural adaptation and validation of the CTSPC for use in Brazil were conducted by Paiva and Figueiredo (2006) and Reichenheim and Moraes (2003). The CTSPC comprises 22 items categorized into five subscales measuring parental behaviors towards the child over the previous 12 months: non-violent discipline (4 items); psychological aggression (5 items); and physical assault, including corporal punishment (5 items), physical maltreatment (4 items), and severe physical maltreatment (4 items; not administered in this study). Consistent with two previous studies, harsh parenting was defined as the sum scores of the psychological aggression, corporal punishment, and physical maltreatment subscales (Pinquart, 2017a, 2017b). Each item was rated on a 5-point Likert scale. The CTSPC score was calculated by summing all the responses (score range: 0–28) with higher scores indicating more frequent episodes of harsh parenting. The outcome was used in its continuous form.

Potential confounding variables

Variables associated with trajectories of maternal depressive symptoms, harsh parenting, and child outcomes, which were not considered part of the causal pathway, were included in the regression models as confounders. Potential confounding factors comprised variables collected at the adolescent's birth, such as monthly family income (a continuous variable representing the total income in Reais in the month before delivery), maternal education (a continuous variable measured in years of formal education), self-reported maternal skin color (categorized as white, black, brown, yellow/indigenous), maternal age, and parity (defined as the number of previously born children and categorized as 1, 2, and ≥3). Smoking during pregnancy was retrospectively assessed at birth through maternal reporting. Regular smokers were identified as women who smoked at least one cigarette per day during any trimester of pregnancy. Information on the adolescent's sex (male or female) was obtained from birth medical records. Gestational age was estimated using the first day of the last normal menstrual period or by obstetric ultrasound before 20 weeks gestation if menstrual data were unreliable or unavailable. In the absence of both menstrual and ultrasound data, gestational age was assessed using the Dubowitz method (Dubowitz et al., 1970). Preterm birth was defined as gestation <37 weeks. Intrauterine growth was defined according to INTERGROWTH-21st parameters with low birth weight defined as <2500 grams (Villar et al., 2014).

Statistical analysis

Comparisons between socioeconomic, maternal and birth characteristics among the participants in the 15-year follow-up (N=1950) and the total number of participants at baseline (N=4231) were conducted using the chi-square test. Descriptive analysis was performed by calculating the absolute and relative frequencies of the variables included in the analysis. The mean and standard deviation of the outcomes according to maternal and adolescents' characteristics were analyzed using analysis of variance (ANOVA).

A series of separate backward stepwise linear regression models were conducted between exposure and mediator, mediator and outcomes, and exposure and outcomes. Then, each set of potential confounders was included for each pathway in the mediation analysis. Variables were retained in the linear regression model if their significance level was below 0.20 (Maldonado & Greenland, 1993).

Recent methodological advancements have underscored the potential for mediation effects even when the overall effect is not statistically significant (O'Rourke & MacKinnon, 2015; Rucker et al., 2011). It has been recommended that considering mediation in the context of a non-significant overall effect of the independent variable on an outcome can yield crucial insights that underscore the relevance of the analysis (Fairchild & McDaniel, 2017). This implies that significant mediation effects may be present regardless of the statistical significance of the total effect. Consequently, the mediation analysis was undertaken regardless of the presence of a total effect between trajectories of maternal depressive symptoms and executive functions.

Models of mediation analysis were constructed through path analysis for the three adolescent's executive functions: sustained attention, episodic and working memory (Figure 1) (MacKinnon et al., 2007). Given that the trajectories of maternal depressive symptoms encompass multiple categories, we employed a coding system using indicators to depict the distinct groups (Hayes & Preacher, 2014). For each model, it was quantified: the direct pathway between trajectories of maternal depressive symptoms and the correspondent executive function (path c'), the direct effect between trajectories of maternal depressive symptoms and harsh parenting (path a), the direct effect between harsh parenting and the correspondent executive function (path b), the indirect effect (i.e., the mediation effect) through harsh parenting (path a*b), and the total effect (path c). The total effect encompassed both the direct impact of each maternal depression trajectory on adolescents' outcomes and the indirect effect via harsh parenting. Initially, associations between trajectories of maternal depressive symptoms and adolescent executive functions were examined using multivariable linear regression models for each outcome (total effects). Subsequently, structural equation modeling (SEM) was used to examine the mediating role of harsh parenting in the relationship between maternal depressive symptoms trajectories and adolescent executive functions. All models were adjusted for previously identified potential confounders. The results are presented as both unstandardized and standardized coefficients. The unstandardized coefficient represents differences in outcome means in the outcome's respective unit. The standardized coefficient indicates the variations in outcome in terms of standard deviation units, facilitating the comparisons of the exposure effects on the different outcomes. The effect sizes of the indirect pathways are represented by the standardized coefficients in the structural equation modeling, along with their 95% bias-corrected bootstrap confidence intervals (partially standardized effect) (Preacher & Kelley, 2011). The standardized coefficient for the indirect effect can be interpreted as the change in the outcome in standard deviation units when moving from the "low" trajectory (the reference group) to the comparison trajectory (e.g.,

"moderated low", "decreasing", "increasing" or "high-chronic"), while holding other variables constant in the model. All statistical analyses were two-tailed, and significance was established at the 0.05 level. The "proportion explained" was calculated when indirect and total effects were statistically significant, representing the proportion of the total effect that was explained by the mediator (Ditlevsen et al., 2005). Descriptive statistics were performed using Stata version 14.2. Linear regression and path analysis were performed on Mplus version 8.1 with maximum likelihood estimator and bootstrapped standard errors.

Ethics

The Medical Ethics Committee of the Faculty of Medicine of the Federal University of Pelotas, affiliated with the Brazilian National Commission for Research Ethics, approved the study protocol of all follow-ups of the 2004 Pelotas Birth Cohort. At each stage of the study, all subjects' mothers or legal guardians gave written informed consent. In the 11- and 15-year follow-ups, the adolescents also gave written informed consent. Cases of severe maternal mental health problems, as identified by the psychologists, were evaluated and, when necessary, were referred to the psychiatric or psychological care facilities available in the city.

Results

Attrition analysis

Attrition analysis revealed that the participants included in this study displayed more advantageous socioeconomic indicators compared to the original sample (see Table 1). Additionally, the maternal age at birth was higher among the participants included in the analysis compared to the participants at birth. Regarding birth characteristics, the analyzed sample comprised fewer adolescents who were born preterm or with low birth weight compared to the perinatal sample. There were no differences in the self-reported maternal skin color and the sex of the adolescents between the analyzed and original samples.

Description of the sample characteristics

The sample analyzed was predominantly composed of adolescents with mothers who self-reported white skin color (63.4%), aged 20 to 34 years at the child's birth (66.5%), and had nine or more years of formal education (44.9%) (Table 1). Most of the mothers reported not smoking during pregnancy (74.9%). In terms of birth characteristics, 13.2% of the adolescents were born preterm, and 8.9% had low birth weight. Boys constituted 51.1% of the sample (Table 1). The majority (67.0%) of adolescents had at least one sibling. Regarding trajectories of maternal depressive symptoms, 75.0% (N=1424) of the mothers belonged to the low or moderate low trajectories of depressive symptoms. Additionally, decreasing and increasing trajectories included 10.9% (N=206) and 9.0% (N=171) of the mothers, respectively. High-chronic depressive symptoms trajectory included 5.2% of the mothers (N=98).

Results of bivariate analysis showed that family income, maternal schooling and non-white maternal skin color were associated with lower sustained attention, episodic memory, and working memory (Table S2). Smoking during pregnancy, higher parity and a greater number of siblings were associated with lower levels of all executive functions. Adolescents whose mothers belonged to the increasing or high-chronic depression trajectories presented the lowest levels of sustained attention, episodic memory, and working memory compared to those of mothers belonging to the other trajectories of depressive symptoms. Moreover, adolescents born with low birth weight and/or prematurely exhibited lower episodic and working memory. Finally, the results revealed sex differences, indicating that girls exhibited lower performance in sustained attention, episodic memory, and working memory compared to boys.

Executive functions

Sustained attention, episodic memory, and working memory showed strong positive correlations with each other ($r = 0.94$; $r = 0.94$; $r = 0.96$, respectively) (Table S3). The mean (SD) number of total errors in the Episodic memory subtest was 10.70 (11.20), with a range of 0 to 68. Sustained attention, assessed via rapid visual processing subtest, yielded a mean (SD) sensitivity of 0.82 (0.07), with a range of 0.28 to 0.98. Furthermore, the mean (SD) number of total errors in working memory, assessed through spatial working memory subtest, was 14.21 (8.18), with a range from 0 to 44.

Multiple regression models

Multiple regression models provided evidence that sustained attention, episodic and working memory were associated with trajectories of maternal depressive symptoms (Tables S05-S07). Specifically, adolescents

whose mothers belonged to the high-chronic trajectory of depressive symptoms exhibited poorer sustained attention, on average 0.036 less sensitivity (B = -0.036; 95% CI [-0.0518; -0.020]), worse episodic memory with an average of 2.889 more errors (B = 2.889; 95% CI [0.457; 5.319]), and poorer working memory with an average of 2.461 more errors (B = 2.461; 95% CI [0.688; 4.235]) compared to adolescents whose mothers belonged to the low trajectory of depressive symptoms. After adjusting for confounding variables, the association remained significant for sustained attention (B = -0.017; 95% CI [-0.033; -0.001]) but not for episodic (B = 0.522; 95% CI [-1.897; 3.390]) and working memory (B = 0.504; 95% CI [-1.309; 2.318]). The adjusted analyses showed that harsh parenting was associated with all trajectories of maternal depressive symptoms, and the magnitude of association was higher in the high-chronic trajectory (B = 2.431; 95%CI [1.893; 2.968]) (Table S6). Harsh parenting was associated with poor sustained attention (B = -0.003; 95%CI [-0.004; -0.002]) and episodic memory (B = 0.241; 95%CI [0.030; 0.452]). No association was found between harsh parenting and working memory (B= 0.103; 95%CI [-0.054; 0.261]).

Results of mediation analysis for adolescent's sustained attention

Figure 2 and Table2 present the results of the mediation analysis of harsh parenting on the association of maternal depressive symptoms trajectories and adolescents' sustained attention. Adolescents with mothers in the high-chronic depressive symptoms trajectory exhibited lower mean sustained attention sensitivity by 0.016 points compared to those with mothers in the low depressive symptoms' trajectory group (unstandardized coefficient of the total effects; Table 2). There was no evidence of a direct effect of maternal depressive symptoms trajectories on sustained attention. However, evidence from total and indirect effects indicates that this association was partially mediated by harsh parenting (indirect effect (a_3*b): B=-0.003; SE=0.001; 95%CI [-0.004; -0.001]; indirect effect (a_4*b): B=-0.007; SE=0.002; 95%CI [-0.010; -0.004]) in adolescents of mothers belonging to the increasing (proportion explained: 19% [18%; 45%]) and high-chronic trajectories (proportion explained: 42% [34%; 186%]) in comparison to the low trajectory of maternal depressive symptoms. Harsh parenting had a negative association with sustained attention (Path b: B=-0.003; SE=0.001; 95%CI [-0.004; -0.002]) (Figure 2).

In summary, our findings indicate that while maternal depressive symptom trajectories do not directly affect sustained attention in adolescents, we did observe a mediating effect of harsh parenting in this relationship, particularly in adolescents whose mothers belonged to the high-chronic trajectory of depressive symptoms.

Results of mediation analysis for adolescent's episodic memory

Figure 3 and Table 3 present the results of the mediation analysis of harsh parenting on the association of maternal depressive symptoms trajectories and adolescents' episodic memory. Adolescents with mothers in the high-chronic depressive symptoms trajectory displayed a higher number of total errors in episodic memory, with a difference of 0.252 points compared to those with mothers in the low depressive symptoms trajectory group (as indicated by the unstandardized coefficient of the total effects; Table 3). Our analyses did not reveal direct or total effects of maternal depressive symptoms trajectories on adolescent episodic memory. Indirect effects between all trajectories of maternal depressive symptoms and episodic memory were observed,

suggesting that this association was mediated by harsh parenting. The magnitude of the indirect effect was higher in increasing (indirect effect (a_3*b): B=0.288; SE=0.127; 95%CI [0.109; 0.532]) and high-chronic (indirect effect (a_4*b): B=0.717; SE=0.304; 95%CI [0.262; 1.266]) trajectories of maternal depressive symptoms. Harsh parenting was negatively associated with adolescent episodic memory (Path b: B=0.288; SE=0.113; 95%CI [0.099; 0.473]) (Figure 3).

As a synthesis, harsh parenting partially mediated the association between maternal depressive symptoms trajectories and adolescents' episodic memory, with higher mediating effects observed in the high-chronic depressive symptoms trajectory.

Results of mediation analysis for adolescent's working memory

No evidence of an indirect effect of trajectories of maternal depressive symptoms on episodic memory was found, indicating that this association was not mediated by harsh parenting (indirect effect (a_3*b): B=0.085; SE=0.090; 95%CI [-0.052; 0.248]; indirect effect (a_4*b): B=0.199; SE=0.206; 95%CI [-0.131; 0.544]) (Table S11). Total effects showed that adolescents whose mothers were in the increasing (B=1.277; SE=0.636; 95%CI [0.277; 2.322]) and moderated low (B=1.064; SE=0.419; 95%CI [0.353; 1.751]) trajectories of depressive symptoms presented worse working memory than adolescents whose mothers belonged to the low trajectory of depressive symptoms.

Bringing together the findings, our study did not find evidence that the effects of maternal depressive symptoms trajectories on working memory are mediated by harsh parenting. However, our results showed that adolescents whose mothers belonged to the moderated low and increasing trajectories of depressive symptoms exhibited poorer working memory compared to those of mothers in the low depressive symptoms trajectory.

Discussion

Utilizing data from the 2004 Pelotas Birth Cohort, a Brazilian birth cohort, this study examined the total and direct effects of maternal depressive symptom trajectories on offspring's sustained attention, episodic memory, working memory, and children's executive functions at age 15. Our study also evaluates the mediating effect by harsh parenting. Total effects were found between increasing and high-chronic trajectories of maternal depressive symptoms and adolescents' sustained attention. No direct effects were found between the trajectories of maternal depressive symptoms and adolescents' sustained attention, episodic memory and working memory. However, when examining the indirect effects, harsh parenting emerged as a mechanism by which the trajectories of maternal depressive symptoms negatively affect sustained attention and episodic memory. When considering harsh parenting as a mediator, adolescents with mothers in the "high-chronic" trajectory had the poorest outcomes in sustained attention and episodic memory. This was followed by adolescents whose mothers were in the "decreasing," "increasing," "moderately low," and "low" trajectories.

Our findings indicate that there is no direct effect between maternal depressive symptoms and adolescents' sustained attention, episodic memory, or working memory across all examined trajectories. Previous studies applying mediation analysis on different cohorts have similarly reported the absence of a direct association between maternal depressive symptoms and children's executive functions. For instance, Baker et al. (2018) found no direct association between maternal depressive symptoms at age 3 and children's executive function at age 4. One potential explanation for this finding is that executive functions are not fully developed by age 3, so the impact of maternal depressive symptoms may not yet be evident. Ku et al. (2021) conducted a study on 1,364 mother-child dyads, evaluating maternal depressive symptoms from 6 months postpartum to the child's age of 10 years and assessing child executive functions at age 10. They found no direct effect of maternal depressive symptoms on child executive functions. Instead, they identified maternal sensitivity at 54 months as a mechanism through which maternal depressive symptoms negatively impact executive functions in childhood. Our study builds upon these previous findings by demonstrating that this lack of direct effect continues into adolescence for offspring.

Even in the absence of a total effect, we conducted a mediation analysis to examine the potential mediated role of harsh parenting between maternal depressive symptom trajectories and adolescents' executive functions. This approach differs from the traditional Baron and Kenny method which established that the first requisite for conducting a mediation analysis is the existence of an effect of the independent variable on the dependent variable (Baron & Kenny, 1986). The Baron and Kenny method relies on a sequence of steps to establish mediation, focusing on checking if significant paths are met rather than directly testing for the presence of an indirect effect (Hayes, 2009). However, It's possible for some paths to not show significance even when mediation exists (e.g. the total path between the exposure and outcome) (Shrout & Bolger, 2002). Our study followed the contemporary approach to mediation analysis, which states that the only requirement for mediation is a significant indirect effect (Zhao et al., 2010). This contemporary approach is especially valuable for understanding complex psychological and behavioral relationships where total or direct effects may not always be evident, as shown in previous research (Baker, 2018; Ku & Feng, 2021).

Although trajectories of maternal depressive symptoms do not directly affect adolescents' executive functions, our analysis reveals that harsh parenting is a key mechanism through which these symptoms negatively impact on sustained attention and episodic memory. Our findings are consistent with a study of 1,292 families in rural, low-income communities in the United States (Gueron-Sela et al., 2018), which found that maternal depressive symptoms at both 15 and 24 months were not directly associated with executive functions at age 3. The mediating roles of harsh-intrusiveness, dyadic joint attention, and language were also examined, showing that only harsh-intrusive interactions partially mediated this association. This indirect effect observed might possibly be due to maternal depressive symptoms being associated with negative behaviors and emotions that hinder mothers' ability to meet their children's social and emotional needs (Gelaye et al., 2016a). When these needs go unmet for prolonged periods, it can lead to toxic stress, which has lasting effects on brain development and disrupts children's stress response systems (Saftic et al., 2021; Shonkoff et al., 2012). Harsh parenting strategies create rapidly shifting sources of arousal and stimulation, which interfere with a child's ability to practice effective control of attention and goal-directed behavior (Berthelon et al., 2020), both of which, are crucial for developing executive functions (Garon et al., 2008; Perone et al., 2018; Tovo-Rodrigues et al., 2024).

Moreover, our research findings indicate that the more severe and persistent the depressive symptoms experienced during childhood, the more frequent harsh parenting practices were observed at 11 years old. This in turn was linked to poorer sustained attention and episodic memory at 15 years old. This dose-response pattern suggests that the severity and duration of maternal depressive symptoms during childhood may have an accumulative effect on parenting behaviors, impacting cognitive development during adolescence. Previous longitudinal studies consistently demonstrate a dose-response relationship between prolonged exposure to maternal depressive symptoms and impaired executive functions in offspring (Oh et al., 2020; Park et al., 2018; Rinne et al., 2022). However, these studies were conducted in high-income countries, focusing only on maternal depression from pregnancy to age three and examining children's executive functions between ages three and seven, without accounting for potential underlying mechanisms. Our study extends these findings by identifying one significant mechanism while examining the long-term effects of enduring maternal depression on adolescents' executive functions throughout their entire childhood.

The present study has some limitations. The 15-year follow-up had to be interrupted due to the COVID-19 pandemic, resulting in a loss of nearly 50% from the original cohort. Participants assessed at 15 years had better socioeconomic conditions. Therefore, we cannot rule out attrition bias in our analyses. Given that higher socioeconomic status is associated to improved executive functions in offspring (Hackman et al., 2015), it's possible that our results were underestimated. Additionally, harsh parenting was based only on parent report and could be affected by social desirability bias. This could potentially skew the results towards a more positive perception of parenting practices.

Nevertheless, our findings have important implications on intervention strategies targeting children and adolescents of depressed mothers. The current findings build on prior research on maternal depression and offspring executive function by examining total, direct and indirect effects between these variables in a Brazilian population-based birth cohort study. Moreover, the prospective design of our study ensures temporal

order between exposure, mediator and outcome measurements, increasing the confidence on the inference of specific causal pathways. Additionally, maternal depressive symptoms were evaluated through developmental trajectories along the first 11 years of the child, which allowed us to describe the different patterns and progression of symptoms over time, and identifying the adolescents' most vulnerable groups. Finally, executive functions were assessed through standardized tests, avoiding information bias.

Conclusion

Mothers with high depressive symptoms during childhood exhibited more harsh parenting practices, which in turn were associated with poorer executive functions in adolescents at age 15. While we did not observe direct effects between maternal depressive symptom trajectories and adolescents' executive functions, our findings show that harsh parenting at age 11 serves as a key mechanism through which severe and persistent depressive symptoms impact sustained attention and episodic memory in adolescents. Our findings from a Brazilian birth cohort highlight the importance of parenting in mediating the link between continuous exposure to maternal depressive symptoms during childhood and impairments in adolescents' executive functions. These results emphasize the need for interventions that consider parental relationships when addressing children's cognitive development, aiming to mitigate adverse outcomes and promote child and adolescent well-being.

Acknowledgments

We thank all the cohort participants and their families who took part in the study, and the whole research team. The Pelotas 2004 Birth Cohort study is conducted by the Postgraduate Program in Epidemiology at Universidade Federal de Pelotas, with the collaboration of the Brazilian Public Health Association (ABRASCO). From 2009 to 2013, the 2004 Pelotas Birth Cohort was funded by the Wellcome Trust. Earlier phases of the study were funded by the World Health Organization [No. 03014HNI], the Program for the Support of Centers of Excellence (PRONEX) [grant 04/0882.7]; the National Council for Scientific and Technological Development (CNPq) [grants 481012-2009-5; 484077-2010-4; 470965-2010-0; 481141-2007-3; 426024/2016-8]; the Brazilian Ministry of Health [grant 25000.105293/2004-83]; the São Paulo Research Foundation (FAPESP) [grant 2014/13864-6]; and Pastoral da Criança. LTR, ISS, AJDB, and AM are Research Productivity Fellows of CNPq. JR is supported by FAPESP [grants #2020/12325-3, #2023/00522-9].

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Figure Captions

Figure 1. Schematic representation of a path model examining the mediating role of harsh parenting on the association between the trajectory of maternal depressive symptoms and sustained attention, episodic and working memory in adolescents. In the figure, path "a" represents the direct effect between trajectories of maternal depressive symptoms and harsh parenting; path "b" represents the direct effect between harsh parenting and the correspondent executive function; path "c'" represents the direct effect between trajectories of maternal depressive symptoms and the correspondent executive function.

Figure 2. Statistical model exploring the mediating role of harsh parenting on the association between the trajectory of maternal depressive symptoms and sustained attention in adolescents (**p<0.001; SE=Bias-corrected bootstrap standard Errors; B=unstandardized coefficients). In the figure, path "a" represents the direct effect between trajectories of maternal depressive symptoms and harsh parenting; path "b" represents the direct effect between harsh parenting and the correspondent executive function; path "c'" represents the direct effect between trajectories of maternal depressive symptoms and the correspondent executive function. Bold lines represent statistically significant pathways.

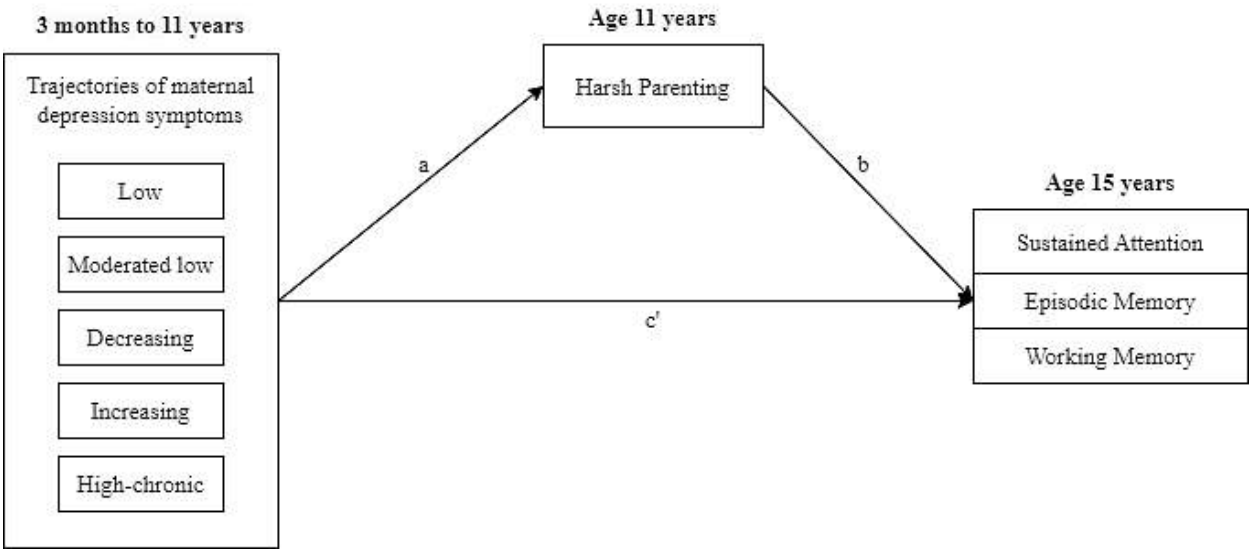
Figure 3. Statistical model exploring the mediating role of harsh parenting on the association between the trajectory of maternal depressive symptoms and episodic memory in adolescents ((*p<0.05; **p<0.001; SE=Bias-corrected bootstrap standard Errors; B=unstandardized coefficients). In the figure, path "a" represents the direct effect between trajectories of maternal depressive symptoms and harsh parenting; path "b" represents the direct effect between harsh parenting and the correspondent executive function; path "c'" represents the direct effect between trajectories of maternal depressive symptoms and the correspondent executive function. Bold lines represent statistically significant pathways.

Table Captions

Table 1. Maternal and adolescent characteristics of participants in the 15-year follow-up, compared to those from the perinatal period.

Table 2. Indirect, direct and total effects of maternal depressive symptoms trajectories on adolescent's sustained attention mediated by harsh parenting.

Table 3. Indirect, direct and total effects of maternal depressive symptoms trajectories on episodic memory mediated by harsh parenting.



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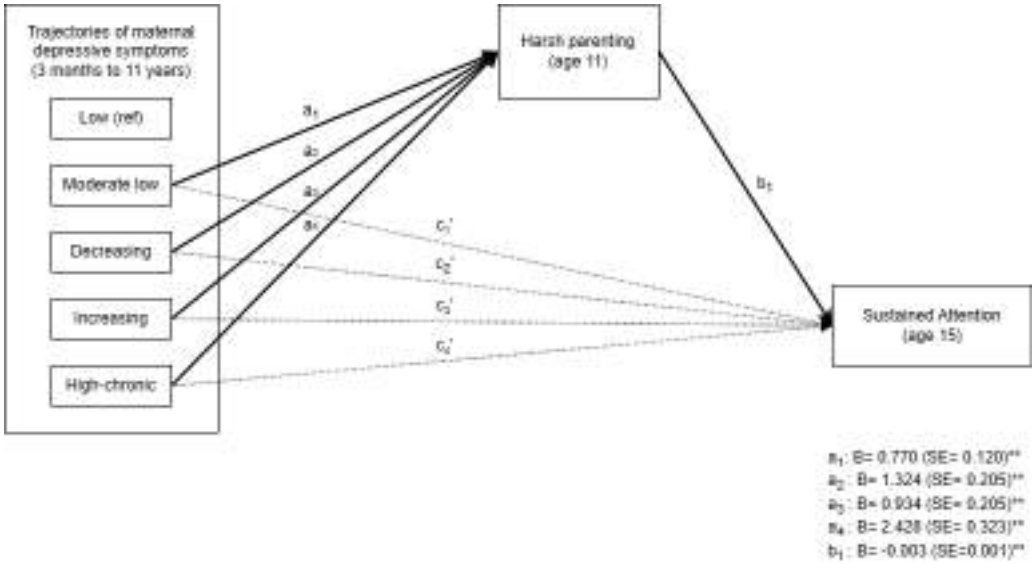

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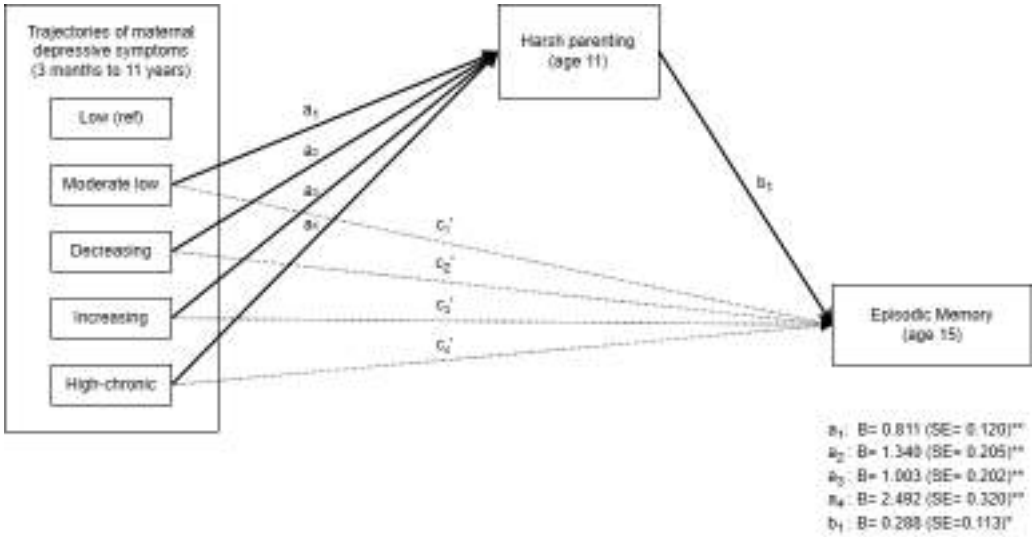

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Table 1. Maternal and adolescent characteristics of participants in the 15-year follow-up, compared to those from the perinatal period.

	Follow-ups	
Variables	**Perinatal** (N=4231)	**15 years** (N=1949)
	N(%)	N(%)
Family income (quintiles)		*p=0.001*
5th quintile (wealthiest)	830 (19.6)	362 (18.6)
4th quintile	858 (20.3)	432 (22.2)
3rd quintile	816 (19.3)	407 (20.9)
2nd quintile	854 (20.2)	383 (19.7)
1st quintile (poorest)	871 (20.6)	365 (18.7)
Maternal education (years)		*p=0.021*
≥ 9	1801 (43.0)	868 (44.9)
5-8	1731 (41.4)	790 (40.8)
1-4	611 (14.6)	264 (13.6)
0	43 (1.0)	13 (0.7)
Self-reported maternal skin color		*p=0.057*
White	2581 (61.7)	1220 (63.4)
Black	689 (16.5)	316 (16.4)
Brown	868 (20.8)	375 (19.5)
Yellow/Indigenous	43 (1.0)	14 (0.7)
Maternal age at birth (years)		*p<0.001*
20-34	2865 (67.8)	1296 (66.5)
< 20	799 (18.9)	350 (18.0)
≥ 35	563 (13.3)	303 (15.6)
Child' sex		*p=0.350*
Male	2.194 (51.8)	996 (51.1)
Female	2.035 (48.1)	953 (48.9)
Low birth weight		*p=0.024*
No	3803 (90.0)	175 (91.1)
Yes	423 (10.0)	173 (8.9)
Preterm birth		*p=0.025*
No	3603 (85.5)	1689 (86.8)
Yes	612 (14.5)	257 (13.2)

Note. Chi-square test was used for comparison.

Table 2. Indirect, direct and total effects of maternal depressive symptoms trajectories on adolescent's sustained attention mediated by harsh parenting.

Trajectories of maternal depression symptoms	Relative effects [a] for adolescents' sustained attention	B (SE)[b]	95% bias-corrected bootstrap CI	*β* (SE)	95% bias-corrected bootstrap CI	Proportion of total association explained by harsh parenting
Moderated low	Indirect effect (a_1*b)	-0.002 (0.001)**	(-0.003; -0.001)	-0.015 (0.004)**	(-0.022; -0.009)	-
	Direct effect (c_1')	-0.000 (0.004)	(-0.006; 0.006)	-0.002 (0.025)	(-0.043; 0.038)	
	Total effect	-0.002 (0.004)	(-0.008; 0.004)	-0.016 (0.025)	(-0.057; 0.024)	
Decreasing	Indirect effect (a_2*b)	-0.004 (0.001)**	(-0.006; -0.002)	-0.016 (0.004)*	(-0.024; -0.009)	-
	Direct effect (c_2')	-0.005 (0.006)	(-0.015; 0.004)	-0.021 (0.024)	(-0.061; 0.018)	
	Total effect	-0.009 (0.006)	(-0.018; 0.001)	-0.036 (0.024)	(-0.075; 0.003)	
Increasing	Indirect effect (a_3*b)	-0.003 (0.001)**	(-0.004; -0.001)	-0.010 (0.003)*	(-0.017; -0.005)	19% (18%; 45%)
	Direct effect (c_3')	-0.011 (0.007)*	(-0.023; 0.000)	-0.042 (0.026)	(-0.087; 0.000)	
	Total effect	-0.013 (0.007)*	(-0.025; -0.003)	-0.052 (0.026)*	(-0.097; -0.011)	
High-chronic	Indirect effect (a_4*b)	-0.007 (0.002)**	(-0.010; -0.004)	-0.020 (0.006)*	(-0.031; -0.013)	42% (34%; 186%)
	Direct effect (c_4')	-0.009 (0.009)	(-0.023; 0.005)	-0.027 (0.026)	(-0.069; 0.015)	
	Total effect	-0.016 (0.009)	(-0.030; -0.002)	-0.048 (0.025)*	(-0.090; -0.007)	

B unstandardized coefficient; *β* standardized coefficient; *CI* confidence interval; *SE* standard error

A higher score indicates better performance in measuring adolescents' sustained attention (sensitivity)

[a] Relative effect to the reference group (low depressive symptoms trajectory)

[b] Estimates for the fully adjusted model including family income, maternal education, maternal self-reported skin color, living arrangement, and adolescent's sex in all pathways

*p<0.05

** p<0.001

Table 3. Indirect, direct and total effects of maternal depressive symptoms trajectories on episodic memory mediated by harsh parenting.

Trajectories of maternal depression symptoms	Relative effects [a] for adolescents' episodic memory	B (SE)[b]	95% bias-corrected bootstrap CI	β (SE)	95% bias-corrected bootstrap CI
Moderated low	Indirect effect (a_1*b)	0.233 (0.098)*	(0.089; 0.413)	0.010 (0.004)*	(0.004; 0.018)
	Direct effect (c_1')	-0.922 (0.568)	(-1.889; -0.010)	-0.041 (0.025)	(-0.083; -0.000)
	Total effect	-0.689 (0.557)	(-1.604; 0.227)	-0.030 (0.025)	(-0.071; 0.010)
Decreasing	Indirect effect (a_2*b)	0.385 (0.162)*	(0.143; 0.677)	0.011 (0.004)*	(0.004; 0.019)
	Direct effect (c_2')	0.201 (0.926)	(-1.290; 1.801)	0.006 (0.025)	(-0.035; 0.049)
	Total effect	0.587 (0.910)	(-0.804; 2.303)	0.016 (0.025)	(-0.023; 0.060)
Increasing	Indirect effect (a_3*b)	0.288 (0.127)*	(0.109; 0.532)	0.007 (0.003)*	(0.003; 0.013)
	Direct effect (c_3')	-0.282 (0.974)	(-1.839; 1.400)	-0.007 (0.025)	(-0.047; 0.035)
	Total effect	0.006 (0.974)	(-1.554; 1.668)	0.000 (0.025)	(-0.040; 0.042)
High-chronic	Indirect effect (a_4*b)	0.717 (0.304)*	(0.262; 1.266)	0.014 (0.006)*	(0.005; 0.025)
	Direct effect (c_4')	-0.464 (1.344)	(-2.561; 1.804)	-0.009 (0.026)	(-0.049; 0.035)
	Total effect	0.252 (1.383)	(-1.936; 2.557)	0.005 (0.027)	(-0.037; 0.050)

B unstandardized coefficient; β standardized coefficient; *CI* confidence interval; *SE* standard error

A higher score indicates worst performance in measuring adolescents' episodic memory (error)

[a] Relative effect to the reference group (low depressive symptoms trajectory)

[b] Estimates for the fully adjusted model including family income, maternal education, maternal self-reported skin color, living arrangement, and adolescent's sex in all pathways

*$p<0.05$

** $p<0.001$

Supplementary material

Examining pathways between trajectories of maternal depressive symptoms, harsh parenting, and adolescent executive functions: insights from the 2004 Pelotas Birth Cohort

Júlia de Souza Rodrigues, Maria Pastor-Valero, Jéssica Mayumi Maruyama, Tiago N. Munhoz, Iná S. Santos, Aluísio J. D. Barros, Luciana Tovo-Rodrigues, Alicia Matijasevich

Table S1. Overview of Cambridge Neuropsychological Test Automated Battery (CANTAB) outcomes.

Cognitive function	CANTAB subtest	Outcome
Episodic memory	Paired Associate Learning (PAL)	Total Errors refers to the total count of instances where the subject selected the incorrect box for a stimulus during assessment problems. This count is adjusted to estimate the number of errors they would have made on any problems, attempts, and recalls they did not reach. This metric facilitates the comparison of error performance across all subjects, irrespective of whether they terminated the task early or completed its final stage. In the variant PALTEA task, the 12-box level is excluded to allow for a direct comparison to the Recommended Standard.
Sustained attention	Rapid visual processing (RVP)	A prime: is the signal detection measure of a subject's sensitivity to the target sequence (string of three numbers), regardless of response tendency (the expected range is 0.00 to 1.00; bad to good). In essence, this metric is a measure of how good the subject is at detecting target sequences.
Working memory	Spatial working memory (SWM)	Between Errors: the number of times the subject incorrectly revisits a box in which a token has previously been found. Calculated across all assessed four, six and eight token trials.

Table S2. Sustained attention, episodic memory and working memory according to maternal and child characteristics, 2004 Pelotas Birth Cohort (N = 1949)

	Frequency	Sustained attention (Range: 0.28-0.98)		Episodic memory (Range: 0-68)		Working memory (Range: 0-44)	
Variables	**N (%)**	**Mean (SD)**	**p-value**	**Mean (SD)**	**p-value**	**Mean (SD)**	**p-value**
Family income (quintiles)							
1st quintile (poorest)	420 (21.55)	0.81 (0.07)	p<0.001	13.23 (13.04)	p<0.001	16.73 (7.63)	p<0.001
2nd quintile	361 (18.52)	0.81 (0.08)		12.70 (12.33)		15.25 (7.93)	
3rd quintile	391 (20.06)	0.83 (0.07)		10.50 (10.51)		14.38 (8.10)	
4th quintile	415 (21.29)	0.83 (0.07)		8.90 (9.52)		12.73 (8.11)	
5th quintile (wealthiest)	362 (18.57)	0.85 (0.07)		8.07 (9.12)		11.80 (8.21)	
Maternal education (years)							
1-4	277 (14.32)	0.80 (0.07)	p<0.001	14.25 (12.89)	p<0.001	16.86 (7.70)	p<0.001
5-8	790 (40.83)	0.81 (0.07)		12.01 (11.92)		15.54 (7.85)	
≥ 9	868 (44.86)	0.84 (0.07)		8.30 (9.17)		12.21 (8.16)	
Self-reported maternal skin color							
White	1220 (63.38)	0.83 (0.07)	p<0.001	9.58 (10.39)	p<0.001	13.34 (8.30)	p<0.001
Black	316 (16.42)	0.80 (0.07)		14.22 (12.24)		16.29 (7.34)	
Brown	375 (19.48)	0.81 (0.08)		11.36 (12.23)		15.18 (8.16)	
Yellow/Indigenous	14 (0.73)	0.81 (0.07)		10.07 (12.33)		17.00 (8.25)	
Maternal age at birth (years)							
< 20	350 (17.96)	0.81 (0.07)	p<0.001	11.34 (10.77)	p=0.408	15.36 (8.09)	p=0.006
20-34	1296 (66.50)	0.83 (0.07)		10.65 (11.22)		14.11 (8.20)	
≥ 35	303 (15.55)	0.83 (0.07)		10.17 (11.60)		13.36 (8.08)	
Number of siblings							
0	603 (32.52)	0.83 (0.07)	p<0.001	9.98 (10.72)	p<0.001	13.25 (8.13)	p<0.001
1	726 (39.16)	0.83 (0.08)		9.40 (9.67)		13.68 (8.18)	
≥2	525 (28.32)	0.81 (0.07)		12.75 (12.56)		16.17 (7.83)	
Parity							

1	744 (38.17)	0.83 (0.07)	p<0.001	13.81 (8.23)	p<0.001	9.95 (10.45)	p<0.001
2	546 (28.01)	0.83 (0.08)		13.50 (8.14)		9.97 (10.64)	
≥3	659 (33.81)	0.81 (0.07)		15.27 (8.06)		12.16 (12.31)	
Smoking during pregnancy							
No	1440 (73.88)	0.83 (0.07)	p<0.001	10.07 (10.96)	p<0.001	13.66 (8.20)	p<0.001
Yes	509 (26.12)	0.81 (0.08)		12.48 (11.70)		15.80 (7.92)	
Low birth weight							
No	1775 (91.22)	0.82 (0.07)	p=0.134	10.42 (10.98)	p<0.001	14.04 (8.19)	p=0.002
Yes	173 (8.88)	0.82 (0.07)		13.61 (13.00)		16.06 (7.80)	
Prematurity							
No	1689 (86.79)	0.82 (0.07)	p=0.372	10.44 (11.10)	p<0.001	13.96 (8.26)	p=0.008
Yes	257 (13.21)	0.82 (0.07)		12.45 (11.74)		15.95 (7.36)	
Child sex							
Male	973 (50.94)	0.83 (0.07)	p<0.001	9.38 (10.31)	p<0.001	13.03 (8.14)	p<0.001
Female	937 (49.06)	0.82 (0.07)		12.07 (11.91)		15.44 (8.04)	
Trajectories of maternal depressive symptoms							
Low	593 (31.23)	0.83 (0.07)	p<0.001	10.18 (10.91)	p=0.007	13.03 (8.14)	p<0.001
Moderated low	831 (43.76)	0.83 (0.07)		10.13 (10.81)		15.44 (8.04)	
Decreasing	206 (10.85)	0.81 (0.07)		12.46 (12.05)		13.03 (8.14)	
Increasing	171 (9.00)	0.81 (0.08)		11.70 (11.62)		15.44 (8.04)	
High Chronic	98 (5.16)	0.80 (0.08)		13.06 (12.65)		15.44 (8.04)	

BRL=Brazilian real (2.89 BRL=1 USD in January 2004 when recruitment of the families commenced). The score ranges in parenthesis represent the minimum and maximum values found in the study sample.

Table S3. Means, standard deviations and correlation coefficients for the study variables.

		Mean (SD)	1	2	3	4	5	6	7	8	9	10	11	12	13
1	Sustained attention (range: 0.28-0.80)	0.82 (0.07)	1.00												
2	Episodic memory (range: 0-68)	10.70 (11.20)	0.94***	1.00											
3	Working memory (range: 0-44)	14.21 (8.18)	0.96***	0.94***	1.00										
4	CTSPC (range: 0-13)[a]	3.71 (2.43)	0.52*	0.03	0.04	1.00									
5	Family income, BRL (range:0-15000)	811.95 (1089.90)	0.00	0.00	0.00	-0.11***	1.00								
6	Maternal schooling (range: 0-17)	8.25 (3.41)	0.03	0.05*	0.02	-0.09**	0.45***	1.00							
7	Maternal age (range: 13-45)	26.57 (6.96)	0.01	0.02	0.01	-0.17***	0.21***	0.11***	1.00						
8	Number of siblings (range: 0-7)	1.13 (1.13)	-0.01	-0.01	0.00	-0.01	-0.11***	-0.31***	0.17***	1.00					
9	Parity (range: 1-11)	2.31 (1.54)	-0.02	-0.02	-0.01	-0.05*	-0.10***	-0.34***	0.46***	0.62***	1.00				
10	Maternal depression trajectories		-0.02	-0.03	-0.03	-.24***	-0.17***	-0.23***	-0.05*	0.15***	0.18***	1.00			
11	Maternal skin colour, 0 = non-white		-0.00	-0.02	-0.01	0.06*	-0.17***	-0.20***	-0.09***	0.09***	0.08***	0.10***	1.00		
12	Marital status, 0 = not living with partner		0.02	0.04	0.03	-0.08***	0.10***	0.09***	0.20***	0.12***	0.09**	-0.04	-0.12***	1.00	
13	Sex, 0 = female		0.02	-0.01	0.15***	-0.09***	-0.02	-0.03	0.01	0.06**	0.07**	0.00	-0.00	-0.02	1.00

* p<0.05; ** p< 0.01; ***p<0.001

[a] CTSPC: Parent-Child Conflict Tactics Scale; Cronbach's alpha = 0.73

BRL = Brazilian real (2.89 BRL = 1 USD in January 2004)

The score ranges in parenthesis represent the minimum and maximum values found in the study sample.

Table S4: Association between trajectories of maternal depression and harsh parenting at 11 years.

Trajectories of maternal depression (N=1949)	Harsh parenting			
	Crude		Adjusted[a]	
	B (SE)	CI 95%	B (SE)	CI 95%
	p<0.001		p<0.001	
Low	ref	ref	ref	ref
Moderate low	0.889 (0.128)**	(0.638; 1.140)	0.777 (0.128)**	(0.525; 1.029)
Decreasing	1.503 (0.193)**	(1.125; 1.881)	1.267 (0.196)**	(0.882; 1.652)
Increasing	1.165 (0.208)**	(0.757; 1.573)	0.919 (0.210)**	(0.507; 1.331)
High-chronic	2.499 (0.267)**	(1.975; 3.023)	2.431 (0.274)**	(1.893; 2.968)

[a] adjusted for family income, maternal age, smoking during pregnancy, self-reported maternal skin-color , prematurity, parity, sex
** p<0.001

Table S5: Association between trajectories of maternal depression and sustained attention at 15 years.

Trajectories of maternal depression	Sustained attention			
	Crude		Adjusted[a]	
	B (SE)	CI 95%	B (SE)	CI 95%
	p<0.001		p=0.062	
Low	ref	ref	Ref	ref
Moderate low	-0.008 (0.004)*	(-0.016; -0.001)	-0.003 (0.004)	(-0.011; 0.005)
Decreasing	-0.022 (0.006)**	(-0.339; -0.011)	-0.009 (0.006)	(-0.021; 0.002)
Increasing	-0.026 (0.006)**	(-0.388; -0.014)	-0.014 (0.006)*	(-0.027; -0.002)
High-chronic	-0.036 (0.008)**	(-0.518; -0.020)	-0.017 (0.008)*	(-0.033; -0.001)

A higher score indicates better performance in measuring adolescents' sustained attention (sensitivity)
[a] adjusted for maternal education, maternal age, smoking during pregnancy, self-reported maternal skin-color, parity, sex
* p<0.05
** p<0.001

Table S6: Association between trajectories of maternal depression and episodic memory at 15 years.

Trajectories of maternal depression	Episodic memory			
	Crude		Adjusted[a]	
	B (SE)	CI 95%	B (SE)	CI 95%
	p=0.008		p=0.692	
Low	ref	ref	Ref	ref
Moderate low	-0.043 (0.605)	(-1.231; 1.144)	-0.412 (0.593)	(-1.575; 0.752)
Decreasing	2.282 (0.909)*	(0.500; 4.064)	0.708 (0.906)	(-1.068; 2.485)
Increasing	1.521 (0.976)	(-0.394; 3.436)	0.250 (0.955)	(-1.624; 2.124)
High-chronic	2.889 (1.240)*	(0.457; 5.319)	0.522 (1.233)	(-1.897; 3.390)

A higher score indicates worst performance in measuring adolescents' episodic memory (errors)
[a] adjusted for maternal education, maternal age, self-reported maternal skin color, low birth weight, parity, sex
* p<0.05

Table S7: Association between trajectories of maternal depression and working memory at 15 years.

Trajectories of maternal depression	Working memory			
	Crude		Adjusted[a]	
	B (SE)	CI 95%	B (SE)	CI 95%
	p<0.001		p=0.076	
Low	ref	ref	ref	ref
Moderate low	1.648 (0.441)**	(0.782; 2.513)	1.231 (0.437)*	(0.374; 2.089)
Decreasing	2.054 (0.663)*	(0.754; 3.354)	0.566 (0.670)	(-0.748; 1.879)
Increasing	2.572 (0.712)**	(1.175; 3.969)	1.112 (0.708)	(0.278; 2.501)
High-chronic	2.461 (0.904)*	(0.688; 4.235)	0.504 (0.925)	(-1.309; 2.318)

A higher score indicates worst performance in measuring adolescents' working memory (errors)

[a] adjusted for family income, maternal education, maternal age, self-reported maternal skin color, number of siblings, prematurity, low birth weight, sex

* $p<0.05$

** $p<0.001$

Table S8: Association between harsh parenting and episodic memory, sustained attention and working memory at 15 years.

	Episodic memory				Sustained attention				Working memory			
	Crude		Adjusted[a]		Crude		Adjusted[b]		Crude		Adjusted[c]	
	B (SE)	CI 95%	B (SE)	CI 95%	B (SE)	CI 95%	B (SE)	CI 95%	B (SE)	CI 95%	B (SE)	CI 95%
Harsh parenting	0.331 (0.108)*	0.120; 0.542	0.241 (0.107)*	0.030; 0.452	-0.004 (0.001)*	-0.054; -0.003	-0.003 (0.001)**	-0.004; -0.002	0.201 (0.080)*	0.045; 0.356	0.103 (0.080)	-0.054; 0.261

[a] adjusted for maternal education, maternal age, self-reported maternal skin color, low birth weight, parity, sex
[b] adjusted for family income, maternal education, maternal age, smoking during pregnancy, self-reported maternal skin color, low birth weight, parity, sex
[c] adjusted for family income, maternal education, maternal age, self-reported maternal skin color, number of siblings, prematurity, low birth weight, sex
* $p<0.05$
** $p<0.001$

Table S9. Indirect, direct and total effects of maternal depressive symptoms trajectories on adolescent's working memory scores mediated by harsh parenting.

Trajectories of maternal depression symptoms	Relative effects [a] for adolescents' working memory	B (SE)[b]	95% bias-corrected bootstrap CI	β (SE)	95% bias-corrected bootstrap CI
Moderated low	Indirect effect (a_1*b)	0.067 (0.069)	(-0.043; 0.185)	0.004 (0.004)	(-0.003; 0.011)
	Direct effect (c_1')	0.997 (0.424)*	(0.301; 1.700)	0.060 (0.026)	(0.018; 0.102)
	Total effect	1.064 (0.419)*	(0.353; 1.751)	0.064 (0.025)*	(0.021; 0.105)
Decreasing	Indirect effect (a_2*b)	0.109 (0.114)	(-0.069; 0.308)	0.004 (0.004)	(-0.003; 0.012)
	Direct effect (c_2')	0.352 (0.636)	(-0.693; 1.379)	0.013 (0.024)	(-0.026; 0.052)
	Total effect	0.461 (0.629)	(-0.576; 1.488)	0.017 (0.024)	(-0.021; 0.056)
Increasing	Indirect effect (a_3*b)	0.085 (0.090)	(-0.052; 0.248)	0.003 (0.003)	(-0.002; 0.009)
	Direct effect (c_3')	1.191 (0.646)	(0.136; 2.272)	0.041 (0.022)	(0.004; 0.078)
	Total effect	1.277 (0.636)*	(0.227; 2.322)	0.044 (0.022)*	(0.008; 0.081)
Chronic-high	Indirect effect (a_4*b)	0.199 (0.206)	(-0.131; 0.544)	0.005 (0.006)	(-0.003; 0.015)
	Direct effect (c_4')	0.086 (0.833)	(-1.291; 1.460)	0.002 (0.022)	(-0.035; 0.039)
	Total effect	0.285 (0.810)	(-1.033; 1.631)	0.008 (0.022)	(-0.028; 0.044)

B unstandardized coefficient; β standardized coefficient; *CI* confidence interval; *SE* standard error

Higher scores indicates worst performance in measuring adolescents' working memory

[a] Relative effect to the reference group (low depressive symptoms trajectory)

[b] Estimates for the fully adjusted model including family income, maternal education, maternal self-reported skin color, living arrangement, and adolescent's sex in all pathways

*$p<0.05$

** $p<0.001$

ANEXOS

Anexo A. Parecer da Oficina de Investigación Responsable emitida pelo *Vicerrectorado de Investigación y Transferencia da Universidad Miguel Hernández de Elche.*

INFORME DE EVALUACIÓN DE INVESTIGACIÓN RESPONSABLE

Elche, a 10/07/2023

Director/a	María Asunción Pastor-Valero
Codirectores/as	Alicia Matijasevich Manitto
Estudiante	Júlia de Souza Rodrigues
Programa de doctorado	Salud Pública, Ciencias Médicas y Quirúrgicas
Título de la tesis doctoral	Estudio de los factores de riesgo para el compromiso de las funciones ejecutivas en la adolescencia: Cohorte de Nacimiento de Pelotas 2004.
Tipo de actividad	Adherido a un proyecto autorizado
Evaluación de riesgos laborales	**No solicitado/No procede**
Evaluación ética	**No solicitado/No procede**
Código provisional	**2306231210SR**
Código de autorización COIR	**ADH.SPU.MAP.JDSR.23**
Caducidad	**8 años***

***Importante: La caducidad de las autorizaciones de tesis, basadas en la adhesión a un proyecto de investigación, están condicionadas a la vigencia de la autorización de dicho proyecto en este sentido: todas las actividades de la tesis que tengan implicaciones ético-legales deberán realizarse mientras dicho proyecto esté vigente. Dicho de otro modo, sólo podrán realizarse actividades de carácter intelectual una vez el proyecto al que se adhiere haya caducado.**

Se considera que la presente actividad no supone riesgos laborales adicionales a los ya evaluados en el proyecto de investigación al que se adhiere. No obstante, es responsabilidad del tutor/a informar y/o formar al estudiante de los posibles riesgos laborales de la presente actividad.

La necesidad de evaluación ética del trabajo titulado: **Estudio de los factores de riesgo para el compromiso de las funciones ejecutivas en la adolescencia: Cohorte de Nacimiento de Pelotas 2004.** ha sido realizada en base a la información aportada en el formulario online: "Solicitud Código de Investigación Responsable (COIR)", habiéndose determinado que no requiere ninguna evaluación adicional. Es importante destacar que si la información aportada en dicho formulario no es correcta este informe no tiene validez.

Por todo lo anterior, **se autoriza** la realización de la presente actividad.

Atentamente,

Alberto Pastor Campos
Jefe de la Oficina de Investigación Responsable
Vicerrectorado de Investigación y Transferencia

COMITÉ DE ÉTICA E INTEGRIDAD EN LA INVESTIGACIÓN
VICERRECTORADO DE INVESTIGACIÓN Y TRANSFERENCIA
UNIVERSIDAD MIGUEL HERNÁNDEZ DE ELCHE

Información adicional:

- En caso de que la presente actividad se desarrolle total o parcialmente en otras instituciones es responsabilidad del investigador principal solicitar cuantas autorizaciones sean pertinentes, de manera que se garantice, al menos, que los responsables de las mismas están informados.
- Le recordamos que durante la realización de este trabajo debe cumplir con las exigencias en materia de prevención de riesgos laborales. En concreto: las recogidas en el plan de prevención de la UMH y en las planificaciones preventivas de las unidades en las que se integra la investigación. Igualmente, debe promover la realización de reconocimientos médicos periódicos entre su personal; cumplir con los procedimientos sobre coordinación de actividades empresariales en el caso de que trabaje en el centro de trabajo de otra empresa o que personal de otra empresa se desplace a las instalaciones de la UMH; y atender a las obligaciones formativas del personal en materia de prevención de riesgos laborales. Le indicamos que tiene a su disposición al Servicio de Prevención de la UMH para asesorarle en esta materia.

La información descriptiva básica del presente trabajo será incorporada al repositorio público de tesis autorizadas por la Oficina de Investigación Responsable de la Universidad Miguel Hernández. También se puede acceder a través de https://oir.umh.es/solicitud-de-evaluacion/proyectos-de-investigacion/

Anexo B. Declaração de dupla titulação

MEDICINA USP | Departamento de Medicina Preventiva

Declaração

São Paulo, 24 de setembro de 2024

Eu, Patricia Coelho de Soárez, declaro que a tese de doutorado intitulada "Estudo dos fatores de risco associados ao comprometimento das funções executivas na adolescência: Coorte de Nascimentos de Pelotas 2004", de autoria de Júlia de Souza Rodrigues, sob a orientação da Profa. Dra. Alicia Matijasevich e coorientação da Profa. Dra. Maria Pastor Valero, foi desenvolvida no âmbito do Convênio de Dupla Titulação de Doutorado Internacional. Este convênio é celebrado entre o Programa de Pós-Graduação em Saúde Coletiva da Faculdade de Medicina da Universidade de São Paulo, no Brasil, e o Programa de Doctorado en Salud Pública, Ciencias Médicas y Quirúrgicas da Facultad de Medicina da Universidad Miguel Hernández de Elche, na Espanha. A tese mencionada encontra-se em conformidade com as normas e regulamentos para a obtenção do grau de doutorado de ambas as instituições participantes. A doutoranda Júlia de Souza Rodrigues permaneceu na Faculdade de Medicina da Universidade de São Paulo no período de 01/11/2022 a 31/05/2023.

Atenciosamente,

Profa. Dra. Patrícia Coelho de Soárez
Coordenadora do Programa de Pós-Graduação em Saúde Coletiva
Faculdade de Medicina da Universidade de São Paulo

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Patrícia Coelho de Soárez

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