PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
MESTRADO EM CIÊNCIAS DA SAÚDE

PRISCILA VIEIRA DE LUCENA MANTOVANI

A INFLUÊNCIA DA INFECÇÃO VIRAL EM MULHERES GRÁVIDAS NA PATOLOGIA DO TRANSTORNO DO ESPECTRO AUTISTA: UMA REVISÃO SISTEMÁTICA COM METANÁLISE

Presidente Prudente - SP
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DEDICATÓRIA

Dedico este trabalho primeiramente a Deus, que me acompanhou durante os anos intensos de estudo e trabalho. Também aos meus pais, que sempre me apoiaram em toda trajetória acadêmica.

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Por isso não tema, pois estou com você;
não tenha medo, pois sou o seu Deus.
Eu o fortalecerei e o ajudarei;
eu o segurarei
com a minha mão direita vitoriosa.
- Isaías 41:10 NVI

RESUMO

A influência da infecção viral em mulheres grávidas na patologia do transtorno do espectro autista: uma revisão sistemática com metanálise

Transtorno do Espectro Autista (TEA) é um distúrbio do neurodesenvolvimento caracterizado por dificuldades na comunicação social, interesses restritos e comportamentos repetitivos. A infecção é um fator ambiental comum que pode influenciar o desenvolvimento do TEA e quando causada por vírus é altamente prevalente em todas as faixas etárias, inclusive, no período intrauterino. A etiologia do TEA tem sido um tema de intensa pesquisa, porém, há lacunas a serem preenchidas. **Objetivo**: Analisar a interação entre infecção viral durante a gestação e o TEA. **Métodos**: A revisão sistemática com metanálise foi realizada para responder à seguinte pergunta: Qual é a influência da infecção viral em mulheres grávidas no desenvolvimento do Transtorno do Espectro Autista? Os artigos incluídos foram de 1979 a 2023. Os artigos foram estudos observacionais, retrospectivos, prospectivos, caso-controle e coorte que descreviam o desfecho clínico de crianças cujas mães foram expostas a infecções durante a gestação, com foco no desenvolvimento ou não de distúrbios psicológicos. A metodologia utilizada seguiu o PRISMA e o *software Review Manager* 5.4 foi utilizado para os cálculos da metanálise. **Resultados**: Um total de 32 estudos foi incluído e após análise, o resultado combinado trouxe OR= 0.29, que demonstrou que infecção viral durante a gestação elevou em 71% a probabilidade de TEA nos filhos, um resultado estatisticamente significativo, já que o intervalo de confiança não cruza o valor 1. **Conclusão:** De fato, essa revisão sistemática com metanálise constatou um risco aumentado de TEA em casos de infecção materna durante a gravidez. Esses resultados podem ser úteis para a preparação e o desenvolvimento de medidas profiláticas contra o TEA, pois podemos estar próximos de descobrir sua etiologia.

Palavras-chave: infecções; vírus; febre; autismo; gestação.

ABSTRACT

The influence of virus infection in pregnant women on the pathology of autism spectrum disorder: a systematic review with meta-analysis

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by difficulties in social communication, restricted interests, and repetitive behaviors. Infection is a common environmental factor that can influence the development of ASD and, when caused by viruses, is highly prevalent in all age groups, including the intrauterine period. The etiology of ASD has been the subject of intense research, but there are gaps to be filled. **Objective**: To analyze the interaction between viral infection during pregnancy and ASD. **Methods:** A systematic review with meta-analysis was conducted to answer the following question: What is the influence of viral infection in pregnant women on the development of Autism Spectrum Disorder? Articles were from the period of 1979 until 2023. The articles were observational, retrospective, prospective, case-control, and cohort studies that described the clinical outcome of children whose mothers were exposed to infections during pregnancy, focusing on the development or not of psychological disorders. The methodology used followed PRISMA, and Review Manager 5.4 software was used for meta-analysis calculations. **Results:** A total of 32 studies were included, and after analysis, the combined result yielded an OR of 0.29, demonstrating that viral infection during pregnancy increased the probability of ASD in offspring by 71%, a statistically significant result, since the confidence interval does not cross the value 1. **Conclusion:** In fact, this systematic review with meta-analysis found an increased risk of ASD in cases of maternal infection during pregnancy. These results may be useful for the preparation and development of prophylactic measures against ASD, as we may be close to discovering its etiology.

Keywords*:* infections; virus, fever, autism, pregnancy

LISTA DE SIGLAS

AIM – Ativação Imune Materna
CAPSi – Centro de Atenção Psicossocial Infantil
CDC – Centro de Controle de Doenças
CMV – Citomegalovírus
DSM – Manual de Diagnóstico e Estatístico de Transtornos Mentais
HERVS – Retrovírus Endógenos Humanos
HSV – Herpes Simplex Virus
IFN-γ – Interferon Gama
PRISMA – Itens de Relatório Preferidos para Revisões Sistemáticas e Meta-análises
RCSA – Registo de Cuidados de Saúde Ambulatoriais
SNC – Sistema Nervoso Central
Taux – Células T auxiliares
TEA – Transtorno do Espectro Autista
TNF-α – Fator de necrose tumoral α
Treg – Células T reguladoras

LISTA DE FIGURAS

SUMÁRIO

O trabalho está apresentado sob a forma de artigo, segundo as normas do periódico o qual será submetido: Journal of Autism and Developmental Disorders, JIF - 2.8 (2024)

ARTIGO - A INFLUÊNCIA DA INFECÇÃO VIRAL EM MULHERES GRÁVIDAS NA PATOLOGIA DO TRANSTORNO DO ESPECTRO AUTISTA: UMA REVISÃO SISTEMÁTICA COM METANÁLISE

RESUMO

Transtorno do Espectro Autista (TEA) é um distúrbio do neurodesenvolvimento caracterizado por dificuldades na comunicação social, interesses restritos e comportamentos repetitivos. A infecção é um fator ambiental comum que pode influenciar o desenvolvimento do TEA e quando causada por vírus é altamente prevalente em todas as faixas etárias, inclusive, no período intrauterino. A etiologia do TEA tem sido um tema de intensa pesquisa, porém, há lacunas a serem preenchidas. Objetivo: Analisar a interação entre infecção viral durante a gestação e o TEA. Métodos: A revisão sistemática com metanálise foi realizada para responder à seguinte pergunta: Qual é a influência da infecção viral em mulheres grávidas no desenvolvimento do Transtorno do Espectro Autista? Os artigos incluídos foram de 1979 a 2023. Os artigos foram estudos observacionais, retrospectivos, prospectivos, caso-controle e coorte que descreviam o desfecho clínico de crianças cujas mães foram expostas a infecções durante a gestação, com foco no desenvolvimento ou não de distúrbios psicológicos. A metodologia utilizada seguiu o PRISMA e o software Review Manager 5.4 foi utilizado para os cálculos da metanálise. Resultados: Um total de 32 estudos foi incluído e após análise, o resultado combinado trouxe OR= 0.29, que demonstrou que infecção viral durante a gestação elevou em 71% a probabilidade de TEA nos filhos, um resultado estatisticamente significativo, já que o intervalo de confiança não cruza o valor 1. Conclusão: De fato, essa revisão sistemática com metanálise constatou um risco aumentado de TEA em casos de infecção materna durante a gravidez. Esses resultados podem ser úteis para a preparação e o desenvolvimento de medidas profiláticas contra o TEA, pois podemos estar próximos de descobrir sua etiologia.

Palavras-chave: **infecções; vírus; febre; autismo; gestação**

A influência da infecção viral em mulheres grávidas na patologia do transtorno do espectro autista: uma revisão sistemática com metanálise

O Transtorno do Espectro Autista (TEA) é um distúrbio do neurodesenvolvimento caracterizado por *déficits* na comunicação social e pela presença de interesses restritos e comportamentos repetitivos. O conceito de espectro, de acordo com o Manual Diagnóstico e Estatístico de Transtornos Mentais, 5.ª edição (DSM-5), foi criado pela combinação de distúrbios do desenvolvimento incluídos no DSM-IV, o manual predecessor, tais como autismo, síndrome de Asperger, transtorno desintegrativo da infância e transtorno invasivo do desenvolvimento (Hodges et al., 2020).

Hodiernamente, a etiologia do autismo é entendida como uma complexa interação entre fatores genéticos, ambientais e imunológicos, sendo que cada um contribui interativamente com a sua manifestação, tanto que, uma grande quantidade de estudos pré-clínicos e epidemiológicos destacou a relação direta entre ativação imune materna (AIM) durante a gravidez e predisposições genéticas que influenciam no desenvolvimento de condições neuropsiquiátricas, incluindo o TEA (Vitor-Vieira et al., 2024).

A AIM é um fator ambiental mediado pela ativação de segmentos inflamatórios, o que resulta em níveis elevados de citocinas (como a IL-6) e quimiocinas que atravessam a barreira placentária e atingem o sistema neurológico fetal (Massrali et al. 2022).

Estudos epidemiológicos têm mostrado um crescimento rápido na prevalência do TEA nos últimos anos, sendo que os casos em meninos são de 4 a 5 vezes maiores. A prevalência média de TEA na Ásia, Europa e América do Norte está estimada em 1%. De acordo com o Centro de Controle de Doenças dos EUA (CDC), a prevalência do TEA em crianças de 8 anos foi de 1 em 59 em 2014 e 1 em 54 em 2016, enquanto nos adolescentes a prevalência foi de 2,5% de 2014 a 2016. Na Itália, as crianças de 7 a 9 anos tiveram uma prevalência de 1,15% e na Ásia de 3,9% (Salari et al. 2022).

Em um estudo conduzido no Brasil em 2023, focado em crianças em tratamento no Centro de Atenção Psicossocial Infantil (CAPSi), baseado no Registo de Cuidados de Saúde Ambulatoriais (RCSA), 21.107 crianças foram incluídas e 37,3% dessas foram diagnosticadas com autismo (Tomazelli, Girianelli, Fernandes, 2023).

A epidemiologia do TEA tem demonstrado um aumento global de sua prevalência. Esse aumento pode ser explicado por uma combinação de fatores como: melhores ferramentas para diagnóstico, critérios diagnósticos mais amplos e aumento do conhecimento e dispersão de informações sobre o distúrbio (Ribeiro, 2022).

A infecção é um fator ambiental comum que influencia o desenvolvimento do TEA. Quando causada por vírus, é altamente prevalente em todas as faixas etárias, inclusive, no período de desenvolvimento intrauterino, elevando o risco do autismo, especialmente nos estágios críticos iniciais do desenvolvimento neurológico (Al-Beltagi et al., 2023).

Como exemplo, podemos citar o citomegalovírus (CMV) como um fator de risco para o TEA, já que recém-nascidos infectados têm apresentado distúrbios do Sistema Neurológico Central (SNC) como microcefalia, calcificações periventriculares e perda auditiva. Essa classe de vírus pode ser

transmitida verticalmente, sendo definida, portanto, como uma infecção congênita por CMV (Zhang et al., 2023).

Outro vírus, a rubéola, pode ser transmitido verticalmente em 90% dos casos. Após a infecção materna pelo sistema respiratório, o vírus é replicado nos gânglios linfáticos próximos e na nasofaringe, podendo atingir o feto entre 5 a 7 dias por via transplacentária, levando a morte celular e interrupção da mitose enquanto circula pelo organismo. A rubéola congênita pode incluir: surdez, catarata, cardiopatias, distúrbios neurológicos e algumas complicações tardias como diabetes, hipo ou hipertireoidismo, deficiência de hormônio do crescimento e panencefalite progressiva (Bibi et al., 2025).

A razão deste estudo se dá pela falta de dados baseados em evidencias cientificas na literatura em relação às possíveis etiologias do autismo, uma vez que existe um aumento relevante no quadro epidemiológico atual no Brasil e demais países, quanto ao número de casos de TEA entre outras alterações do neurodesenvolvimento, incluídas as dificuldades enfrentadas pelos pacientes em sua vida diária, de seus cuidadores ou responsáveis, muitas vezes sobrecarregados e sem rede de apoio social.

O objetivo dessa revisão foi aumentar os níveis de evidencia sobre a indução de autismo por infecções virais durante a gestação e desenvolvimento uterino, investigando a relação de causa/efeito entre as variáveis, além de avaliar as possíveis etiologias desse distúrbio neurológico.

Metodologia

Esta revisão foi realizada seguindo as diretrizes dos Itens de Relatório Preferidos para Revisões Sistemáticas e Meta-análises (PRISMA) (Page et.al., 2021) e está registrada sob o protocolo PROSPERO CRD42024524222.

Os artigos foram analisados por dois investigadores (P.V.L.M e L.R.O). Os artigos que não estavam relacionados com o tema foram excluídos após a análise dos títulos e resumos. Assim, foram excluídos os seguintes itens: resumos expandidos; artigos completos não escritos em inglês, português ou espanhol; artigos que não analisavam infeções virais; artigos cujo texto completo não estavam disponíveis e estudos com desenhos não aplicáveis à metodologia.

Em casos de conflito, um terceiro autor foi consultado (H.B. N). A revisão incluiu estudos observacionais, retrospectivos, prospectivos, caso-controle e coortes que descrevem o desfecho clínico de crianças cujas mães foram expostas às infecções virais durante a gestação, com foco nos filhos que desenvolveram algum distúrbio neurológico. Não foram encontrados ensaios clínicos randomizados sobre o tema. Duplicatas e estudos não relacionados com os objetivos planejados foram excluídos (*figura 1*). Dos estudos encontrados, 16 também estavam em uma versão anterior desta revisão (Jiang et al., 2016) e foram incluídos na seleção final.

Os critérios diagnósticos para o TEA nos artigos incluídos foram encontrados nos manuais diagnósticos DSM (American Psychiatric Association) e CID (World Health Organization, 1968).

Estratégia de Pesquisa

Para essa revisão sistemática foi desenvolvida a seguinte questão de pesquisa: Qual é a influência da infecção viral em mulheres grávidas no desenvolvimento do Transtorno do Espectro Autista?

Os estudos foram pesquisados nas bases de dados Pubmed, Science Direct, Cochrane Library, Embase e Scopus usando uma estratégia de pesquisa com as seguintes palavras chaves: infecções; vírus; febre; autismo; gestação.

Extração de dados

Os estudos foram listados e categorizados usando a planilha eletrônica Rayyan® (Ouzzani et al., 2016), onde as informações sobre o desenho dos estudos, dados epidemiológicos da amostra, tempo de intervenção e dados laboratoriais foram analisados.

Os dados relevantes foram extraídos utilizando uma ficha desenvolvida pelos autores contendo: autor e ano de publicação, critérios diagnósticos, tipos de infecções virais estudados e dados do desfecho clínico. Dados adicionais podem ser encontrados nos Recursos Online 1 e 2. Os parâmetros de interesse foram divididos em: primários, infecção viral durante a gestação e autismo; e secundários: ativação da resposta imunológica materna induzida por infecção viral e desenvolvimento consequente de distúrbios neurológicos, infecção viral em mulheres grávidas, infecção congênita e sua associação com o autismo.

Dadas as diferenças metodológicas entre os estudos, estes foram separados entre a classificação do agente etiológico (bactérias, vírus entre outros) e o patógeno específico (rubéola, citomegalovírus etc.).

Diversos estudos investigaram mais de um agente etiológico; contudo, considerando que o foco da presente revisão são as infecções virais, foram incluídos aqueles que analisaram vírus, ainda que também tenham contemplado outros tipos de infecção.

Os artigos incluídos foram de 1979 a 2023.

O software Review Manager 5.4 (The Cochrane Collaboration, 2022) foi utilizado para organizar os dados e completar os cálculos da metanálise.

Risco de viés

A análise do risco de viés foi desenvolvida de acordo com a escala Robins-E (Higgins, 2024) por três autores (P.V.L. M; R.K. e H.B.N.). Essa escala é utilizada para estudos não randomizados com sete domínios: domínio de confusão; seleção da amostra; classificação das intervenções; desvios das intervenções pretendidas; dados faltantes; medida dos desfechos; seleção dos resultados reportados.

Resultados

Durante a revisão sistemática de artigos relevantes que tratavam sobre influência da infecção viral na patologia do autismo, 12.866 estudos foram encontrados e catalogados na plataforma eletrônica Rayyan, as duplicatas foram resolvidas, restando 8169 estudos que foram analisados de acordo com título e resumo.

Do número total de estudos, restaram 75 artigos após análise de título e resumo.

Um dos estudos não foi incluído na seleção final, já que o texto completo não estava disponível e não houve sucesso em se contatar o autor. No final 32 artigos foram eleitos para serem metanalisados após a leitura do texto completo, sendo 24 quantitativos e os demais qualitativos.

O risco de viés foi analisado pela escala Robins-E para estudos não randomizados. Os dados foram classificados de acordo com os sete domínios da escala e encontram-se resumidos na *figura 2.*

Não houve domínios com risco alto ou muito alto de viés e apenas os domínios 1, 3 e 4 (confusão, seleção dos participantes e intervenções pós-exposição, respectivamente) trouxeram algumas preocupações.

De acordo com a escala, a análise geral apontou algumas preocupações sobre viés no resultado, todavia, sem risco significativo. Um resultado adequado para um estudo não randomizado, mas com limitações.

De acordo com o local de desenvolvimento do estudo, observa-se que treze estudos foram desenvolvidos na Europa: Noruega (2), Dinamarca (4), Suécia (4), Itália (2) Holanda (1); nove na América do norte: Estados Unidos (8) e Canada (1); dois na Oceania: Austrália (2); cinco na Ásia: Japão (1), China (3) Índia (1) e apenas um na América do Sul de acordo com as informações na planilha de extração de dados (Tabela Suplementar 1).

Metanálise

Com base nos resultados, foi produzida uma metanálise, como demonstrado na *figura 3*, utilizando o software Rev-Man 4.

A síntese quantitativa mostrou que as variáveis obtiveram significância estatística, ou seja, a infecção na gestação teve influência no risco do desenvolvimento de TEA (OR =0,29; IC100%: 0.16-0.55; p < 0,00001)

A análise individual, porém, apresentou grande variabilidade entre os estudos, sendo que alguns apresentaram resultado positivo entre as variáveis e outros não identificaram efeito significativo.

Conforme gráfico de floresta na *figura 3* houve correlação entre as variáveis em 16 itens, (OR < 1), sendo que os tipos de infecção que apareceram nos estudos com correlação positiva foram: citomegalovirus (3), rubéola (1), herpes (1), pneumonia (1), não especificada (3), influenza (2), zika vírus (1), genital (1), febre de origem desconhecida (1), sarampo (1), catapora (1).

Além disso, houve certa heterogeneidade entre os estudos (I^2 = 100%, p <0,00001), o que sugere uma grande variedade dos resultados. Tal heterogeneidade está relacionada com os subgrupos presentes nos estudos como a diversidade do tipo de infecção, idade gestacional, características sociodemográficas da população presente nas amostras ou métodos utilizados para diagnóstico do autismo.

Alguns estudos com populações menores (ex.: Chess, Deykin, Glasson) mostraram OR < 1, porém com IC largos, mostrando pouco poder estatístico. Já estudos maiores como Fang (2015), mostraram resultados diferentes: alguns subgrupos apontaram aumento do risco (OR > 1) e, outros, redução (OR < 1). Além disso, há estudos com OR nos dois extremos, muito elevados ou muito baixos (ex.: Sakamoto 2014 OR = 80.25; Gazeta 2021 OR = 31.01), contribuindo para a heterogeneidade.

A maioria dos estudos que mostram uma correlação positiva entre as variáveis analisou infecções virais, demonstrando que existe de fato uma ligação entre a infecção viral durante a gravidez e o desenvolvimento de TEA nos filhos.

Sob análise, o resultado combinado dos subgrupos mostrou OR= 0.29 o que mostra que a infecção durante a gestação aumentou em 71% a chance do desenvolvimento do TEA nos filhos, sendo o resultado estatisticamente significativo, já que o intervalo de confiança não cruza 1.

Discussão

A maioria dos estudos disponíveis na literatura sugere que

infecções durante a gestação são fatores de risco para o TEA devido à AIM, febre ou inflamação (Paraschivescu et al., 2020). Além disso, a literatura mostra que infecções intrauterinas podem levar ao desenvolvimento neurológico alterado e distúrbios de comportamento e cognitivos, a longo prazo, independentemente do patógeno causador da infecção (Vitor-Vieira et al., 2024).

Entretanto, estudos recentes têm apontado que a principal causa para essa complicação é a infecção viral como catapora, CMV, caxumba e herpes simplex (HSV), que aumentam a probabilidade do feto desenvolver TEA (Massrali et al., 2022).

Através da interpretação da metanálise desse estudo, podemos ver correlação positiva entre nossos achados e as hipóteses disponíveis na literatura, já que a variável infecção durante gestação (principalmente viral) aumentou em 71% a chance do desenvolvimento de TEA nos filhos, sendo estatisticamente significativa (OR = 0.88; 95% CI: 0.85–0.91), indicando que as infecções, principalmente virais através da indução de processos inflamatórios, agem como fatores de risco para complicações no neurodesenvolvimento fetal, causando distúrbios como o TEA.

Dados prévios sugerem que essas complicações surgem da ativação do sistema imunológico materno, mediada pela liberação de citocinas pró-inflamatórias que podem interferir nos processos de desenvolvimento neurológico, aumentando a vulnerabilidade a patologias (Jash & Sharma, 2022).

Uma grande quantidade de citocinas (como a IL-6) e quimiocinas tem a capacidade de transpor a barreira placentária e hematoencefálica, vias com grande potencial de interrupção do desenvolvimento fetal. Entretanto, as citocinas podem exercer seus efeitos apenas se ligando a receptores da interface placentária, sem de fato atravessar a membrana, o que leva a efeitos subsequentes tanto na placenta quanto no feto. Esse papel das citocinas e quimiocinas pró-inflamatórias na fisiopatologia do TEA foi corroborado ainda pelos níveis elevados dessas substâncias no nascimento ou durante o desenvolvimento em subgrupo de indivíduos com TEA, estando ainda correlacionado com a gravidade dos sintomas do distúrbio (Patel et al., 2020).

Outro estudo sugere que a expressão da IL-6, após a AIM, leva a liberação de células $T_{reguladoras}$ (T_{reg}) e $T_{auxiliares}$ 17 (Th17), enquanto modula negativamente a expressão de células T_{reg}, levando ao comprometimento da função placentária e a uma potencial resposta autoimune ao feto. Corroborando essa hipótese, foram encontrados marcadores neuronais e linfocitários no soro de mães de crianças autistas, o que levou a formação de um subgrupo de pacientes autistas, chamado Transtorno Autista Autoimune. Esse subgrupo apresenta elevação das citocinas pró-inflamatórias, além de outras desregulações imunológicas como autoanticorpos contra a proteína básica da mielina cerebral, o que os pesquisadores atribuíram como consequência do aumento de células Th17 provavelmente precedido por infecção viral durante a gestação, indo de encontro às hipóteses dessa revisão (Parker-Athill & Tan, 2010)

O envolvimento da microbiota intestinal com a AIM também foi proposto como uma possível causa do TEA, uma vez que induz alterações no eixo cérebro-intestino-microbiota, causando *déficits* comportamentais e um perfil de microbiota semelhante ao observado no TEA. Por outro lado, retrovírus endógenos humanos (HERVs) como o HERVh, podem

também contribuir para alguns aspectos do desenvolvimento do autismo.

Estudos revelaram níveis elevados de um tipo específico de HERV, o HERV-h, em crianças com TEA e Transtorno de Déficit de Atenção e Hiperatividade, quando comparadas a pessoas sem patologias e estes estavam relacionados a fenótipos clínicos graves, mais prevalentes em crianças com deficiências motoras e de comunicação significativas (Balestrieri et al., 2013).

Ainda, alguns estudos também demonstraram que pode haver uma associação entre mãe e filho no TEA, já que ambos apresentam níveis elevados de HERV-h, além de citocinas como o fator de necrose tumoral alfa (TNF-α), interferon gama (IFN-γ), IL-10 e HEMO, que pode ser descrito como um gene envelope, chamado MER34 endógeno humano (Heidmann et al. 2017).

Além disso, a literatura mostra que infecções intrauterinas podem levar ao desenvolvimento neurológico alterado e distúrbios de comportamento e cognitivos, em longo prazo, independentemente do patógeno causador da infecção (Vitor-Vieira et al., 2024)

Quanto à relação entre infecção e autismo há postulados teóricos que sugerem que a biossíntese da proteína spike (proteína S), pode induzir problemas psiquicos, especialmente na COVID-19, que usa a proteína S como método de fusão com a célula hospedeira. A infecção leva ao desenvolvimento de uma “tempestade” de citocinas pró-inflamatórias, como IL-6 e IL-1β (Theoharides, 2022).

Ademais, estudos recentes sobre placenta, embriões e organoides cerebrais têm sugerido que os órgãos fetais, inclusive o cérebro, também podem ser suscetíveis ao coronavírus. Alguns resultados indicam que, embora dois dos três interagentes conhecidos da proteína spike (ACE2 e TMPRSS2) estejam presentes em baixos níveis no cérebro fetal, outros interagentes (ZDHHC5, GOLGA7 e ATP1A1), têm altos níveis de expressão e podem desempenhar um papel direto ou indireto na patogênese do SARS-CoV-2 no cérebro, principalmente no segundo e terceiro trimestres da gravidez, o que pode levar à interrupção da função neuronal, afetando principalmente a atividade pós-sináptica (Varma et al., 2021).

Como já mencionado anteriormente, os vírus foram os agentes infecciosos mais prevalentes, o que sugere que há uma conexão entre a infecção viral e o TEA. Estudos indicam que as infecções virais são capazes de atravessar a barreira placentária e atingir o feto, causando efeitos devastadores no seu desenvolvimento. Essa violação da barreira imunológica pode ser explicada pelo tropismo de alguns vírus, que permite o acesso à decídua através da corrente sanguínea ou mesmo através do trato genital inferior com alguns só sendo capazes de se infiltrarem durante um período gestacional específico (Racicot & Mor, 2017).

A associação entre infecção viral e distúrbios do desenvolvimento, descrita pela primeira vez em 1941, foi descoberta através da ligação entre a infecção por rubéola durante a gravidez e a catarata (Gregg, 1991). Na maioria dos casos, os dados apontam para uma correlação importante entre o período gestacional em que a infecção ocorreu e o desenvolvimento ou não de TEA nos filhos. Alguns estudos apontam para evidências de que a infecção no primeiro trimestre aumenta o risco da TEA, sugerindo que a inflamação induzida pela infecção durante um período específico da gravidez pode ser um fator etiológico para o distúrbio (Mahboub et al., 2023).

O CMV foi o principal agente infeccioso identificado nos estudos estatisticamente significativos. O CMV é a infecção congênita mais comum no mundo, com uma incidência entre 0,6% e 0,7% dos nascidos vivos e é uma das principais causas de distúrbios do desenvolvimento neurológico infantil. Portanto, pode haver uma relação importante entre o CMV e o TEA. Num estudo recente, houve uma maior frequência de diagnóstico de TEA em crianças com CMV numa incidência de 2,5% em crianças autistas em comparação com 0,7% na população geral (Dos & Silva, 2025).

O citomegalovírus pode infectar quase todo tipo de célula, incluindo células epiteliais, endoteliais, células musculares lisas, neurocitos e células do SNC, células epiteliais da retina, fibroblastos dérmicos e monócitos/macrófagos. Além disso, o ser humano é o seu único hospedeiro. O processo de maturação do sistema nervoso é complexo e exige a proliferação de muitas células, portanto o CMV pode invadir o SNC durante qualquer estágio do seu desenvolvimento, resultando em infecção congênita, distúrbios do neurodesenvolvimento, como o TEA, e outras doenças neurológicas, através da infecção viral aguda ou crônica que impede a proliferação e diferenciação de células tronco neurais (Zhang & Fang, 2019).

Por fim, a neuroinflamação desencadeada por infecções em geral tem sido fortemente associada a fatores de risco para o desenvolvimento de distúrbios degenerativos e neuropsiquiátricos (Clara et al., 2024), e os dados desta revisão reforçam essa associação, apontando para uma maior vulnerabilidade em casos de infecções virais, especificamente.

Deve ser mencionado que os estudos incluídos nesta revisão apresentaram certa heterogeneidade (I^2 = 99%), o que pode sugerir diferenças metodológicas importantes, como o tipo de agente infeccioso, a idade gestacional no momento da infecção, o método de diagnóstico para TEA e o tipo de coleta de dados sobre a infecção (autorrelato ou prontuário médico).

Além disso, é possível que haja uma relação especifica entre a intensidade e especificidade da infecção com o desenvolvimento de TEA e que, quando agrupadas com outras condições menos intensas e inespecíficas o efeito de tais efeitos tenha sido diluído no resultado geral.

As limitações dos estudos incluídos foram: a falta de descrição do tipo de doença infecciosa estudada e a não especificação da classe do microrganismo patogênico, o que poderia ter proporcionado resultados mais amplos e robustos para a revisão, além da falta de estudos clínicos randomizados que se encaixem nos critérios de inclusão. Tais aspectos podem ter aumentado a heterogeneidade dos resultados.

Em suma, embora os índices de evidencias desta revisão sejam estatisticamente significativos, devem ser interpretados com cautela devido as limitações dos estudos incluídos, sendo necessários ainda mais estudos, que forneçam dados padronizados principalmente que estratifiquem o tipo e o tempo na gestação da infecção além da necessidade de estudos que e ajustem outras variáveis como a, características sociodemográficas da população presente nas amostras ou métodos utilizados para diagnóstico do autismo para elucidar a hipótese apresentada de forma menos heterogenia.

Os resultados dessa revisão podem ser úteis para a preparação e o desenvolvimento de medidas profiláticas contra o TEA, porém devem ser interpretados com cautela. São necessários novos estudos prospectivos, principalmente estudos clínicos

randomizados, com melhor definição da exposição e divisão por idade gestacional no momento da infecção, para fornecer uma evidencia mais robusta entre essas variáveis.

Tais achados, poderiam trazer novas perspectivas à saúde pública, visando não só as doenças infectocontagiosas, mas também aos distúrbios neurológicos, trazendo expectativas para a prevenção e consequentemente melhorias na qualidade de vida, uma vez que os distúrbios neurológicos envolvem uma série de aspectos sociais tanto do indivíduo afetado quanto das pessoas ao seu redor.

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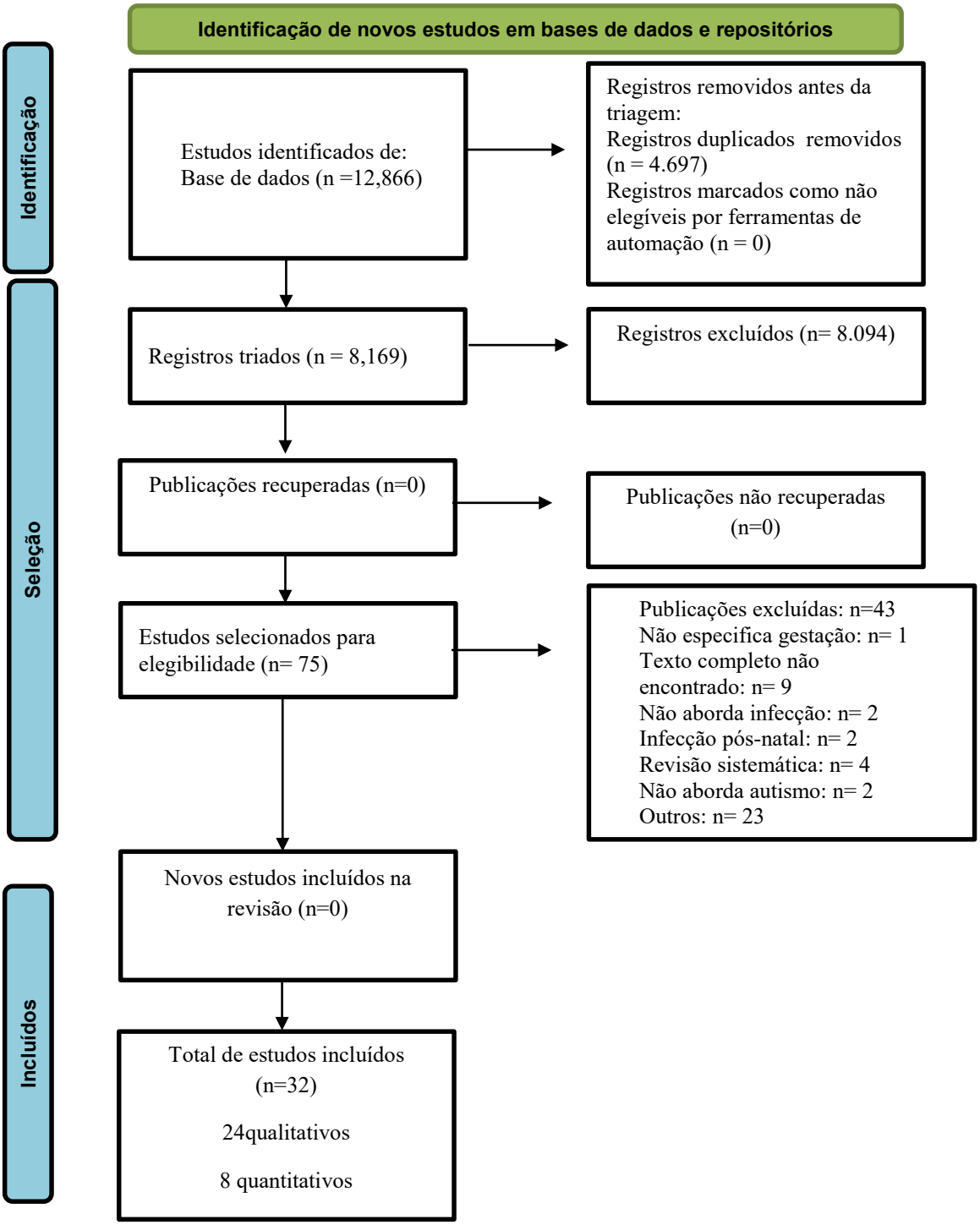
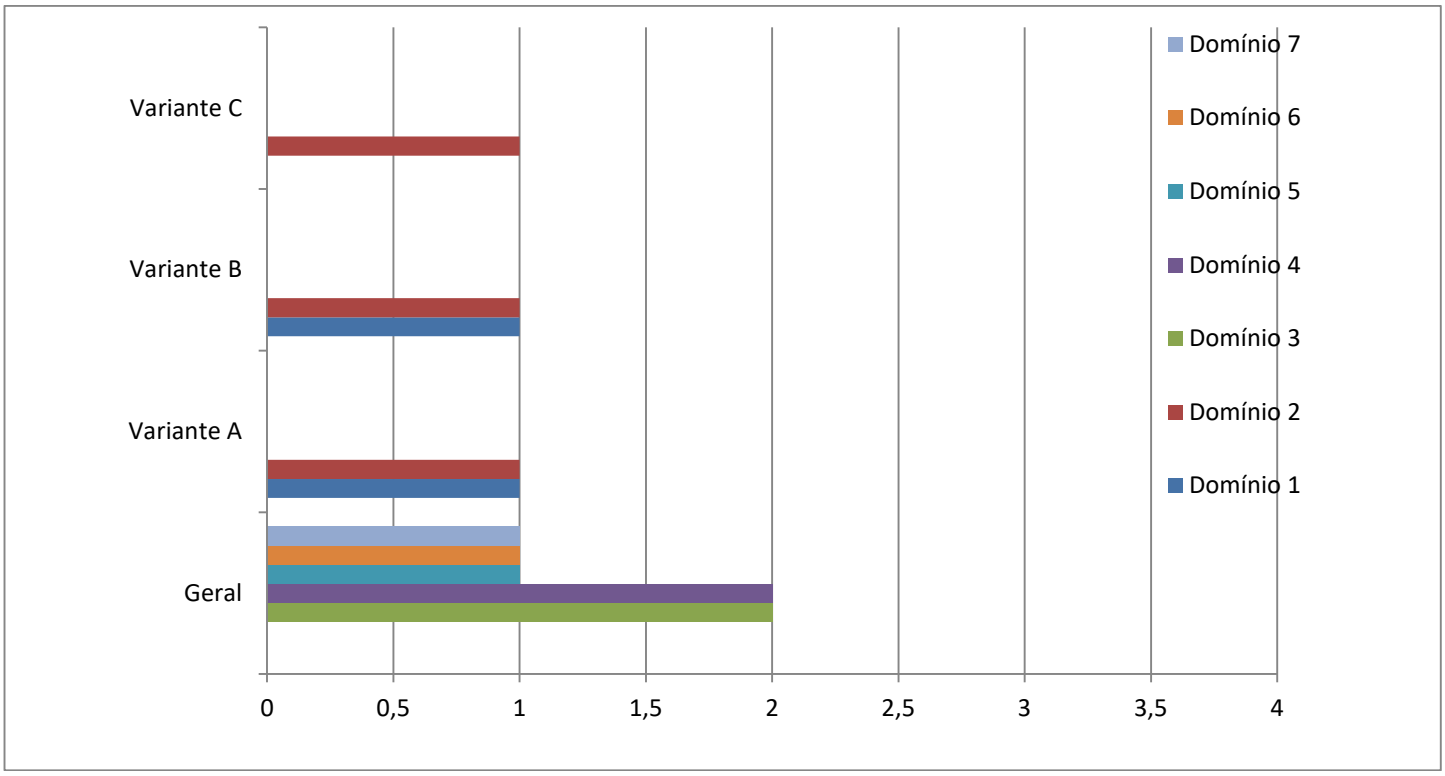
Legendas das Figuras[i]

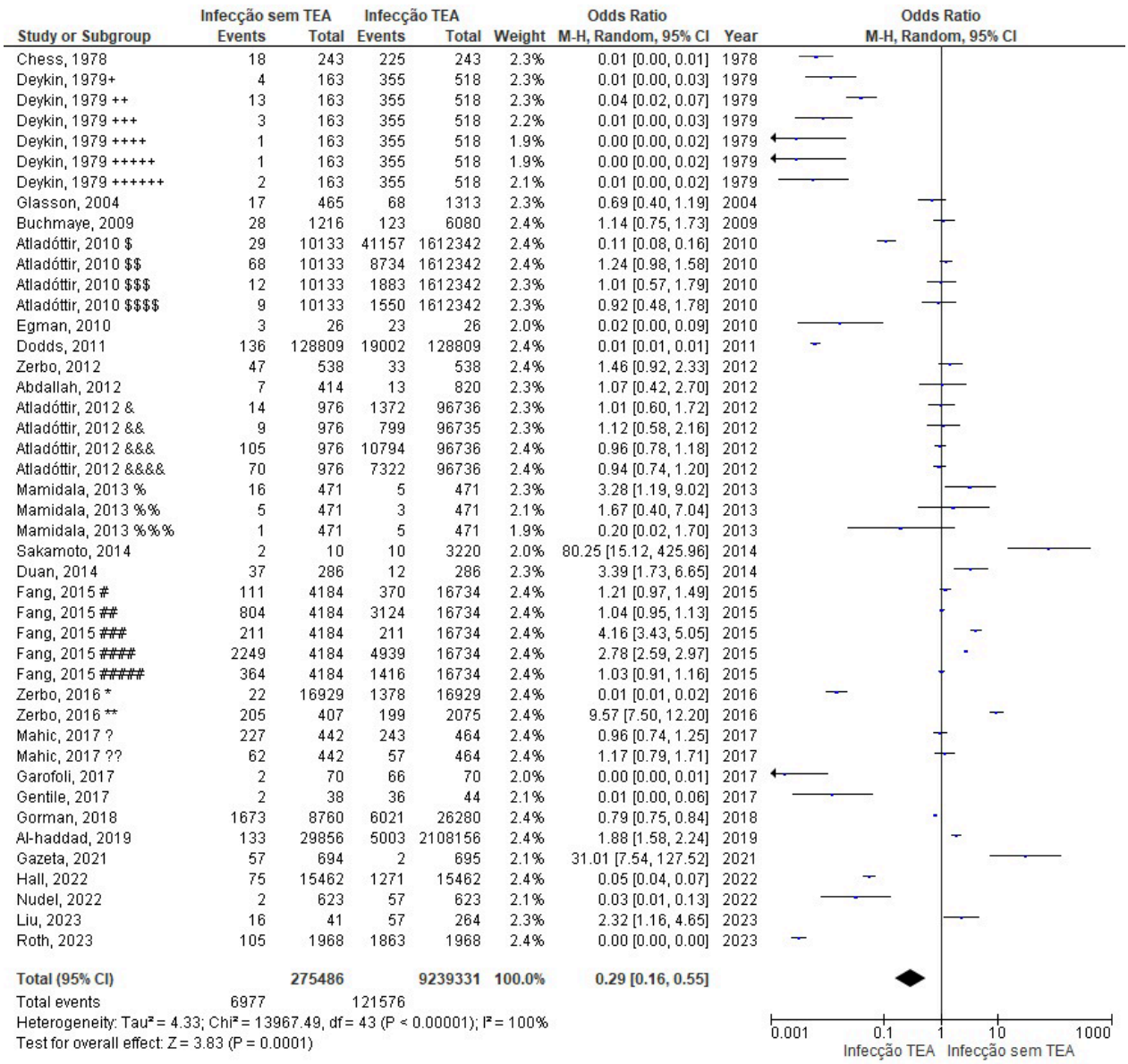
Fig. 1 Fluxograma PRISMA para identificar, selecionar e avaliar artigos incluídos na revisão. Roteiro baseado no modelo PRISMA 2020

Fig. 2 Propriedade do autor. 1- baixo risco de viés; 2- algumas preocupações; 3- alto risco de viés; 4- risco muito alto de viés

*Fig. 3. Propriedade do autor. Tipos de infecção: +herpes; ++ gripe; +++ pneumonia; ++++ varicela; +++++ sarampo; ++++++ febre não especificada; $ genital; $$ infecção urinária; $$$ cutânea; $$$$ viral; & herpes genital; && gripe; &&& herpes labial; &&&& trato respiratório; %%% trato respiratório; # ITU; ## genital; ### influenza; #### trato respiratório; ##### viral; * influenza; ** não especificado; ? herpes simplex 1; ?? herpes simplex 2*


Identificação de novos estudos em bases de dados e repositórios
Identificação
Seleção
Incluídos
Estudos identificados de:
Base de dados (n =12,866)
Registros removidos antes da triagem:
Registros duplicados removidos (n = 4.697)
Registros marcados como não elegíveis por ferramentas de automação (n = 0)
Registros triados (n = 8,169)
Registros excluídos (n= 8.094)
Publicações recuperadas (n=0)
Publicações não recuperadas (n=0)
Estudos selecionados para elegibilidade (n= 75)
Publicações excluídas: n=43
Não especifica gestação: n= 1
Texto completo não encontrado: n= 9
Não aborda infecção: n= 2
Infecção pós-natal: n= 2
Revisão sistemática: n= 4
Não aborda autismo: n= 2
Outros: n= 23
Novos estudos incluídos na revisão (n=0)
Total de estudos incluídos (n=32)
24qualitativos
8 quantitativos


Variante C
Variante B
Variante A
Geral
0
0,5
1
1,5
2
2,5
3
3,5
4
Domínio 7
Domínio 6
Domínio 5
Domínio 4
Domínio 3
Domínio 2
Domínio 1


Infecção sem TEA
Infecção TEA
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
Chess, 1978 18 243 225 243 2.3% 0.01 [0.00, 0.01] 1978
Deykin, 1979+ 4 163 355 518 2.3% 0.01 [0.00, 0.03] 1979
Deykin, 1979 ++ 13 163 355 518 2.3% 0.04 [0.02, 0.07] 1979
Deykin, 1979 +++ 3 163 355 518 2.2% 0.01 [0.00, 0.03] 1979
Deykin, 1979 ++++ 1 163 355 518 1.9% 0.00 [0.00, 0.02] 1979
Deykin, 1979 +++++ 1 163 355 518 1.9% 0.00 [0.00, 0.02] 1979
Deykin, 1979 ++++++ 2 163 355 518 2.1% 0.01 [0.00, 0.02] 1979
Glasson, 2004 17 465 68 1313 2.3% 0.69 [0.40, 1.19] 2004
Buchmaye, 2009 28 1216 123 6080 2.4% 1.14 [0.75, 1.73] 2009
Atladóttir, 2010 $ 29 10133 41157 1612342 2.4% 0.11 [0.08, 0.16] 2010
Atladóttir, 2010 $$ 68 10133 8734 1612342 2.4% 1.24 [0.98, 1.58] 2010
Atladóttir, 2010 $$$ 12 10133 1883 1612342 2.3% 1.01 [0.57, 1.79] 2010
Atladóttir, 2010 $$$$ 9 10133 1550 1612342 2.3% 0.92 [0.48, 1.78] 2010
Egman, 2010 3 26 23 26 2.0% 0.02 [0.00, 0.09] 2010
Dodds, 2011 136 128809 19002 128809 2.4% 0.01 [0.01, 0.01] 2011
Zerbo, 2012 47 538 33 538 2.4% 1.46 [0.92, 2.33] 2012
Abdallah, 2012 7 414 13 820 2.3% 1.07 [0.42, 2.70] 2012
Atladóttir, 2012 & 14 976 1372 96736 2.3% 1.01 [0.60, 1.72] 2012
Atladóttir, 2012 && 9 976 799 96735 2.3% 1.12 [0.58, 2.16] 2012
Atladóttir, 2012 &&& 105 976 10794 96736 2.4% 0.96 [0.78, 1.18] 2012
Atladóttir, 2012 &&&& 70 976 7322 96736 2.4% 0.94 [0.74, 1.20] 2012
Mamidala, 2013 % 16 471 5 471 2.3% 3.28 [1.19, 9.02] 2013
Mamidala, 2013 %% 5 471 3 471 2.1% 1.67 [0.40, 7.04] 2013
Mamidala, 2013 %%% 1 471 5 471 1.9% 0.20 [0.02, 1.70] 2013
Sakamoto, 2014 2 10 10 3220 2.0% 80.25 [15.12, 425.96] 2014
Duan, 2014 37 286 12 286 2.3% 3.39 [1.73, 6.65] 2014
Fang, 2015 # 111 4184 370 16734 2.4% 1.21 [0.97, 1.49] 2015
Fang, 2015 ## 804 4184 3124 16734 2.4% 1.04 [0.95, 1.13] 2015
Fang, 2015 ### 211 4184 211 16734 2.4% 4.16 [3.43, 5.05] 2015
Fang, 2015 #### 2249 4184 4939 16734 2.4% 2.78 [2.59, 2.97] 2015
Fang, 2015 ##### 364 4184 1416 16734 2.4% 1.03 [0.91, 1.16] 2015
Zerbo, 2016 * 22 16929 1378 16929 2.4% 0.01 [0.01, 0.02] 2016
Zerbo, 2016 ** 205 407 199 2075 2.4% 9.57 [7.50, 12.20] 2016
Mahic, 2017 ? 227 442 243 464 2.4% 0.96 [0.74, 1.25] 2017
Mahic, 2017 ?? 62 442 57 464 2.4% 1.17 [0.79, 1.71] 2017
Garofoli, 2017 2 70 66 70 2.0% 0.00 [0.00, 0.01] 2017
Gentile, 2017 2 38 36 44 2.1% 0.01 [0.00, 0.06] 2017
Gorman, 2018 1673 8760 6021 26280 2.4% 0.79 [0.75, 0.84] 2018
Al-haddad, 2019 133 29856 5003 2108156 2.4% 1.88 [1.58, 2.24] 2019
Gazeta, 2021 57 694 2 695 2.1% 31.01 [7.54, 127.52] 2021
Hall, 2022 75 15462 1271 15462 2.4% 0.05 [0.04, 0.07] 2022
Nudel, 2022 2 623 57 623 2.1% 0.03 [0.01, 0.13] 2022
Liu, 2023 16 41 57 264 2.3% 2.32 [1.16, 4.65] 2023
Roth, 2023 105 1968 1863 1968 2.4% 0.00 [0.00, 0.00] 2023
Total (95% CI) 275486 9239331 100.0% 0.29 [0.16, 0.55]
Total events 6977 121576
Heterogeneity: Tau² = 4.33; Chi² = 13967.49, df = 43 (P < 0.00001); I² = 100%
Test for overall effect: Z = 3.83 (P = 0.0001)
0.001
0.1
1
10
1000
Infecção TEA
Infecção sem TEA

Recurso online 1 – Tabela Suplementar 1: Planilha de extração de dados dos estudos incluídos

Autor, ano	Local	Desenho	Período	Critério Diagnóstico	Infecção	Infecção sem TEA		Infecção TEA	
						Eventos	Total	Eventos	Total
Glasson, 2004	Austrália	Caso-controle	19 years	DSM	ITU	17	465	68	1.313
Gentile, 2017	Itália	Caso-controle	2010-2013	DSM - IV	CMV	2	38	36	44
Roth, 2023	Porto Rico	Observacional	2016-2018	M-CHAT-R/F, ASQ: SE-2	Zika Virus	105	1.968	1.863	1.968
Mahic, 2017	Noruega	Coorte	1999-2008	/	HSV-1	227	442	243	464
					HSV-2	62	442	57	464
					Toxoplasma gondii	45	442	46	464
					Rubéola	435	442	462	464
					CMV	246	442	261	464
Deykin, 1979	Massachussets		1975-1977	/	Varicela	1	163	355	518
					Rubéola	2	163	355	518
					Sarampo	1	163	355	518
					Herpes	4	163	355	518

Autor, ano	Local	Desenho	Período	Critério Diagnóstico	Infecção	Infecção sem TEA		Infecção TEA	
						Eventos	Total	Eventos	Total
					Pneumonia	3	163	355	518
					Influenza	13	163	355	518
Sakamoto, 2014	Nagasaki	Retrospectivo	1994-2003	DSM - V	CMV	2	10	10	3.220
Chess, 1978	Nova York	Longitudinal	1978	/	Rubéola	18	243	225	243
Liu, 2023	China	Caso-controle	2018-2019	DSM - V	Infecção não Especificada	16	41	57	264
Nudel, 2022	Dinamarca	Caso-controle	1977-1994	CID-8 e CID-10	Infecção não Especificada	2	623	57	623
Hall, 2022	Reino Unido	Coorte	2000-2017	CID-10	Infecção não Especificada*	75	15.462	1.271	15.462
Gazeta, 2021	Jundiai	Coorte	2016-2019	/	Zikavirus	57	694	2	695
Croen, 2019’	EUA	Caso-controle	2007-2011	SQC, ADOS, MSEL, VABS-II, ADI-R	Vírus	82	606	104	796
Al-Haddad, 2019	Suécia	Coorte	1973-2014	CID-8, CID-9, CID-10	Infecção durante a gestação, infecção severa e ITU	133	29.856	5.003	2.108.56

Autor, ano	Local	Desenho	Período	Critério Diagnóstico	Infecção	Infecção sem TEA		Infecção TEA	
						Eventos	Total	Eventos	Total
MacKinsey, 2018	Jamaica	Caso-controle	/	DSM-IV, CARS	Infecção não Especificada	51	298	22	298
Gorman, 2018	EUA	Coorte	2000-2013	CID-9	Infecção não Especificada	1.673	8.760	6.021	26.280
Guisso, 2018	Líbano	Caso-controle	2018	DSM-IV + DSM-V	Influenza	10	136	8	178
Garofoli, 2017	Itália	Retrospectivo	2007-2012	DSM-IV	CMV	2	70	66	70
Zerbo, 2017	São Francisco	Coorte	2000-2010	CID-9	Influenza	22	196.929	1.378	196.929
Zerbo, 2017	Califórnia	Caso-controle	1995-1999	CID-9	Infecção não Especificada	205	407	199	2,075
Lee, 2014	Suécia	Coorte	1984-2011	CID-9, CID-10	Viral	11	2.362.262	8.980	2.371.403
Fang, 2015	Taiwan	Caso-controle	1998-2007	CID-9	ITU	111	4.184	370	16.734
					Respiratória	2.249	4.184	4.939	16.734
					Genital	804	4.184	3.124	16.734
					Viral	364	4.184	1.416	16.734
					Influenza	211	4.184	211	16.734

*Figura Suplementar 1

Autor, ano	Local	Desenho	Período	Critério Diagnóstico	Infecção	Infecção sem TEA		Infecção TEA	
						Eventos	Total	Eventos	Total
Mamidala, 2013	Índia	Caso-controle	2010-2012	DSM-IC, CID-10	GI	16	471	5	471
					Respiratória	1	471	5	471
					ITU	5	471	3	471
Langridge, 2013	Austrália	Caso-controle	1994-1999	DSM-IIIR, DSM-IV, DSM-IV-TR	ITU	7	727	5	452
Zerbo, 2012	Califórnia	Caso-controle	2003-2010	The Mullen Scales of Early Learning; Vineland; Adaptive Behavior Scales; Autism Diagnostic Interview-Revised; Autism Diagnostic; Observation Schedules-Generic Social Communication Questionnaire	Influenza	47	538	33	538
Atladóttir, 2012	Dinamarca	Coorte	1996-2002	CID-10	Influenza	9	976	799	96.736
					Respiratória	70	976	7.322	96.736
					Herpes Genital	14	976	1.372	96.736
					Herpes Labial	105	976	10.794	96.736

Abdallah, 2012	Dinamarca	Caso-controle	1982-2000	CID-8, CID-10	Infecção não Especificada	7	414	13	820
Autor, ano	Local	Desenho	Período	Critério Diagnóstico	Infecção	Infecção sem TEA		Infecção TEA	
						Eventos	Total	Eventos	Total
Dodds, 2011	Canada	Coorte	1990-2002	CID-9, CID-10	Infecção não Especificada	136	128.809	19.002	128.809
Atladóttir, 2010	Dinamarca	Coorte	1980-2005	CID-8, CID-10, DSM-IV	Viral	9	10.133	1.550	1.612.342
					Respiratória	12	10.133	1.883	1.612.342
					ITU	68	10.133	8.734	1.612.342
					Genital	29	10.133	41.157	1.612.342
Engman, 2010	Suécia	Retrospectivo	1988-2008	/	CMV	3	26	23	26
Buchmayer, 2009	Suécia	Caso-controle	1987-2002	CID-9, CID-10	Infecção não Especificada	28	1.216	123	6.080
Duan, 2014	China	Coorte	2011-2013	CARS	Infecção não Especificada	37	286	12	286

Online Resource 1 – Supplementary table 1: Data extraction spreadsheet for included articles

Author, year	Location	Design	Period	Diagnostic criterion	Type of infection	Infection no ASD		Infection ASD	
						Events	Total	Events	Total
Glasson, 2004	Australia	Case-control	19 years	DSM	ITU	17	465	68	1313
Gentile, 2017	Italy	Case-control	2010-2013	DSM - IV	CMV	2	38	36	44
Roth, 2023	Puerto Rico	Observacional	2016-2018	M-CHAT-R/F, ASQ: SE-2	Zika Virus	105	1968	1863	1968
Mahic, 2017	Norway	Cohort	1999-2008	/	HSV-1	227	442	243	464
					HSV-2	62	442	57	464
					Toxoplasma gondii	45	442	46	464
					Rubella	435	442	462	464
					CMV	246	442	261	464
Deykin, 1979	Massachussets		1975-1977	/	Chicken Pox	1	163	355	518
					Rubella	2	163	355	518
					Measles	1	163	355	518
					Herpes	4	163	355	518

Author, year	Location	Design	Period	Diagnostic criterion	Type of infection	Infection no	ASD	Infection	ASD
						Events	Total	Events	Total
					Pneumonia	3	163	355	518
					Influenza	13	163	355	518
Sakamoto, 2014	Nagasaki	Retrospective	1994-2003	DSM - V	CMV	2	10	10	3,220
Chess, 1978	New York	Longitudinal	1978	/	Rubella	18	243	225	243
Liu, 2023	China	Case-control	2018-2019	DSM - V	Unspecified infection	16	41	57	264
Nudel, 2022	Denmark	Case-control	1977-1994	CID-8 e CID-10	Unspecified infection	2	623	57	623
Hall, 2022	United Kingdom	Cohort	2000-2017	CID-10	Unspecified infection*	75	15,462	1,271	15,462
Gazeta, 2021	Jundiai	Cohort	2016-2019	/	Zikavirus	57	694	2	695
Croen, 2019’	USA	Case-control	2007-2011	SQC, ADOS, MSEL, VABS-II, ADI-R	Virus	82	606	104	796
Al-Haddad, 2019	Sweden	Cohort	1973-2014	CID-8, CID-9, CID-10	Maternal infection during pregnancy, severe infection and UTI	133	29,856	5,003	2,108,156
MacKinsey, 2018	Jamaica	Case-control	/	DSM-IV, CARS	Unspecified infection	51	298	22	298

Author, year	Location	Design	Period	Diagnostic criterion	Type of infection	Infection no	ASD	Infection	ASD
						Events	Total	Events	Total
Gorman, 2018	USA	Cohort	2000-2013	CID-9	Unspecified infection	1,673	8,760	6,021	26,280
Guisso, 2018	Lebanon	Case-control	2018	DSM-IV + DSM-V	Influenza	10	136	8	178
Garofoli, 2017	Italy	Retrospective	2007-2012	DSM-IV	CMV	2	70	66	70
Zerbo, 2017	San Fran.	Cohort	2000-2010	CID-9	Influenza	22	196,929	1,378	196,929
Zerbo, 2017	California	Case-control	1995-1999	CID-9	Unspecified infection	205	407	199	2,075
Lee, 2014	Sweden	Cohort	1984-2011	CID-9, CID-10	Viral	11	2,362,262	8,980	2,371,403
Fang, 2015	Taiwan	Case-control	1998-2007	CID-9	UTI	111	4,184	370	16,734
					Respiratory	2,249	4,184	4,939	16,734
					Genital	804	4,184	3,124	16,734
					Viral	364	4,184	1,416	16,734
					Influenza	211	4,184	211	16,734
Mamidala, 2013	India	Case-control	2010-2012	DSM-IC, CID-10	GI	16	471	5	471

*Supplementary Figure 1

Author, year	Location	Design	Period	Diagnostic criterion	Type of infection	Infection no ASD		Infection ASD	
						Events	Total	Events	Total
					Respiratory	1	471	5	471
					UTI	5	471	3	471
Langridge, 2013	Australia	Case-control	1994-1999	DSM-IIIR, DSM-IV, DSM-IV-TR	UTI	7	727	5	452
Zerbo, 2012	California	Case-control	2003-2010	The Mullen Scales of Early Learning; Vineland; Adaptive Behavior Scales; Autism Diagnostic Interview-Revised; Autism Diagnostic; Observation Schedules-Generic Social Communication Questionnaire	Influenza	47	538	33	538
Atladóttir, 2012	Denmark	Cohort	1996-2002	CID-10	Influenza	9	976	799	96,736
					Respiratory	70	976	7,322	96,736
					Genital herpes	14	976	1,372	96,736
					Cold sores	105	976	10,794	96,736
Abdallah, 2012	Denmark	Case-control	1982-2000	CID-8, CID-10	Unspecified infection	7	414	13	820
Dodds, 2011	Canada	Cohort	1990-2002	CID-9, CID-10	Unspecified infection	136	128,809	19,002	128,809

Author, year	Location	Design	Period	Diagnostic criterion	Type of infection	Infection no ASD		Infection ASD	
						Events	Total	Events	Total
Atladóttir, 2010	Denmark	Cohort	1980-2005	CID-8, CID-10, DSM-IV	Viral	9	10,133	1,550	1,612,342
					Respiratory	12	10,133	1,883	1,612,342
					UTI	68	10,133	8,734	1,612,342
					Genital	29	10,133	41,157	1,612,342
Engman, 2010	Sweden	Retrospective	1988-2008	/	CMV	3	26	23	26
Buchmayer, 2009	Sweden	Case-control	1987-2002	CID-9, CID-10	Unspecified infection	28	1,216	123	6,080
Duan, 2014	China	Cohort	2011-2013	CARS	Unspecified infection	37	286	12	286

Recurso Online 2 – Figura Suplementar 1, materiais suplementares de Hall et al.

Supplementary Materials Hall et. Al.

Table S1. ICD-10 codes representing infection from prenatal maternal hospital records.

Code Description	N
A04 Other bacterial intestinal infections	1
A49 Bacterial infection of unspecified site	5
A56 Other sexually transmitted chlamydial diseases	3
A60 Anogenital herpesviral [herpes simplex] infections	8
A63 Other predominantly sexually transmitted diseases, not elsewhere classified	8
A64 Unspecified sexually transmitted disease	1
B01 Varicella [chickenpox]	1
B16 Acute hepatitis B	2
B18 Chronic viral hepatitis	1
B37 Candidiasis infection	37
B95 Streptococcus, Staphylococcus, and Enterococcus as the cause of diseases classified elsewhere	93
B96 Other bacterial agents as the cause of diseases classified elsewhere	30
G00 Meningitis	1
I38 Emdocarditis	2
J22 Unspecified acute lower respiratory infection	6
L08 Other local infections of skin and subcutaneous tissue	2
N12 Tubulo-interstitial nephritis, not specified as acute or chronic	1
N30 Cystitis	1
N73 Other female pelvic inflammatory diseases	7
N76 Other inflammation of vagina and vulva	2
N77 Vulvovaginal ulceration and inflammation in diseases classified elsewhere	14
O23 Infections of genitourinary tract in pregnancy	148
O91 Infections of breast associated with pregnancy, the puerperium and lactation	2
R50 Fever of other and unknown origin	1
T88 Infection following immunization	3
Z20 Contact with and (suspected) exposure to communicable diseases	1

Figura suplementar 1 – Dados extraídos de Hall et al., 2022

Online Resource 2 – Suplementary Figure 1 , suplementary materials on Hall et al.

Supplementary Materials Hall et. Al.	
Table S1. ICD-10 codes representing infection from prenatal maternal hospital records.	
Code Description	
	N
A04 Other bacterial intestinal infections	1
A49 Bacterial infection of unspecified site	5
A56 Other sexually transmitted chlamydial diseases	3
A60 Anogenital herpesviral [herpes simplex] infections	8
A63 Other predominantly sexually transmitted diseases, not elsewhere classified	8
A64 Unspecified sexually transmitted disease	1
B01 Varicella [chickenpox]	1
B16 Acute hepatitis B	2
B18 Chronic viral hepatitis	1
B37 Candidiasis infection	37
B95 Streptococcus, Staphylococcus, and Enterococcus as the cause of diseases classified elsewhere	93
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G00 Meningitis	1
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J22 Unspecified acute lower respiratory infection	6
L08 Other local infections of skin and subcutaneous tissue	2
N12 Tubulo-interstitial nephritis, not specified as acute or chronic	1
N30 Cystitis	1
N73 Other female pelvic inflammatory diseases	7
N76 Other inflammation of vagina and vulva	2
N77 Vulvovaginal ulceration and inflammation in diseases classified elsewhere	14
O23 Infections of genitourinary tract in pregnancy	148
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R50 Fever of other and unknown origin	1
T88 Infection following immunization	3
Z20 Contact with and (suspected) exposure to communicable diseases	1

Suplementary figure 1 – Extracted data from Hall et al., 2022

ANEXO

Normas de Submissão Journal of Austim and Developmental Disorders

Instructions for Authors
Editorial procedure
Double-Anonymous Peer Review
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Back to top
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To ensure objectivity and transparency in research and to ensure that accepted principles of ethical and professional conduct have been followed, authors should include information regarding sources of funding, potential conflicts of interest (financial or non-financial), informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals.

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Back to top
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Summary of requirements
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Back to top
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Back to top
Research involving human participants, their data or biological material
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When reporting a study that involved human participants, their data or biological material, authors should include a statement that confirms that the study was approved (or granted exemption) by the appropriate institutional and/or national research ethics committee (including the name of the ethics committee) and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. If doubt exists whether the research was conducted in accordance with the 1964 Helsinki Declaration or comparable standards, the authors must explain the reasons for their approach, and demonstrate that an independent ethics committee or institutional review board explicitly approved the doubtful aspects of the study. If a study was granted exemption from requiring ethics approval, this should also be detailed in the manuscript (including the reasons for the exemption).

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It is recommended that authors check the NCBI database for misidentification and contamination of human cell lines. This step will alert authors to possible problems with the cell line and may save considerable time and effort.

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The above should be summarized in a statement and placed in a ‘Declarations’ section before the reference list under a heading of ‘Ethics approval’.

Examples of statements to be used when ethics approval has been obtained:

• All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Medical University of A (No. ...).

• This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University B (Date.../No. ...).

• Approval was obtained from the ethics committee of University C. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

• The questionnaire and methodology for this study was approved by the Human Research Ethics committee of the University of D (Ethics approval number: ...).

Examples of statements to be used for a retrospective study:

• Ethical approval was waived by the local Ethics Committee of University A in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

• This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the IRB of XYZ who determined that our study did not need ethical approval. An IRB official waiver of ethical approval was granted from the IRB of XYZ.

• This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of University B approved this study.

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• The data reproduced from Article X utilized human tissue that was procured via our Biobank AB, which provides de-identified samples. This study was reviewed and deemed exempt by our XYZ Institutional Review Board. The BioBank protocols are in accordance with the ethical standards of our institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Back to top

Informed consent

All individuals have individual rights that are not to be infringed. Individual participants in studies have, for example, the right to decide what happens to the (identifiable) personal data gathered, to what they have said during a study or an interview, as well as to any photograph that was taken. This is especially true concerning images of vulnerable people (e.g. minors, patients, refugees, etc) or the use of images in sensitive contexts. In many instances authors will need to secure written consent before including images.

Identifying details (names, dates of birth, identity numbers, biometrical characteristics (such as facial features, fingerprint, writing style, voice pattern, DNA or other distinguishing characteristic) and other information) of the participants that were studied should not be published in written descriptions, photographs, and genetic profiles unless the information is essential for scholarly purposes and the participant (or parent/guardian if the participant is a minor or incapable or legal representative) gave written informed consent for publication. Complete anonymity is difficult to achieve in some cases. Detailed descriptions of individual participants, whether of their whole bodies or of body sections, may lead to disclosure of their identity. Under certain circumstances consent is not required as long as information is anonymized and the submission does not include images that may identify the person.

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Regardless of whether material is collected from living or dead patients, they (family or guardian if the deceased has not made a pre-mortem decision) must have given prior written consent. The aspect of confidentiality as well as any wishes from the deceased should be respected.

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When biological material is donated for or data is generated as part of a research project authors should ensure, as part of the informed consent procedure, that the participants are made aware what kind of (personal) data will be processed, how it will be used and for what purpose. In case of data acquired via a biobank/biorepository, it is possible they apply a broad consent which allows research participants to consent to a broad range of uses of their data and samples which is regarded by research ethics committees as specific enough to be

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Please see the various examples of wording below and revise/customize the sample statements according to your own needs.

Sample statements for "Consent to participate":

Informed consent was obtained from all individual participants included in the study.

Informed consent was obtained from legal guardians.

Written informed consent was obtained from the parents.

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The authors affirm that human research participants provided informed consent for publication of the images in Figure(s) 1a, 1b and 1c.

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Back to top
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