UNIVERSIDADE FEDERAL DE PERNAMBUCO
CENTRO ACADÊMICO DA VITÓRIA

NATALIA REIS DE SOUZA NEGROMONTE

INFLUÊNCIA DA DIETA MATERNA PERINATAL SOBRE O ESTRESSE OXIDATIVO NO SISTEMA NERVOSO CENTRAL DA PROLE E SUA RELAÇÃO COM DOENÇAS NEUROGÊNICAS

VITÓRIA DE SANTO ANTÃO

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UNIVERSIDADE FEDERAL DE PERNAMBUCO
CENTRO ACADÊMICO DA VITÓRIA
PROGRAMA DE PÓS-GRADUAÇÃO EM NUTRIÇÃO, ATIVIDADE FÍSICA E PLASTICIDADE FENOTÍPICA

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Dissertação apresentada ao Programa de Pós-Graduação em Nutrição, Atividade Física e Plasticidade Fenotípica do Centro Acadêmico de Vitória de Santo Antão da Universidade Federal de Pernambuco, como requisito parcial para obtenção de título de mestre em Nutrição, Atividade Física e Plasticidade Fenotípica.

Orientadora: Prof.ª Dra. Raquel da Silva Aragão
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RESUMO

A dieta materna durante a gestação e lactação influencia a atividade de enzimas e níveis de biomarcadores relacionados ao estresse oxidativo no sistema nervoso da descendência. Trata-se de uma revisão sistemática da literatura para investigar os efeitos da dieta materna durante o período perinatal sobre o estresse oxidativo no sistema nervoso central (SNC) da prole e sua contribuição para o desenvolvimento das doenças neurogênicas. Foram realizadas buscas nas bases de dados Pubmed, Embase, Web of Science, Scopus, Lilacs e Cochrane entre dezembro de 2020 a janeiro de 2021 com atualização em janeiro de 2022. Dois revisores independentes extraíram os dados e avaliaram a qualidade dos estudos incluídos. Foram encontrados 2.563 trabalhos, que passaram por etapas de exclusão de duplicatas, leituras e avaliações. Vinte e seis artigos foram incluídos na revisão. Em relação às dietas, os tipos mais encontrados foram: hipoproteicas, modificadas na quantidade ou tipo de gordura e mudanças na quantidade de micronutrientes (como vitaminas C, D, E, B9, B12, cobalamina, colina, e o mineral vanádio). As regiões do SNC mais estudadas foram encéfalo, tronco encefálico, córtex cerebral, cerebelo e hipocampo. Dentre os marcadores mais estudados de estresse oxidativo, estavam níveis de malondialdeído (MDA), proteínas carboniladas, glutationa (GSH) e glutationa dissulfeto (GSSG) e atividades de enzimas, como superóxido dismutase (SOD), catalase (CAT), glutationa peroxidase (GPx), glutationa redutase (GR). Nos estudos com dieta materna hipoproteica, foi observada, em sua maioria, níveis aumentados de MDA e redução da atividade da SOD e CAT. Os resultados em relação aos níveis de carbonilas e GSH foram divergentes. Os trabalhos com modificações de lipídios na dieta materna também apresentaram resultados conflitantes. Poucos trabalhos realizaram análises comportamentais ou outros testes em conjunto com o estudo do estresse oxidativo. Naqueles que realizaram alguma análise secundária, os resultados encontrados também foram mistos. Desequilíbrios na dieta materna durante a gestação e/ou lactação podem influenciar o aumento dos biomarcadores de estresse oxidativo e prejudicar a atividade das enzimas antioxidantes, reduzindo sua atividade no sistema nervoso central. Contudo, diferenças nas elaborações das dietas, no período realizado e estrutura de análise do estresse oxidativo nos filhotes levam a divergências nos resultados. Devido às divergências, não foi possível fazer uma relação direta entre as mudanças no equilíbrio oxidativo e as repercussões secundárias.

Palavras-chave: nutrição materna; balanço oxidativo; espécies reativas de oxigênio; antioxidante; comportamento; filhotes.

ABSTRACT

Maternal diet during pregnancy and lactation influences the activity of enzymes and levels of biomarkers related to oxidative stress in offspring central nervous system (CNS). This is a systematic review of the literature to investigate the effects of maternal diet during the perinatal period on oxidative stress in the offspring's central nervous system (CNS) and its contribution to the development of neurogenic diseases. Pubmed, Embase, Web of Science, Scopus, Lilacs, and Cochrane databases were searched between December 2020 and January 2021 with an update in January 2022. Two independent reviewers extracted data and assessed the quality of included studies. A total of 2,563 works were found, which underwent steps of deleting duplicates, readings, and evaluations. Twenty-six articles were included in the review. Regarding the diets, the most common were protein restriction, modification of amount or type of fat, and modification of micronutrients (such as vitamins C, D, E, B9, B12, cobalamin, choline, and the mineral vanadium). The most studied CNS regions were brain, brainstem, cerebral cortex, cerebellum, and hippocampus. Among the most studied markers of oxidative stress were levels of malondialdehyde (MAD), carbonyl proteins, glutathione (GSH), and glutathione disulfide (GSSG) and enzyme activities such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR). In studies with low-protein maternal diet, increased levels of MDA and reduced activity of SOD and CAT were observed. Results regarding carbonyl and GSH levels were divergents. The studies with modifications of lipids in the maternal diet also presented conflicting results. Few studies performed behavioral analyzes or other tests in conjunction with the study of oxidative stress. In those who performed some secondary analysis, the results were also mixed. Imbalances in the maternal diet during pregnancy and/or lactation may influence the increase of oxidative stress biomarkers levels and impair the activity of antioxidant enzymes, reducing their activity in the central nervous system. However, differences in elaboration of diets and the age and sample of analysis of oxidative stress in pups lead to divergences in the results. Due to divergences, it was not possible to make a direct relationship between changes in oxidative balance and secondary repercussions.

Keywords: maternal nutrition; oxidative balance; reactive oxygen species; antioxidant; behavior; brain.

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6-OHDA	6-hidrodopamina
8-OHdG	8-hidroxi-2-deooxiguanosina
8OHG	8-hidroxiguanosina
B12	Cobalamina
B2	Riboflavina
B6	Piridoxina
B9	Ácido fólico
CAT	Catalase
CC	Córtex cerebral
CDD	*Choline-deficient diet* (dieta deficiente em colina)
CSD	*Cortical spreading depression* (depressão alastrante cortical)
CTR	Grupo controle
Cu	Cobre
DHA	Ácido docosahexaenóico
DNA	Ácido desoxirribonucleico
EO	Estresse oxidativo
EPMT	*Elevated plus maze* (labirinto elevado em cruz)
EROS	Espécies reativas de oxigênio
FD	*Folate-depleted* (dieta deficiente em folato)
G6PDH	Glicose-6-fosfato deidrogenase
GD	*Gestacional day* (dia de gestação)
GPx	Glutationa peroxidase
GR	Glutationa redutase
GSH	Glutationa, glutationa reduzida
GSSG	Glutationa dissulfeto, glutationa oxidada
GST	Glutationa-S-Transferase
HHE	Hexenal
HNE	4-hidroxi-2-nonenal
LP	*Low-protein diet* (dieta deficiente em proteína)
MBP	*Myelin basic protein* (proteína básica de mielina)
MDA	Malondialdeído
MET	Metionina

Mn	Manganês
MS	*Maternal separation* (separação materna)
N	*Number* (número)
OFT	*Open field test* (teste de campo aberto)
OH	Radical hidroxila
OOED	*Olive oil-enriched diet* (dieta enriquecida com óleo de oliva)
PND	*Posnatal day* (dia pós-natal)
RBD	*Regional basic diet* (dieta básica regional)
Se	Selênio
SG	Grupo Safflower
SNC	Sistema nervoso central
SOD	Superóxido dismutase
SPT	*Sucrose preference test* (teste de preferência de sacarose)
SUPP	Suplementada
TAS	Estado antioxidante total
TBA	Ácido tiobarbitúrico
TBARS	Substâncias reativas ao ácido tiobarbitúrico
ZDD	*Zinc deficient diet* (dieta deficiente em zinco)
Zn	Zinco

SUMÁRIO

1 INTRODUÇÃO

Sabe-se que, no sistema nervoso central, o encéfalo, é um órgão bastante sensível à ação das espécies reativas (MORITZ, 2013). Isto acontece devido a fatores como elevado consumo de oxigênio, cerca de 20% do total consumido pelo corpo, que promove elevada formação de espécies reativas (DE SOUSA *et al.*, 2018). Além disso, a composição lipídica da membrana plasmática e a presença de íons metálicos colaboram para maior formação destes agentes oxidantes (DE SOUSA *et al.*, 2018). O mecanismo de geração de espécies reativas ocorre de modo fisiológico nas mitocôndrias, nas membranas celulares e no citoplasma (BARBOSA *et al.*, 2010) Essa atividade acontece naturalmente no organismo e é limitada pelos sistemas de defesa antioxidante (BARBOSA *et al.*, 2010). Quando há aumento na formação destes compostos reativos e/ou alteração nos sistemas antioxidantes, com o predomínio de agentes oxidantes, surge o estresse oxidativo (HALLIWELL, 1992).

A presença do estresse oxidativo influencia a progressão de doenças neurodegenerativas, cardiovasculares, diabetes e câncer (BARBOSA *et al.*, 2010; VANHEES *et al.*, 2014). Na Doença de Alzheimer, é mencionada a elevação natural do estresse oxidativo que, ao associar-se com proteínas oxidadas e inflamação local, ocasiona a morte neuronal (GEMELLI, *et al.*, 2013). Em casos de Doença de Parkinson, defende-se que a sua progressão esteja relacionada à excessiva produção de espécies reativas, gerando lesões contínuas em neurônios (PÔRTO, 2001).

O fator de maior de impacto durante a fase inicial da vida para o surgimento de danos relacionados ao desenvolvimento cerebral do feto é a nutrição materna (MORGANE; MOKLER; GALLER, 2002). Pesquisas têm associado insultos nutricionais durante as primeiras fases da vida com doenças na idade adulta, aumentando a predisposição ao desenvolvimento de patologias como doenças cardiovasculares, diabetes mellitus e alterações neurogênicas - como má-programação de funções cerebrais e repercussões no neurodesenvolvimento (EDLOW, 2017; FISHER; STEELE; KARROW, 2012). Por exemplo, o quadro de desnutrição materna pode refletir de modo permanente no cérebro do filhote, interferindo na sua anatomia, na sua fisiologia e na sua bioquímica (SOUZA; FERNANDES; CARMO, 2011). A restrição de proteína durante o período de gestação e lactação pode contribuir para atraso e danos no desenvolvimento cerebral do

embrião (AUGUSTO *et al.*, 2017). A deficiência de micronutrientes, como o folato, pode trazer prejuízos ao embrião por participar da divisão celular e da síntese proteica (VITOLO, 2008). Sua carência também está relacionada a defeitos no desenvolvimento do tubo neural, atraso no crescimento pós-natal e desordens cerebrais a longo termo (KEREK *et al.*, 2013).

A dieta restrita em proteína durante o período de gestação e lactação pode alterar o status oxidativo do tronco encefálico de ratas jovens (BRAZ *et al.*, 2017). Este fato pode ser justificado pelo fato desta alimentação promover mudanças nas concentrações de biomarcadores do estresse oxidativo, como malondialdeído (MDA) e carbonilas, e aumento na atividade de algumas enzimas, como superóxido dismutase (SOD) (BRAZ *et al.*, 2017). Por outro lado, é sugerido que os efeitos de uma má nutrição no cérebro não sejam justificados exclusivamente pela diminuição de proteína, existindo outros parâmetros a serem avaliados (FEOLI *et al.*, 2006).

Modificações nos lipídios da dieta materna também são descritos como importantes contribuidores para o surgimento de doenças na prole e têm sido evidenciadas as consequências da suplementação/deficiência dos ácidos graxos na expressão gênica de diversas proteínas no sistema nervoso central (PASE *et al.*, 2015). As características das gorduras dietéticas consumidas durante o período crítico do desenvolvimento podem influenciar em importantes etapas do progresso do sistema nervoso, como a neurogênese, a diferenciação celular e a formação das sinapses (QUEIROZ *et al.*, 2019).

Desta forma, em virtude das informações apresentadas, percebe-se a importância de se investigar os efeitos da dieta materna durante a gestação e lactação sobre o estresse oxidativo no sistema nervoso central da prole e o desenvolvimento de doenças neurogênicas. A hipótese deste trabalho é que o desequilíbrio da dieta materna durante a gestação e lactação é capaz de aumentar o estresse oxidativo no sistema nervoso central da prole, contribuindo para o desenvolvimento de doenças neurogênicas.

2 REVISÃO DA LITERATURA

2.1 Plasticidade fenotípica

A plasticidade fenotípica se refere às possibilidades de um mesmo genótipo, a depender das condições do ambiente, apresentar-se fenotipicamente de formas distintas quanto a sua morfologia, sua fisiologia e/ou seu comportamento (WEST-EBERHARD, 1989). Quando este evento acontece nos estágios iniciais da vida, fase considerada como bastante sensível e plástica, é chamada de plasticidade do desenvolvimento (WEST-EBERHARD, 1989). Após o período de concepção, ocorrem diversas mudanças no embrião, como as morfológicas, com o surgimento de células embrionárias e placentárias; as genômicas, com modificações epigenéticas; e as no metabolismo, com adaptações para o crescimento e o suprimento energético (FLEMING *et al.*, 2018).

Os primeiros trabalhos populacionais que abordavam os efeitos de eventos ocorridos durante o período intraútero foram relativos à nutrição, especificamente sobre a restrição alimentar sofrida pelo povo holandês (*Dutch Famine*) durante a Segunda Guerra Mundial (SCHULZ, 2010). Devido à diminuição na ingestão de alimentos, com o consumo médio alimentar pela população de 400-800 kcal por dia, verificou-se nos descendentes algumas particularidades no metabolismo, na saúde cardiovascular e declínio cognitivo (SCHULZ, 2010). Percebeu-se que, quando as alterações de restrição alimentar aconteciam no final da gestação, os indivíduos nasciam pequenos e que esta característica perdurava durante a vida adulta. Ao ocorrer contenções no início da gestação, observava-se elevadas taxas de obesidade, alterações lipídicas e doenças cardiovasculares (SCHULZ, 2010).

A partir dessas pesquisas, surgiu a hipótese do Fenótipo Poupador *(Thrifty Phenotype)*, que propõe mecanismos de economia de nutrientes sobre o indivíduo em crescimento, priorizando o desenvolvimento de determinados órgãos em detrimento de outros (HALES; BARKER, 2001). Segundo esta teoria, quando em situação de desnutrição, o organismo impediria o adequado crescimento fetal devido à diminuição no fluxo sanguíneo para músculos, fígado, pâncreas e rins, proporcionando, deste modo, um apropriado suprimento de sangue e nutrientes para o cérebro (BARKER *et al.*, 2002). Desta forma, haveria mudança no metabolismo e resposta fisiológica desses tecidos que, quando o organismo é submetido a um ambiente pós-natal com

melhores condições nutricionais, culminaria no aparecimento de diabetes tipo 2, doenças coronarianas, síndrome metabólica, dentre outros agravos de saúde, na vida adulta (HALES; BARKER, 2001).

Outro modelo teórico apresentado foi o *"Programming"*, no qual se defende que os acontecimentos ocorridos no período da janela crítica do desenvolvimento são estímulos que geram consequências na evolução do ser e possuem relação com o desenvolvimento da maioria das doenças da vida adulta, atuando como uma programação (LUCAS, 1991). Mudanças na nutrição de animais têm sido apresentadas como um preditivo do tamanho do descendente na vida adulta, funcionamento metabólico, pressão arterial, obesidade, diabetes, aprendizado e comportamento (LUCAS, 1998).

Esses modelos propostos resultaram na hipótese da Origem Desenvolvimentista da Saúde e da Doença (do inglês, *Developmental Origins of Health and Disease – DOHaD*) (BARKER, 2007). Este conceito mais abrangente engloba a relação do ambiente materno e precoce no desenvolvimento, na vida adulta da descendência, de hábitos e condições de vida saudável ou de modificações metabólicas, fisiológicas, comportamentais que levam a comportamentos sedentários, compulsivos e desenvolvimento de doenças (BARKER, 2007). O ambiente fetal reage de acordo com o universo materno e com respostas fisiológicas da mãe e da placenta (GLUCKMAN; HANSON, 2004). As mudanças ocorridas durante a gestação permitem transformações nas estruturas e funções de alguns órgãos da prole, influenciando na sua saúde futura (CARPITA; MUTI; DELL'OSSO, 2018; HSU; TAIN, 2019). A nutrição materna, seja a restrição e/ou o excesso de nutrientes, e a presença do fator estresse são elementos que estão fortemente associados ao surgimento de transtornos do desenvolvimento, inclusive relacionados ao sistema nervoso (BALE, 2014; MARQUES *et al.*, 2015).

Eventos circunstanciais ocorridos durante a gestação podem promover mecanismos adaptativos e complexos para proteção do feto, que atuam de acordo com as particularidades genéticas, associados à exposição ambiental e à epigenética de cada indivíduo (HANSON *et al.*, 2011). Essas transformações podem acontecer através de modificações epigenéticas nas células germinativas, como a metilação do DNA, e atuar como uma "programação" de desenvolvimento e manutenção da vida (BALE, 2014; BARKER; OSMOND; LAW, 1989; HANSON *et al.*, 2011).

O momento exato de maior susceptibilidade do organismo, todavia, tem sido investigado a fim de se planejar a devida proteção e traçar as devidas intervenções (FLEMING *et al.*, 2018). Sabe-se que as fases iniciais da vida (gestação e infância) são caracterizadas pela necessidade do consumo equilibrado de nutrientes, especialmente ácido fólico, cobre e vitamina A para a formação adequada da placa neural e do tubo neural, estruturas consideradas bases para o desenvolvimento cognitivo, motor e socioemocional do indivíduo (PRADO; DEWEY, 2014). Os macronutrientes, como os lipídios, também exercem atividades importantes neste período, pois são essenciais para as funções de membrana, sinápticas e mielinização e as proteínas, que responsáveis pelo desempenho cognitivo (PRADO; DEWEY, 2014).

2.2 Radicais Livres e Espécies Reativas de Oxigênio

O conceito de radical livre inclui qualquer espécie que possua um ou mais elétrons desemparelhados em seu orbital (HALLIWELL, 2006). Os radicais superóxido e hidroxila e o não-radical peróxido de hidrogênio surgem da redução univalente do oxigênio e, para que estas atividades ocorram, é necessária a participação de enzimas com função catalisadoras e da presença de íons como o ferro e o cobre (BARBOSA *et al.*, 2010).

A formação de espécies reativas de oxigênio (EROs) é um processo fisiológico, que ocorre nas membranas celulares, no citoplasma e, principalmente, nas mitocôndrias (BARBOSA *et al.*, 2010). Estas moléculas são constituídas por espécies reativas - como o superóxido e o radical hidroxila - e outros não-radicais que possuem funções oxidantes e/ou que são transformados em radicais distintos, como o ácido hipocloroso, o ácido hipobromoso e o peroxinitrito (HALLIWELL, 2006).

O peróxido de hidrogênio, outra espécie reativa de oxigênio, é considerado uma substância tóxica para as células e – em associação com determinados metais – é capaz de produzir espécies reativas, como o radical hidroxila (HALLIWELL, 2006).

Para que ocorra a formação deste radical é necessária a atuação de alguns íons, como o ferro e o cobre, que estão presentes na membrana cerebral (SOUSA, 2016). Eles atuam como enzimas catalisadoras de reações, como na Reação de Fenton, na qual o peróxido de hidrogênio, em associação com o ferro e o cobre, resulta no radical hidroxila; e na Reação de Haber-Weiss, na qual estes metais em questão

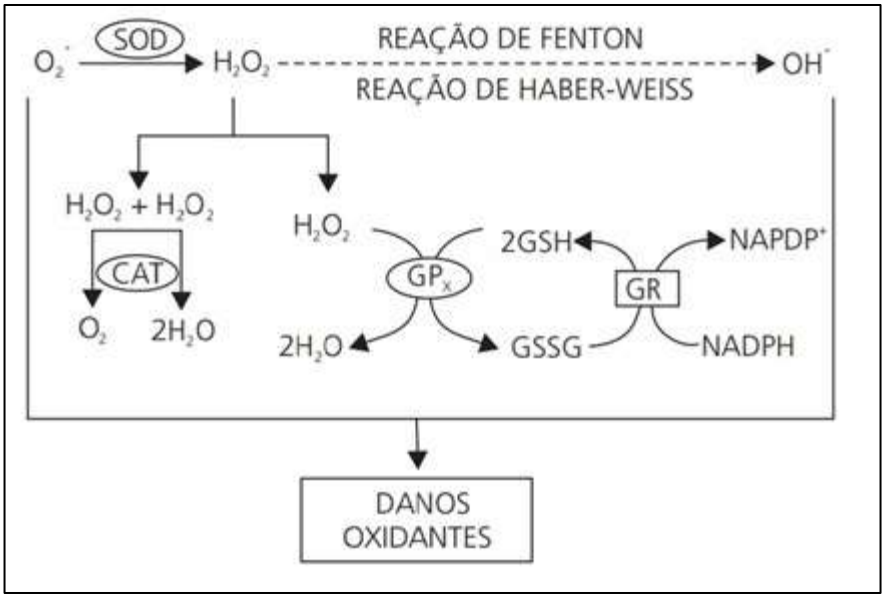
catalisam a reação entre o peróxido de hidrogênio e o radical superóxido a afim de também gerar o mesmo radical (BARBOSA *et al.*, 2010).

2.3 Sistemas de defesa antioxidantes (enzimático e não enzimático)

Dentre os sistemas de defesa antioxidantes, compreende-se o enzimático e o não-enzimático, ao qual fazem parte do enzimático a superóxido dismutase (SOD), a catalase (CAT), as peroxidases (glutationa peroxidase - GPx, tioredoxina peroxidase e citocromo peroxidase), glutationa redutase (GR) e glutationa-S-transferase (GST) (FERREIRA; LAGRANHA, 2013). A enzima superóxido dismutase, considerada a primeira na linha de defesa, apresenta-se de três formas (SOD1, SOD2 e SOD3) a depender da localização e de seu cofator metálico e possui como produto final da reação o peróxido de hidrogênio – produto rapidamente processado por meio das enzimas CAT e GPx (PASCHOAL; NAVES; FONSECA, 2007). A família das peroxidases atua em associação com alguns agentes (ascorbato, ferrocitocromo c, tioredoxina, NADH e glutationa) e atuam com o objetivo de reduzir o peróxido de hidrogênio (H_2O_2) à água (H_2O) e oxigênio (O_2), porém desempenhando uma atividade mais baixa ao compararmos com a CAT (FERREIRA; LAGRANHA, 2013).

As enzimas CAT e GPx impedem e/ou regulam o acúmulo de peróxido de hidrogênio, convertendo-o para água e oxigênio, evitando a consequente formação do radical hidroxila (OH) - um dos precursores da peroxidação lipídica (BARBOSA *et al.*, 2010). A enzima GR é responsável por catalisar a reação de conversão da glutationa dissulfeto (GSSG) em glutationa reduzida (GSH) (BARBOSA *et al.*, 2010). A GSH é considerada a principal molécula endógena antioxidante e que concede hidrogênio ao átomo de enxofre para que aconteça a transformação de um radical em molécula não reativa (RODRIGO; GUICHARD; CHARLES, 2007). A razão GSH/GSSG é um parâmetro da homeostase redox dentro da célula (BURTON; JAUNIAUX, 2011; PÔRTO, 2001; SALIM, 2017). A GST pertence a um grupo de proteínas denominadas citosólicas, mitocondriais e microssomais ou associadas a membranas, a depender da sua localização (FERREIRA; LAGRANHA, 2013). Possuem a função de proteção da célula contra compostos tóxicos (endógenos e exógenos), metabolizando diversos substratos através da associação com a GSH (FERREIRA; LAGRANHA, 2013).

Figura 1 – Integração dos sistemas de defesa enzimático e não-enzimático.



Fonte: Adaptado de Barbosa *et al.* (2010).

O sistema de defesa não-enzimático inclui compostos dietéticos como vitamina A (alfa, beta e gama caroteno), vitamina C (ascorbato), vitamina E (oito diferentes isômeros), ácido alfa-lipóico, fitoquímicos (flavonóides, lignanas, fenóis) e os minerais cobre (Cu), zinco (Zn), manganês (Mn) e selênio (Se) (VINCENT; INNES; VINCENT, 2007). A vitamina A e os fitoquímicos desempenham papel importante contra a oxidação de lipídeos e DNA (BARBOSA *et al.*, 2010). A vitamina C atua na inibição das espécies reativas de oxigênio e contribui para a atividade do selênio e da vitamina E (BARBOSA *et al.*, 2010). Por sua vez, a vitamina E exerce proteção contra a peroxidação dos ácidos graxos (BARBOSA *et al.*, 2010). Os minerais Cu, Zn, Mn e Se atuam como cofatores das enzimas antioxidantes (BARBOSA *et al.*, 2010).

Os elementos que os transportam, armazenam e utilizam o ferro na forma de transferrina, ferritina e ceruloplasmina podem ser incluídos como agentes antioxidantes não-enzimáticos, pois modulam as reações geradoras de espécies reativas (BARBOSA *et al.*, 2010). Modificações no metabolismo deste mineral, agregação de proteínas, estresse oxidativo, disfunções mitocondriais, dentre outros fatores têm sido investigados quanto a sua relação com o surgimento da neurodegeneração (BUTTERFIELD; HALLIWELL, 2019; FERREIRA *et al.*, 2019; HALLIWELL, 2006).

2.4 Estresse oxidativo

O estresse oxidativo (EO) acontece quando há um desequilíbrio na geração de espécies reativas, com predomínio da ação oxidativa, no sistema de defesa antioxidante, ou em ambos, ocasionando a formação de moléculas extremamente reativas, que provocam a oxidação de lipídios, de proteínas e do DNA (HALLIWELL, 2006).

Estudos têm demonstrado a relação da oxidação proteica com o processo de envelhecimento e de adoecimento devido a sua significância para o surgimento do EO e, consequentemente, a associação com o prejuízo na sinalização, estrutura celular, e metabolismo de enzimas (PASCHOAL; NAVES; FONSECA, 2007). Diversos produtos podem ser mensurados para avaliar o dano oxidativo ocorrido nas proteínas, como a 3-nitrosamina, geralmente produzida pela reação do superóxido com o óxido nítrico para formar peroxinitrito; as carbonilas, originadas por meio de mecanismos diversos e aldeídos bastante reativos, como a 4-hidroxi-2-nonenal (HNE), hexenal (HHE) e 2-propeno-1-al (acroleína) (BUTTERFIELD; HALLIWELL, 2019).

A oxidação de lipídeos pode ser indicada pelos conteúdos de peróxidos lipídicos, peróxidos cíclicos e pela família de isoprostanos (F2, F3 e F4) (BUTTERFIELD; HALLIWELL, 2019). Um dos mais importantes indicadores da peroxidação lipídica são os F2-isoprostanos, que – assim como seus metabólitos - podem ser mensurados no plasma, soro ou urina (HALLIWELL; LEE, 2010). A atividade de oxidação surge quando o radical hidroxila retira o hidrogênio presente nos lipídios da membrana, formando um radical de carbono central que, ao reagir com o oxigênio, forma um radical peroxil (PÔRTO, 2001). Este radical, por sua vez, reage com os átomos de hidrogênio dos ácidos graxos, iniciando a formação de hidroxiperóxidos e do malondialdeído (MDA), outro composto conhecido como um dos biomarcadores da peroxidação lipídica e que é quantificado através da reação com o ácido tiobarbitúrico (TBA) (BUEGE; AUST, 1978).

O DNA também é suscetível à ação das espécies reativas e, ao modificar a atividade gênica, também favorece o desenvolvimento de patologias (PASCHOAL; NAVES; FONSECA, 2007). O DNA mitocondrial é mais propenso à ação das espécies reativas, quando comparado ao DNA nuclear e isto é justificado devido à localização próxima à cadeia respiratória mitocondrial – local de grande produção das EROS (PÔRTO, 2001). A avaliação do dano oxidativo do DNA pode acontecer pela mensuração da 8-hidroxi-2-deooxiguanosina (8-OHdG), base oxidativa pesquisada

principalmente na urina (GRAILLE *et al.*, 2020). A oxidação de proteínas é derivada da reação do radical hidroxila e do oxigênio *singlet*, a partir da qual são produzidos peróxidos de aminoácidos e proteínas carboniladas (FRISARD; RAVUSSIN, 2006). Sugere-se que a oxidação de enzimas metabólicas, com atividade na glicólise e ciclo de Krebs, favoreça o estresse oxidativo e, consequentemente, o processo de envelhecimento celular e surgimento de patologias, como as doenças neurogênicas (PASCHOAL; NAVES; FOSECA, 2007; PÔRTO, 2001).

2.5 Modificações na dieta materna e repercussões no estresse oxidativo da prole

Modificações na quantidade e qualidade de diversos nutrientes maternos repercutem na saúde da prole (MOUSA; NAQASH; LIM, 2019). Este fato reforça a importância da adequação nutricional e vincula à possibilidade da realização de um planejamento dos nutrientes ofertados a fim de se prevenir o desenvolvimento de diversas doenças crônico-degenerativas (HSU; TAIN, 2019). Entretanto, especificidades quanto ao tipo de intervenção, à população correta, ao tempo correto em que é utilizado, à quantidade indicada e à duração da terapêutica são algumas variáveis que necessitam uma maior compreensão e bases científicas (HSU; TAIN, 2019).

Diversos nutrientes desempenham funções importantes para que aconteça um satisfatório crescimento fetal (VANHEES *et al.*, 2014). O estado nutricional da gestante revela se as suas demandas fisiológicas estão sendo alcançadas e se há um equilíbrio entre o consumo e o gasto energético - fatores que possuem relação com o previsto crescimento e desenvolvimento do feto (DAL BOSCO, 2015). Neste período, há aumento da necessidade de alguns nutrientes, pois há maior demanda de algumas substâncias pelo organismo e as suas deficiências podem gerar consequências na saúde materna e fetal (DAL BOSCO, 2015).

A carência de nutrientes no feto pode ocorrer em razão de deficiência primária, decorrente da ingestão materna insuficiente, ou decorrer de deficiências secundárias, tais quais fatores genéticos, interações entre os nutrientes da dieta, e até mesmo pela utilização de medicamentos ou pela presença de doenças (HIRSCHI; KEEN, 2000). Alterações na dieta durante o período pré-concepcional e de gestação estão relacionadas ao desenvolvimento de patologias na prole adulta, principalmente as

desordens cardiovasculares e neuropsiquiátricas (CARPITA; MUTI; DELL'OSSO, 2018; RAMÍREZ-LÓPEZ *et al.*, 2015).

A ingestão alimentar energética e proteica da mãe deve ser equilibrada para que ocorra o adequado crescimento fetal e que não haja desvio de nutrientes - com o objetivo de manutenção energética da prole (GOODNIGHT; NEWMAN, 2009). A desnutrição materna durante a gestação é relacionada a desfechos como retardo no crescimento fetal, baixo peso ao nascer e repercussões no desenvolvimento e funções de órgãos, todavia, o excesso de nutrientes acarreta macrossomia, com obesidade e uma predisposição a excesso de peso na infância e doenças cardiovasculares (MORENO-FERNANDEZ *et al.*, 2020).

Mudanças na dieta materna, como a restrição proteica, podem ocasionar alterações no balanço entre oxidantes e antioxidantes, sendo possível induzir um dano oxidativo na prole e levar a uma maior propensão a patologias na vida adulta (FETOUI; GAROUI; ZEGHAL, 2009). O decréscimo de proteínas, pode gerar alterações na capacidade antioxidante, devido às modificações na função mitocondrial, que repercutem em alterações na capacidade de fosforilação; no aumento da produção de peróxido de hidrogênio; na diminuição do sistema antioxidante enzimático, não-enzimático e metabólico, como SOD, CAT, GPx, GR e glicose-6-fosfato desidrogenase (G6PDH); e no status redox (NASCIMENTO *et al.*, 2014). Esse desbalanço entre o sistema oxidante e antioxidante, com o predomínio de agentes oxidantes, propicia o dano oxidativo percebido no cérebro e no cerebelo (FEOLI *et al.*, 2006; FERREIRA *et al.*, 2016a).

A redução de proteínas, mesmo quando não acontece de forma relevante, pode trazer instabilidade e ruptura da integridade da membrana, trazendo danos às estruturas do sistema nervoso central da prole (TATLI *et al.*, 2007). A sua privação durante a gestação e a lactação ocasiona uma diminuição no peso do filhote e do seu cérebro e é considerada um importante fator de risco para o desenvolvimento de doenças, possivelmente em razão de modificações ocorridas no útero, onde podem acontecer alterações na expressão de determinados genes (ALVES *et al.*, 2016; FEOLI *et al.*, 2006).

O decréscimo das enzimas antioxidantes no tronco cerebral de ratos machos tem sido demonstrado nos estudos que realizam a redução da oferta de proteína para as mães (FERREIRA; SELLITTI; LAGRANHA, 2016). A limitação deste componente, durante o período perinatal, pode contribuir para a diminuição das enzimas

antioxidantes também no coração dos filhotes machos e pode favorecer à hipertensão arterial, quando adultos (NASCIMENTO *et al.*, 2014). Estudos em ratos sugerem que a deficiência deste importante macronutriente leva ao aumento na produção de espécies reativas no coração da prole quando adula e promove uma diminuição na capacidade respiratória mitocondrial (NASCIMENTO *et al.*, 2014).

Análises realizadas no tronco cerebral de ratos *Wistar* aos 100 dias de vida cujas mães receberam diferentes ofertas de proteína durante a gestação e lactação, demonstraram importante aumento MDA no grupo de baixa proteína, quando comparados ao grupo normoproteico (FERREIRA *et al.*, 2016b). A diferença no teor deste macronutriente tem apresentado desfechos como o aumento do dano oxidativo, a diminuição da capacidade antioxidante de enzimas como SOD, CAT, GPx e GST (glutationa-s-transferase) e, também, causado impacto no estado REDOX (FERREIRA; SELLITTI; LAGRANHA, 2016).

Os biomarcadores do status oxidativo, quando avaliados nas ratas fêmeas em diferentes idades e com oferecimento de proteína em teores normais e baixos, se apresentam de modo singular a depender de alguns fatores (SOUSA *et al.*, 2018). O dano exibido no tronco cerebral das jovens (22 dias), que possuem baixos níveis de estradiol, foi maior do que o das adultas (122 dias), que apresentam valores mais elevados deste hormônio (DE SOUSA *et al.*, 2018). Por isso, existe a hipótese de que, na prole fêmea, aconteça neuroproteção impulsionada pelas quantidades de estrogênio na fase adulta (SOUSA *et al.*, 2018).

O início da gestação não é, por si só, período de obrigatoriedade no aumento do consumo energético materno, porém, é necessário avaliar as suas necessidades nutricionais, assim como as demandas devem ser reajustadas ao longo do tempo, de acordo com as particularidades específicas (VITOLO, 2008). O desequilíbrio energético pode contribuir para o surgimento de obesidade e alterações glicêmicas na prole adulta (DUMORTIER *et al.*, 2007; GEORGE *et al.*, 2012). Estudo realizado com filhotes de ratos de ambos os sexos no qual havia restrição na quantidade de comida demostrou que não há alteração nos níveis de MDA (STONE *et al.*, 2016). Quanto a atividade das enzimas antioxidantes, naqueles grupos que realizaram redução na dieta, observou-se aumento na atividade da SOD e diminuição das enzimas CAT, GPx e GR, quando analisadas no cerebelo e córtex cerebral de ratas fêmeas (STONE *et al.*, 2016).

Em relação ao excesso de energia, o consumo de dietas hipercalóricas também está associado ao desenvolvimento de doenças degenerativas relacionadas ao envelhecimento, além de câncer, dislipidemia, aterosclerose e doenças cardiovasculares (BURNEIKO *et al.*, 2006). A alimentação com elevados teores de gordura saturada ocasiona o surgimento de diversas alterações metabólicas na prole adulta, como resistência à insulina, obesidade e hipertensão (LIANG; OEST; PRATER, 2009). Por outro lado, estudo realizado em ratos *Wistar* observou que a oferta de gordura proveniente de óleo de peixe associada ao exercício físico provoca aumento das enzimas metabólicas e antioxidantes do coração (PEDROZA *et al.*, 2015). Além disso, a utilização de ácidos graxos ômega 3, especialmente o ácido docosahexaenóico (DHA), influencia o desenvolvimento cognitivo e neurológico (OBERBAUER *et al.*, 2018).

A obesidade materna advinda da dieta rica em gordura sugere um aumento do EO devido a uma falha na remoção das espécies reativas de oxigênio (MANOUSOPOULOU *et al.*, 2015). Todavia, estudo realizado em ratos *Wistar* cujas mães foram alimentadas com dieta rica em ômega 6 durante a gestação e lactação observou diminuição de MDA e das enzimas SOD e CAT; houve aumento, entretanto, na atividade da GST e na concentração de GSH (MENDES-DA-SILVA *et al.*, 2018). Resultado semelhante foi observado em outra pesquisa realizada durante o mesmo período em ratos *Wistar* cujas mães também receberam dieta rica em ômega 6 (ácido linoleico), encontrando-se diminuição do biomarcador MDA e aumento no conteúdo total de glutationa (QUEIROZ *et al.*, 2019). Os dados deste trabalho demonstraram, além da diminuição na peroxidação lipídica no cérebro dos descendentes, efeito ansiolítico confirmado por meio de testes de comportamento (QUEIROZ *et al.*, 2019).

Por outro lado, em trabalhos nos quais houve oferta de ômega 9 durante período semelhante, foi apresentada diminuição no conteúdo da GSH, sem modificação na geração de espécies reativas entre os grupos (PASE *et al.*, 2015). Quando ofertada uma dieta rica em ômega 9, a concentração de MDA demonstrou aumento em várias áreas cerebrais, como córtex cerebral, hipocampo e cerebelo (TOZUKA; WADA; WADA, 2009). A dieta rica em gordura, em especial a rica em óleo de oliva, promoveu modificações no status oxidativo do córtex cerebral e do hipocampo de ratos *Sprague-Dawley*, sendo sua utilização possivelmente positiva em condições neurodegenerativas e neuropsiquiátricas (PASE *et al.*, 2015).

Dieta materna desequilibrada em micronutrientes também possui grande importância durante o período de gestação e lactação e pode trazer consequências para os filhotes e para gerações futuras (MOUSA; NAQASH; LIM, 2019). Vitaminas como B2 (riboflavina), B6 (piridoxina), B12 (cobalamina) e B9 (ácido fólico) estão relacionadas à metilação do DNA, interferindo no epigenoma da prole (VANHEES *et al.*, 2014). A vitamina C (ácido ascórbico), a vitamina A (retinol), o ferro, o cromo, o zinco e os flavonoides também exercem função na programação nas condições de saúde do embrião (VANHEES *et al.*, 2014).

O ferro atua na prevenção da anemia e sua deficiência tem relação com o baixo peso ao nascer e parto prematuro (PASSERINI *et al.*, 2012). A sua necessidade intensificada durante o período gestacional justifica-se pelo aumento da massa eritrocitária materna, suprimento de demandas fetais e como forma de prevenção devido a perdas durante o parto (MILMAN, 2006). Além desses aspectos, sua privação pode retardar o desenvolvimento do sistema nervoso central, modificando a sua morfologia, neuroquímica e bioenergética, interferindo no seu funcionamento (BEARD, 2008). Outro componente importante é o zinco, que contribui para a atuação de mais de 200 enzimas e desempenha atividade na divisão celular, na saúde ocular, em funções imunes e neurológicas (CAULFIELD *et al.*, 1998). É um potente antioxidante e a sua deficiência aumentou os níveis de alguns marcadores de estresse oxidativo, como as carbonilas e TBARS em ratos machos (OTEIZA *et al.*, 1995).

A colina é um composto essencial tratando-se da proliferação das células do tronco, estruturas e funções cerebrais e da medula espinhal (GEORGIEFF, 2007). O aumento de sua ingestão favorece a memória espaço-visual e a renovação de acetilcolina no hipocampo dos filhotes (BLUSZTAJN *et al.*, 1998). Outro nutriente importante é o iodo, que se faz bastante significativo devido ao seu papel na constituição de hormônios atuantes no componente cerebral e contribui para o adequado progresso do sistema nervoso central, assim como em outros diversos órgãos (LEUNG; WIENS; KAPLAN, 2011). Sua ação acontece no crescimento de células nervosas e na formação de sinapses e mielinização (PRADO; DEWEY, 2014).

Dessa forma, a ingestão materna desbalanceada, seja por uma dieta restritiva ou com excessos de nutrientes, é considerada um fator de risco para o surgimento de doenças nos descendentes na vida adulta (RAMÍREZ-LÓPEZ *et al.*, 2015). A dieta é considerada um fator de modulação do estresse oxidativo e pode contribuir para uma maior adequação dos biomarcadores de oxidação. Entretanto, fatores como o

conteúdo dos componentes antioxidantes, a dose e o tempo de suplementação, o sexo e a idade do indivíduo, bem como o estado de saúde, podem prejudicar a interpretação dos resultados (BARBOSA *et al.*, 2010).

2.6 Doenças neurogênicas

O sistema nervoso central (SNC) é constituído pelo encéfalo (cérebro, cerebelo e tronco encefálico) e pela medula espinal (MORITZ, 2013). O desenvolvimento cerebral tem início na gestação, prosseguindo durante a lactação e a infância e seu progresso é dividido em cinco etapas: a proliferação neural; o crescimento dos dendritos e axônios; atividades sinápticas; mielinização e apoptose neural (PRADO; DEWEY, 2014). Diversos nutrientes são essenciais durante esta fase e o déficit de algum deles pode afetar a cognição, o comportamento e a produtividade desde a infância até a vida adulta, entretanto, o nível desta perturbação dependerá da vivência de cada ser e do ambiente inserido, do momento de vida em que ocorreu esta escassez nutricional e do seu grau e da perspectiva de regeneração (PRADO; DEWEY, 2014).

O cérebro possui particularidades na composição da sua membrana, como a presença de ácidos graxos poliinsaturados, ferro e níveis moderados de antioxidantes que o fazem extremamente frágil à ação das espécies reativas (EVANS, 1993). O dano oxidativo pode ser o causador de determinadas alterações clínicas, porém ele tem sido mais frequentemente apontado como a consequência de patologias (PÔRTO, 2001). O surgimento de muitas doenças acontece durante a fase de envelhecimento, entretanto a patogênese das doenças nem sempre está associada à idade cronológica em si, mas a uma produção elevada das espécies reativas (FINKEL; HOLBROOK, 2000). Presume-se que algumas doenças neurodegenerativas, em sua origem, possuam vínculo com níveis exacerbados de espécies reativas (FINKEL; HOLBROOK, 2000). A lesão aos lipídios e às proteínas de membrana celular neuronal ocasiona uma diminuição na fluidez da membrana, na inativação de enzimas metabólicas e na intensificação da perda do potencial de membrana e homeostase iônica (PÔRTO, 2001).

Dentre algumas dessas doenças, estão a Doença de Alzheimer, a Doença de Parkinson, a Doença de Huntington, a Esclerose Lateral Amiotrófica, a Esquizofrenia,

a degeneração de gânglios da base, a atrofia sistêmica múltipla e a degeneração supranuclear progressiva (LOVELL *et al.*, 1995; MORITZ, 2013; PÔRTO, 2001).

A Doença de Alzheimer é uma patologia caracterizada como a forma mais comum de demência, apresentando sintomas como declínio na memória – sendo inicialmente com leves lapsos e posteriormente de modo mais relevante – distúrbios de linguagem, modificações na personalidade e no comportamento (OZBEN; OZBEN, 2019). Outra particularidade é a existência de distorções de memórias, como "falsas memórias", ocorridas em estágios leves a moderados, na qual os indivíduos experimentam lembranças de eventos que não ocorreram (EL HAJ *et al.*, 2020). Verifica-se ainda o acúmulo de placas B-amilóides nos cérebros dos acometidos, alterações no metabolismo da glicose e morte de células neuronais (BROOM; SHAW; RUCKLIDGE, 2019).

A Doença de Parkinson é uma condição também muito comum na população, variando bastante a forma de manifestação entre os indivíduos e podendo a sua evolução atravessar décadas (BLOEM; OKUN; KLEIN, 2021). Possui como sintomas tremores de repouso, disfunção da marcha, lentidão de movimentos, rigidez e instabilidade postural, além da perda de neurônios dopaminérgicos e a presença de corpos de Lewy nas células nervosas (RAZA; ANJUM; SHAKEEL, 2019).

A Doença de Huntington manifesta-se por meio de um conjunto de sintomas como disfunções motoras, declínio cognitivo e distúrbios neuropsiquiátricos e comportamentais (BLUMENSTOCK; DUDANOVA, 2020). Uma particularidade desta patologia é a agregação da proteína mutante de Huntington (mHTT) nas células nervosas, formando oligômeros solúveis e fibrilas insolúveis que interferem em células com atividades importantes, levando-as a uma baixa atividade metabólica e, posteriormente, a morte (JAROSIŃSKA; RÜDIGER, 2021).

Em patologias como as Doença de Alzheimer, de Parkinson e de Huntington acontece a agregação de compostos no cérebro, porém a causa destes agrupamentos proteicos ainda têm sido estudadas (SALIM, 2017). O dano oxidativo é uma das particularidades da Doença de Alzheimer e se caracteriza, principalmente, pela acumulação do peptídeo B-amiloide e hiperfosforilação da proteína TAU nas células nervosas (PÔRTO, 2001). A toxicidade da B-amiloide é justificada, principalmente, pela elevada produção de peróxido de hidrogênio e pela peroxidação lipídica, que promovem a supressão na atividade do glutamato e, consequentemente, a morte celular (PÔRTO, 2001). Os neurônios danificados nesta patologia apresentam uma

diminuição na produção de ATP e na quantidade de Citocromo C Oxidase, sugerindo uma disfunção mitocondrial e, consequentemente, maior geração de espécies reativas, em decorrência do estresse oxidativo (WANG; MICHAELIS, 2010).

Além do aumento de espécies reativas, os estudos têm apresentado baixos níveis plasmáticos do sistema de defesa antioxidante, que possuem a função de neutralizar a formação destes compostos (BERR *et al.*, 1998). A base oxidativa produzida pela ação das espécies reativas mais estudada é a 8-oxo-7,8-dihydro-2'-deoxyguanosina (8-oxo-dG) (LANGIE *et al.*, 2013). Alteração genética na atividade da OOG1 – enzima que exerce a função de reparação na 8-oxo-dG - tem sido encontrada nos neurônios de pacientes com a Doença de Alzheimer (JACOB *et al.*, 2013).

Na Doença de Parkinson, além de justificativas genéticas para o seu surgimento, discutem-se mecanismos relacionados à ação de toxinas, como os pesticidas e fungicidas, que podem atuar no aumento do estresse oxidativo, da peroxidação lipídica e causar danos ao DNA e à mitocôndria (DICK, 2006). Estas modificações causam a morte de neurônios dopaminérgicos, principal aspecto desta patologia e que leva a típicas alterações motoras (ALBIN; YOUNG; PENNEY, 1989). A morte celular por apoptose pode ser impedida, caso haja uma interrupção do estresse oxidativo (JENNER, 2003). Alterações na substância negra, como a diminuição do conteúdo da GSH e aumento de HNE, peróxidos lipídicos, isofuranos, 8OHdG, 8OHG (um produto do dano oxidativo no RNA), proteínas carboniladas e diminuição de dopamina são relacionadas com o Parkinson (HALLIWELL, 2006). Os neurônios dopaminérgicos da substância negra são os primeiros a sofrer a morte celular e os níveis de glutationa diminuídos representam os primeiros sinais de desenvolvimento da doença nesta área (WANG; MICHAELIS, 2010). O excesso de ferro e o aumento na atividade da monoamina oxidase nos neurônios contribuem para a elevada geração de espécies reativas, promovem a oxidação de dopamina e a formação de 6-hidrodopamina (6-OHDA), que se transforma em uma quinona por meio de uma auto-oxidação e leva a formação de superóxido e consequente aumento do EO (WANG; MICHAELIS, 2010).

A Doença de Huntington possui como sintomas os movimentos involuntários, alterações psiquiátricas e declínio cognitivo (MORITZ, 2013). O dano oxidativo presente nesta patologia leva ao acúmulo de algumas substâncias, como a lipofuscina - derivada da peroxidação de ácidos graxos (BRAAK; BRAAK, 1992). Esta patologia possui como marcadores o 8OHdG e o F2-IPS, ambos quando em níveis elevados, e

pode apresentar alterações no metabolismo do ferro, disfunção mitocondrial e de proteassoma e agregação anormal de proteínas (HALLIWELL, 2006). A esclerose lateral amiotrófica é uma patologia neurodegenerativa, progressiva e complexa, pois sua etiologia possui correlação com diferentes genes e com casos de origens diversas, que não genéticas (CERVANTES-ARAGÓN *et al.*, 2019). Possui relação com uma diminuição na atividade da enzima SOD, quando comparada a indivíduos normais, devido a uma falha no gene responsável pela codificação de CuZnSOD (PÔRTO, 2001). Outras características pertencentes a esta enfermidade foram encontradas, como o aumento dos biomarcadores 8OHdG, carbonilas, HNE, produtos de glicoxidação e 3-nitrosamina (HALLIWELL, 2006).

Além das doenças neurodegenerativas, alguns transtornos comportamentais podem estar relacionados ao ambiente precoce (SULLIVAN *et al.*, 2015). Sabe-se que o período perinatal é de suma importância para o adequado progresso cerebral e a regulação do comportamento da prole, sendo a diabetes, hipertensão e pré-eclâmpsia maternas bastante estudadas como fatores de risco para as desordens relativas à saúde mental e ao desenvolvimento apropriado do cérebro da descendência (SULLIVAN *et al.*, 2015). Obesidade, dieta rica em lipídeos e questões metabólicas maternas têm sido vinculadas às disfunções placentárias e sujeitam o feto ao contato com substâncias inflamatórias, prejudicando determinadas áreas cerebrais e que influenciam nas vias de neurotransmissores, como a serotonina e dopamina (SULLIVAN *et al.*, 2015). Esses sistemas demonstram ser/estar afetados em indivíduos obesos e são evidenciados como fatores de risco para as desordens de ansiedade, depressão, hiperatividade e autismo (SULLIVAN *et al.*, 2015).

Estudo com dieta materna rica em gordura observou modificações no comportamento da prole e na capacidade de resposta do sistema serotoninérgico, impactado na resposta de alguns testes e induzindo quadros de hiperatividade e maior comportamento relacionado à ansiedade na prole de ratos *Wistar* (CAVALCANTI *et al.*, 2021). Entretanto, a depender das características da gordura consumida pela mãe, como o ácido linoleico (ômega 6), os filhotes podem apresentar diminuição de comportamentos relacionados à ansiedade e redução nos níveis de peroxidação lipídica cerebral (QUEIROZ *et al.*, 2019).

Além de transtornos comportamentais, algumas patologias crônicas não-transmissíveis podem apresentar sua origem na relação da dieta materna e alterações em regiões encefálicas (ALVES; COSTA-SILVA, 2018). Temos, por exemplo, a

hipertensão arterial que pode ter origem por modificações no controle central da pressão arterial e do ritmo respiratório na região do tronco encefálico de ratos adultos devido à dieta materna hipoproteica durante as fases iniciais da vida (ALVES; COSTA-SILVA, 2018). Quando ratos são expostos a restrição de proteína durante a gestação e lactação, observa-se, na vida adulta, aumento na pressão arterial da prole associada a elevadas atividades simpáticas e respiratórias (ALVES *et al.*, 2016). Além dessas modificações fisiológicas são observadas aumento de biomarcadores do EO e diminuição de SOD, CAT, GPx, GST, GR e G6PDH no tronco encefálico (FERREIRA *et al.*, 2016b).

De acordo com os trabalhos apresentados, é de fundamental importância o estudo acerca da influência da dieta materna nos estágios iniciais da vida sobre o estresse oxidativo no sistema nervoso central da prole e sua relação com o desenvolvimento de doenças a partir de alterações neurogênicas.

3 OBJETIVOS

3.1 Objetivo Geral

Investigar os efeitos da dieta materna durante o período perinatal sobre o estresse oxidativo no sistema nervoso central da prole e sua contribuição para o desenvolvimento das doenças neurogênicas.

3.2 Objetivos Específicos

- Identificar as repercussões de modificações da dieta materna no período perinatal sobre parâmetros de estresse oxidativo no sistema nervoso central da prole;
- Analisar como as alterações dos parâmetros metodológicos dos estudos modificam os resultados de estresse oxidativo na prole;
- Correlacionar as modificações do equilíbrio oxidativo com o aparecimento de doenças neurogênicas e as alterações nutricionais.

4 MATERIAIS E MÉTODOS

4.1 Tipo de estudo

Este trabalho trata-se de uma revisão sistemática de literatura e foi realizada seguindo as recomendações PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). O protocolo foi elaborado e enviado à PROSPERO (International Prospective Register of Systematic Reviews) e tem como número de registro CRD42021211306 (ANEXO A).

4.2 Estratégia de busca

A busca bibliográfica foi realizada nas seguintes bases de pesquisa: Pubmed, Embase, Web of Science, Scopus, Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) e Cochrane.

Foram utilizadas os seguintes termos: Diet, "Dietary supplements", Nutrients, "Infant Nutrition", "Maternal Nutrition", Pregnancy, Gestation, "Prenatal Exposure", Lactation, "Breast Feeding", "Oxidative Stress", "Lipid Peroxidation", Scavenger, Antioxidants, "Free Radical", "Reactive Oxygen Species", "Central nervous system", Brain, Brainstem, Diencephalon, Prosencephalon, Hypothalamus, Hippocampus, Telencephalon, Cerebrum, Mesencephalon, Cerebellum, "Cerebral cortex", "Basal ganglia", Amygdala, Thalamus, "Corpus striatum".

As palavras foram combinadas por operadores booleanos e houve a distribuição de 4 grupos de palavras: dieta, período de intervenção, desfechos e estruturas do sistema nervoso central. O operador OR foi utilizado entre as palavras dentro de um mesmo grupo, o operador AND foi utilizado entre os grupos e os descritores foram adaptados para cada base de dados. A estratégia de busca completa para as bases encontra-se no APÊNDICE A.

Não foram aplicados limites de data e de idioma. A investigação foi realizada por dois pesquisadores, NN e AP, de maneira independente, durante o período de dezembro de 2020 a janeiro de 2021, com atualização em janeiro de 2022. Os artigos científicos foram baixados das bases e inseridos no programa Start.

4.3 Estratégia de seleção

Os artigos foram inseridos no programa Start por cada um dos revisores de forma independente e, em seguida, foi realizada a exclusão automática dos artigos duplicados pelo próprio software. Posteriormente, foi feita a exclusão manual de outras duplicatas, com a conferência do título e dos nomes dos autores.

Após a retirada dos artigos em duplicata, foi realizada a leitura do título e do resumo. Desta forma, os trabalhos que não eram estudos primários (revisões, conferências, livros) ou que se enquadravam dentro dos critérios de exclusão PICO (Quadro 1) foram eliminados. A etapa seguinte caracterizou-se pela leitura completa dos artigos para verificação da presença dos critérios de inclusão/de elegibilidade, de acordo com a estratégia PICO (Quadro1). A seleção final dos trabalhos foi realizada individualmente pelos dois pesquisadores e as discordâncias foram resolvidas por consenso e, caso não houvesse, por decisão de um terceiro revisor (RA).

Quadro 1 – Estratégia PICO

	Inclusão	**Exclusão**
P	Mamíferos.	Humanos; animais geneticamente modificados.
I	Modificação na dieta materna (macro e micronutrientes ou valor calórico dietético), durante a gestação e/ou lactação.	Estudos em que o conteúdo energético da dieta foi modificado pela redução da oferta; estudos em que a manipulação de macronutrientes ou calorias for realizada utilizando bebidas ou gavagem; estudos em que a prole recebeu dieta modificada após o desmame.
C	Exposição materna à dieta controle.	Filhotes de mães que receberam dieta modificada após o desmame.
O	Desfechos primários: Biomarcadores de estresse	Não tem.

	oxidativo no sistema nervoso central da prole; Avaliação do sistema antioxidante. Desfechos secundários: resultados de testes comportamentais, de imagens ou outros que possam indicar algum tipo de doença neurogênica.	

Fonte: A autora (2022).

4.4 Extração e síntese de dados

A primeira revisora (NN) realizou a extração dos dados dos artigos incluídos baseada em um formulário anteriormente elaborado (APÊNDICE B). Este documento foi avaliado previamente a fim de se verificar ajustes necessários antes de sua aplicação nos estudos. Após a finalização desta etapa, o segundo revisor efetuou a conferência por amostragem das informações inseridas. Após a extração, os dados dos artigos selecionados para a revisão foram inseridos em uma tabela para inclusão das informações relativas aos estudos, como a população, a intervenção e os desfechos.

Como este trabalho trata-se de uma revisão sistemática sem metanálise, a síntese de dados foi realizada, inicialmente, através da comparação entre os tipos de dietas utilizadas e os marcadores do estresse oxidativo empregados. Em seguida, aconteceu a análise da relação entre o estresse oxidativo e as doenças neurogênicas.

4.5 Análise de risco de viés

Os dois pesquisadores classificaram, de modo independente, a qualidade dos artigos selecionados para a análise e apresentação na revisão por meio da ferramenta SYRCLE (HOOIJMANS *et al.*, 2014), utilizada para avaliar o risco de viés de estudos em animais. Este instrumento é composto por dez perguntas relativas à metodologia e aos resultados das pesquisas. Nos casos em que houve discrepâncias entre as

classificações realizadas pelos autores, a terceira revisora (RA) fez a mediação. Seguidamente, foi verificado o índice de KAPPA com o objetivo de aferir a concordância da avaliação feita pelos autores. Essa análise proporciona a apreciação da qualidade metodológica dos trabalhos inseridos, aumentando, assim, a confiança dos dados da revisão sistemática (LANDIS; KOCH, 1977).

5 RESULTADOS

O PRESENTE TRABALHO ESTÁ APRESENTADO NO FORMATO DE ARTIGO REQUERIDO PELA REVISTA **NUTRITIONAL NEUROSCIENCE,** CUJAS NORMAS PARA SUBMISSÃO DE ARTIGOS SE ENCONTRAM EM ANEXO.

Maternal diet influences on oxidative stress in offspring's central nervous system: a systematic review of animal studies

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Availability of data and material: All data generated or analyzed during this study are included in this published article.

Code availability: Not applicable

ABSTRACT

Maternal diet during pregnancy and lactation can influence activity of enzymes and levels of biomarkers related to oxidative stress in offspring central nervous system (CNS). This work aimed to carry out a systematic review of the literature to investigate the effects of maternal diet during the perinatal period on oxidative stress in offspring's CNS and its contribution to development of neurogenic diseases. Pubmed, Embase, Web of Science, Scopus, Lilacs, and Cochrane databases were searched between December 2020 and January 2021 with an update in January 2022. Two independent reviewers extracted data and assessed the quality of included studies. A total of 2,563 works were found, which underwent steps of deleting duplicates, readings, and evaluations. Twenty-six articles were included in the review. The most frequent modifications used low-protein diets, modification of lipids (amount or type of fat) and micronutrients changes. Among the most studied markers of oxidative stress were levels of malondialdehyde, carbonyl proteins, and glutathione, and enzyme activities such as superoxide dismutase and catalase. In general, low-protein, HFD or vitamin-depleted maternal diets increased oxidative levels and reduced antioxidative activity. W-6-riche diet had a more antioxidant profile. Offspring sex and age also influences the results, as female adult animals were more resistant to changes in oxidative balance. Few studies performed behavioral analyzes or other tests in conjunction with the study of oxidative stress. But it was possible to observed that oxidative stress changes due to maternal diet were associated with diseases as depression, anxiety, schizophrenia, multiple scleroses, dementias, and hypertension.

Keywords: maternal nutrition; oxidative balance; reactive oxygen species; antioxidant; behavior; brain

INTRODUCTION

Modifications in macro or micronutrients quantity and quality in maternal diet during gestation and/or lactation can have important consequences in progeny health later in life [1–3]. It has been shown that maternal diet can have lifelong influence on offspring tendency to develop metabolic, cardiovascular, and neurobehavioral diseases [4]. Mechanisms underlying this influence is still unclear but may have the participation of epigenetic mechanisms, oxidative stress, tissue remodeling, among others [4]. Regarding the function of the central nervous system (CNS), changes in maternal diet have already been shown to influence neurons morphology, density and, excitability, cognition, hyperactivity depressive-, anxiety-like, aggressive, and feeding behaviors[5–8].

One important aspect to the adequate function of the CNS is the maintenance of oxidative balance [9]. There are a wide range of enzymes and molecules that are responsible to maintain a satisfactory oxidative levels in CNS thus allowing its proper function[10]. When antioxidant enzymes activity and production of reactive species are imbalanced with the later predominance the oxidative stress is characterized [11]. Excessive ROS levels can increase lipids peroxidation, proteins oxidation and DNA damage and may be associated with the onset of neurodegenerative diseases, such as Alzheimer's, Parkinson's and Huntington's, and disorders, such as anxiety and depression [9].

Some aspects are common to some diseases like Alzheimer's, Parkinson's, and Huntington's diseases, such as alteration in reactive species formation, dysregulation of antioxidant system (such as GSH levels) and oxidative stress biomarkers (such as lipid peroxides, isoprostanes, carbonyls and, 8-OHdG) increase [12]. Oxidative stress is a particularity capable of affecting all neurons, but the degree of injury may vary among the injured sites [13]. Another important feature among these diseases is the aggregation of proteins, such as B-amyloid and phosphorylated tau in Alzheimer's Disease; alpha-synuclein in Parkinson's Disease and the mutant protein in Huntington's Disease[9,13]. Studies have been carried out to understand the cause-and-effect relationship between oxidative stress and protein aggregation [9].

Some evidence suggests that oxidative stress is involved in the onset or development of psychiatric disorders[14]. Reduction GSH levels and increasing in lipid

peroxidation were related with depressive-like behavior[15]. Altered SOD and CAT activity and increased lipid peroxidation and protein carbonylation concomitant with increased anxiety-like behavior have been found in animal models using pro-oxidative vitamin A[16]. Moreover, markers of oxidative stress, including lipid peroxidation products and oxidized DNA, have been shown to be elevated in the blood of patients with psychiatric disorders.

Maternal nutrition during the early stages of life can modify oxidative status in progeny's CNS but there are some divergences in the results[10,17–21]. Protein restriction in the maternal diet has been associated with increased levels of MDA in the cortex[22] and medulla[18], while in the cerebellum it is increased[19] and decreased[22] and in the brainstem it is increased[10,17,20] and without difference[21,23]. Some micronutrients, as copper, zinc, vitamins E, C, and A have antioxidant function and they modification in maternal diet can also influence offspring's oxidative stress [24]. Maternal diet deficient in vitamin C increased SOD activity in offspring' brain [25], but vitamin E deficiency had no effect in this enzyme activity[26]. However, both dietary modifications increased MDA levels[25,26]. While maternal choline restriction decreased total antioxidant status in the same tissue [27].

As observed above, maternal diet plays an important role in the determination of oxidative stress in several offspring tissues. On the same way, oxidative stress can influence the development of neurobehavioral and neurodegenerative diseases and disorders. However, some different outcomes were observed in CNS oxidative stress due to modification in maternal diet. Thus, this systematic review aimed to evaluate how maternal diet modifications affect oxidative stress in offspring CNS and how this correlates to changes on cerebral structure or function and behavior.

MATERIAL AND METHODS

This systematic review was developed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) recommendations(28) and the protocol was registered at PROSPERO (International Prospective Register of Systematic Reviews) with the number CRD4202111306.

Search strategy

The search of articles was conducted by two independent reviewers (Negromonte, N.R.S. and Pedroza, A.A.S.) and performed in the Pubmed, Embase, Web of Science, Scopus, Latin American and Caribbean Literature in Health Sciences (LILACS) and Cochrane in December 2020 and updated in January 2022. The following terms were used: Diet, "Dietary supplements", Nutrients, "Infant Nutrition", "Maternal Nutrition", Pregnancy, Gestation, "Prenatal Exposure", Lactation, "Breast Feeding", "Oxidative Stress", "Lipid Peroxidation" , Scavenger, Antioxidants, "Free Radical", "Reactive Oxygen Species", "Central nervous system", Brain, Brainstem, Diencephalon, Prosencephalon, Hypothalamus, Hippocampus, Telencephalon, Cerebrum, Mesencephalon, Cerebellum, "Cerebral cortex", "Basal ganglia ", Amygdala, Thalamus, "Corpus striatum". The terms were assembled in 4 groups of words: diet, intervention period, outcomes, and structures of the central nervous system. The Boolean operator OR was used within the group of words and the Boolean operator AND was used between groups. Duplicates were removed from the articles retrieved through the searches. Initially, titles and abstracts were screened, following by assessment of full texts for eligibility against our pre-specified inclusion/exclusion criteria. Any disagreements between the researchers were resolved by consulting a third independent reviewer (da Silva Aragão, R).

Eligibility criteria

The population of interest was limited to mammalian offspring of dams exposed to dietary modifications during pregnancy and/or lactation, without restriction of sex or age. Our first outcomes included all types of oxidative stress biomarker and antioxidant system assessments. Subsequently, the articles were searched for information on behavioral tests, imaging analyses or other assessments that could indicated any neurogenic disease or alteration. There were no year or language limitations for inclusion of studies. Only original articles were included. Articles that did not meet the eligibility criteria for the population, intervention, comparison, and outcomes were excluded (Table 1). Review, metanalysis, editorial, letters to editor, academic papers (thesis), and conference papers were also excluded.

Table 1 - Eligibility criteria applied in this study

	Inclusion criteria	Exclusion criteria
Population	Mammals.	Humans; genetically modified animals.
Intervention	Modification in maternal diet (macro and micronutrients or dietary caloric value) during pregnancy and/or lactation.	Studies in which the energy content of the diet was modified by offer reduction; studies in which the manipulation of macronutrients or calories is performed using beverages or gavage; studies in which the offspring received a modified diet after weaning.
Comparison	Maternal exposure to the control diet	Puppies which received a modified diet after weaning.
Outcomes	Primary outcomes: Evaluation of oxidative stress or antioxidant system biomarkers in offspring's central nervous system; Secondary outcomes: Behavioral, imaging, or other tests that may indicate some type of neurogenic disease or alteration.	No one
Publication parameters	There was no restriction of articles date and languages	No one

Data extraction

Data extraction was performed after the complete reading of articles previously selected according to the eligibility criteria by two independent researchers. The third researcher was consulted when there were disagreements or doubts. The main data were collected, such as author and year of publication, species and strain of the animal, composition of maternal diets, period of diet intervention, experimental groups, age of weaning, post-weaning diet, pups' sex, age of sample collection or tests, area of nervous system analyzed (primary outcome), parameters analyzed (primary and

secondary outcome) and main results in offspring. The data were transcribed in a table organized by author's name and separated according to the results of oxidative stress biomarkers and assessment of the antioxidant system (primary outcome) or behavioral, imaging analysis or other tests (secondary outcome).

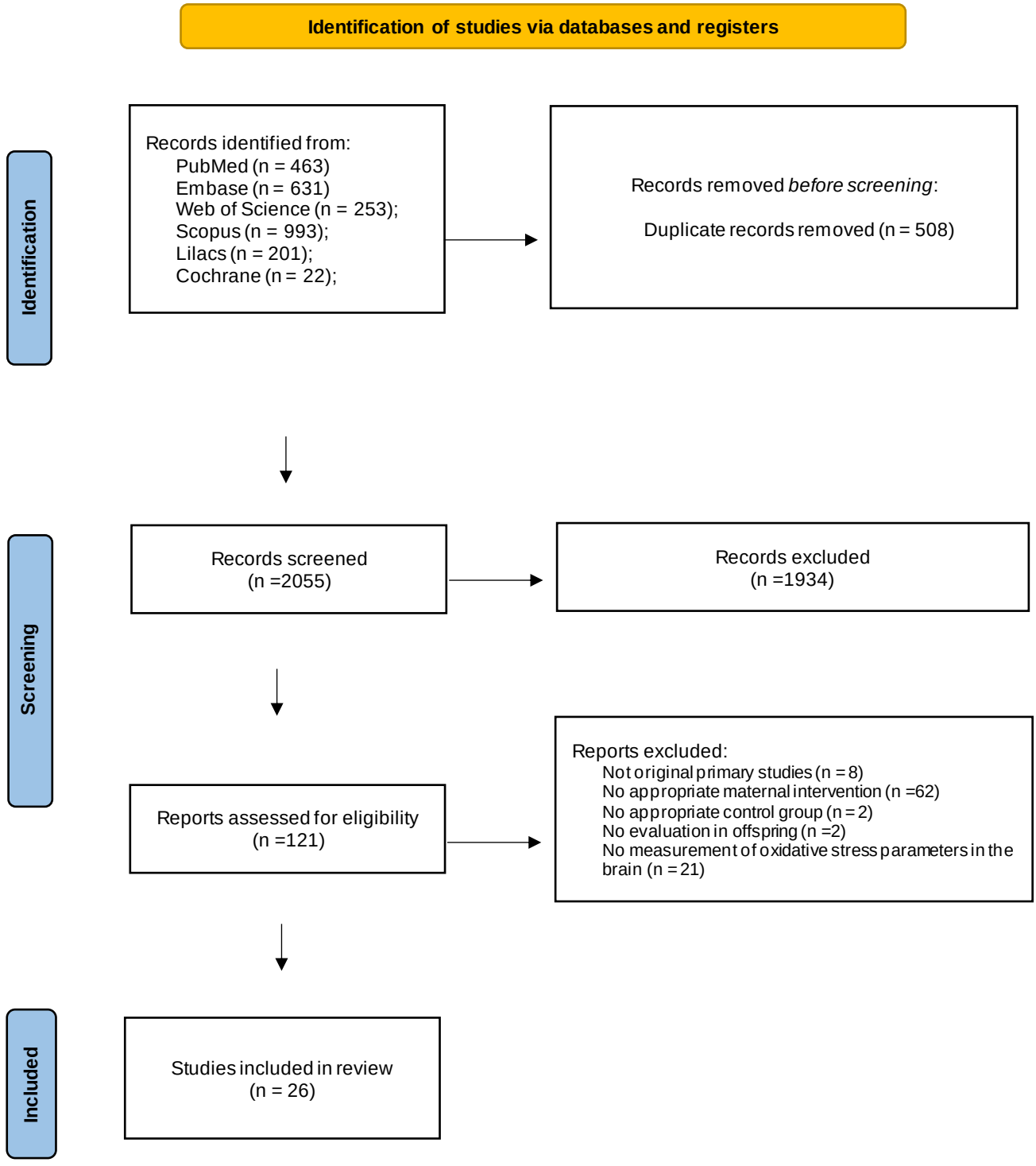
Assessment of methodology quality

Methodological quality of studies included in this systematic review was evaluated by using the tool known as SYRCLE risk of bias (RoB) [29]. The tool was applied independently by the reviewers to each article included. The SYRCLE RoB consists of 10 questions related to random sequence generation, baseline characteristics, allocation concealment, random housing, blinding of participants and personnel, random outcome data, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. These questions were judged as having high, uncertain, or low RoB. The Kappa test was applied after this phase to measure the level of agreement in the assessment of RoB between the first and second reviewers. The information from this step was synthesized through a figure obtained with Review Manager software version 5.3.

RESULTS

Considering the first search in the electronic databases (Pubmed, Embase, Web of Science, Scopus, LILACS and Cochrane) in December 2020 and the update in January 2022, a total of 2563 articles were found. Then, 508 duplicates were removed. A total of 2055 articles had titles and abstracts screened from which 1934 articles were eliminated because they did not address the eligibility criteria (Table 1) in the title or abstract. The full text was read in 121 articles. 95 articles were then excluded through the exclusion criteria (Table 1). Thus, the total of articles included in this review is 26. All articles found were published in English. The steps to carry out the search are described in the flowchart below (Fig. 1).

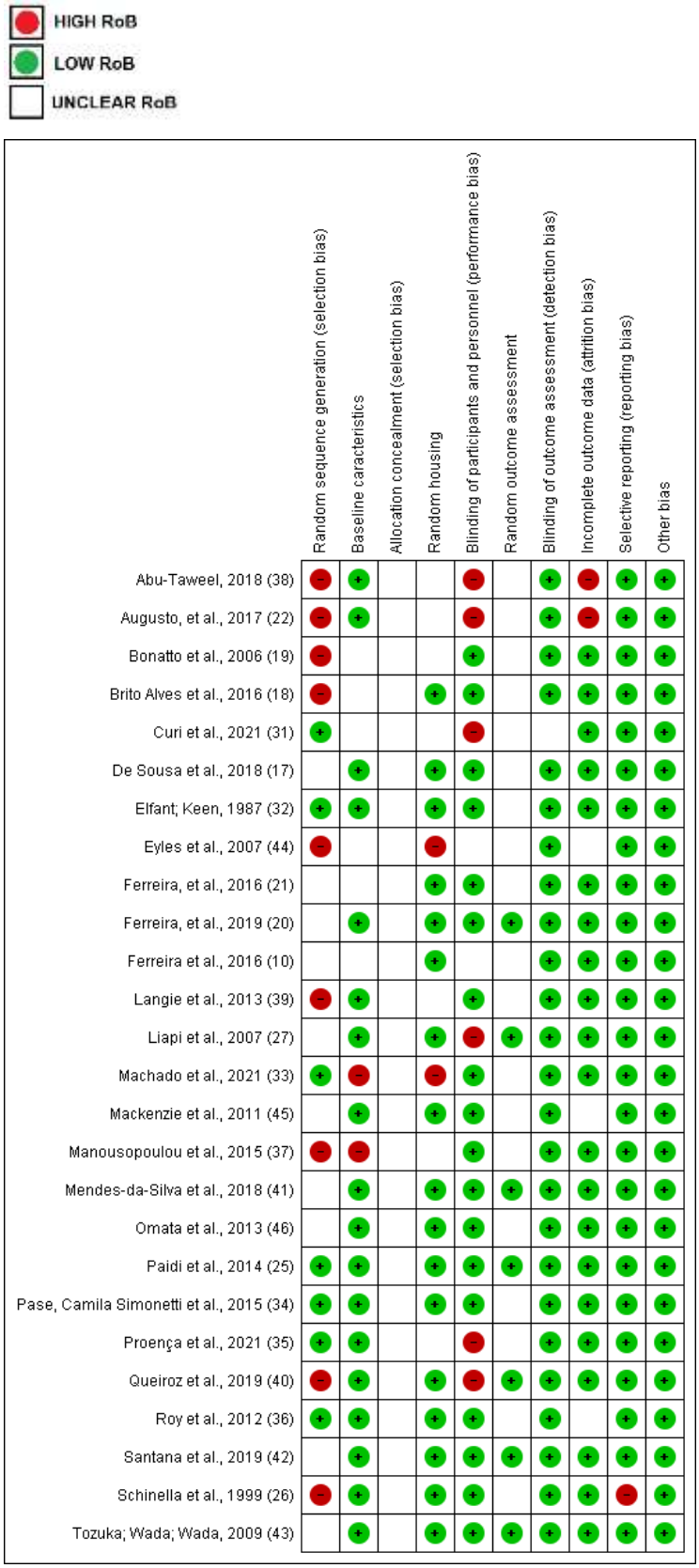
Figure 1. Flowchart of study selection process applied in the present study



Assessment of quality of studies

The Risk of Bias Tool (RoB) assessment applied among the reviewers resulted in Kappa = 0.90, classified as a substantial level of agreement [30]. In the studies, seven authors reported the generation of the animal allocation sequence [25,31–36]. Regarding the subjects' baseline characteristics, only two articles did not report them in the text [33,37]. None of the articles indicated whether the allocation of animals was adequately concealed. Seven studies did not provide sufficient information regarding the random housing of animals [19,22,31,35,37–39]. Six surveys did not indicate that caregivers and researchers were blinded to the knowledge of interventions [22,27,31,35,38,40]. Seven studies indicated the mode of selection of animals to evaluate the results [20,25,27,40–43]. Only one of the studies did not provide enough information about the blinding of the evaluator [31]. Two studies did not use software to balance the results [22,38]. Finally, no other types of risk of bias were identified. Review Manager 5.4 (RevMan) software was used to obtain a table summarizing the judgment of risk of bias.

Figure 2. Risk of bias (RoB) summary of studies.



Methodological profile of studies

Some methodological characteristics of the studies are presented here, and other details can be found in Table 2. Rats from the strains Wistar (n=15)[10,17–21,26,27,33,35,36,40–42] and Sprague-Dawley (n=5)[32,34,44–46] were the most common animals used followed by mice C57BL/J6 in three articles [37,39,43]. Most articles evaluated only male offspring (n=10)[10,18,20–22,37–40,43] . Only five articles (n=5) used male and female offspring[26,27,33,42,44] while six studies (n=6) did not report the sex of animals[19,25,36,41,45,46]. One of the studies analyzed offspring at two ages, being male offspring after birth but did not inform the sex of the fetus that were also evaluated [34].

Reduced protein content, using casein as protein source, was one of the most frequent maternal diet modifications[10,17–22,42] . Changes in lipids were made by increasing it content (high-fat diet)[31,35,37,43] or changing it source[33,34,40,41]. Five articles restricted vitamin availability in maternal diet being Vitamin D [44]; Vitamin C[25]; Vitamin E[26]; Choline[27] and Folate[39].

Most of the articles analyzed offspring during lactation or short after weaning[17,19,22,26,27,32,34,38,43,47]. Six articles used fetus or offspring at birth[25,27,34,36,45,46] . The other ages of offspring evaluation varied from PND30 [38,42] to PND180[39].

Whole brain was the most used region of study[25–27,32,34,36,40,44–46] , followed by brainstem[10,17,20,21,42] and cerebral cortex [19,22,41,43].

Main results of oxidative stress biomarkers

All works presented information about oxidative stress biomarkers or antioxidant system evaluation that were our primary outcomes. Some of these outcomes will be summarized here and others can be found in table 2.

From the studies that reduced protein content in maternal diet, increased levels of MDA in offspring were observed in seven studies[10,17–20,22] while two studies did not find any difference in MDA levels [17,21]. On the other hand, when studying the levels of carbonyl proteins, the results were more mixed with three studies observing increased levels [17,42,47] and two others reduced levels[20,42]. Results from SOD activity were also mixed, with one study observing increased activity [17], four decreased activity[10,18,20,22] , and one with no difference between groups[21]. Maternal low-protein diet influence on antioxidant system was also evaluated. Four studies observed reduction in CAT activity[10,17,18,42] and other two did not observed any difference between groups [20,47].

Regarding GPx activity, three studies showed decreased activity[10,17,18] and two had no differences between groups [20,47]. GST was evaluated in five studies and three of them observed decreased activity[10,21,42] , one found increased activity [20] and the last one found no difference between groups [17]. Glutathione levels were evaluated in five studies, with reduced values in three of them[10,21,22] and no difference in the other two studies [17,42].

Fat source and content modifications in maternal diet differently affected the oxidative stress in offspring. Reduction in MDA levels was observed in two studies that changed lipid source in maternal diet without change the quantity of fat in diet (safflower, rich in linoleic acid [41]; conjugated linoleic acid[40]. On the other hand, maternal diet with increased quantity of fat, mainly oleic acid, increased MDA in offspring cerebral cortex, hippocampus, and cerebellum[43] . The maternal diet enriched with olive oil (also rich in oleic acid) caused different results, as it did not modify the production of reactive species in the offspring[34], but also reduced the production of ROS [33]. Regarding the antioxidant system, the maternal diet with safflower oil decreased SOD and CAT activities and increased GST and GSH activities in[41]. On the other hand, the diet enriched with olive oil increased the activity of SOD and CAT [33].

Vitamin C- or E- deficiency in maternal diet increased MDA levels in offspring [25,26]. Divergent results were observed for SOD and CAT function with vitamin D-deficient diet decreasing SOD2 and CAT expression [44], while vitamin C deficiency increased activity [25] and vitamin E deficiency had no influence on SOD activity [26]. Deficiency in zinc decreased GSH content [46], while vanadium supplementation did not influence GSH content [32].

Table 2 – Primary outcomes retrieved from articles included in systematic review

Type of diets	Author, year	Specie/ strain	Maternal intervention and experimental groups	Age of weaning and postweaning diet	Sex of pups, age and area of sample collection	Parameters analyzed	Results
Low protein diet	**Augusto *et al.*, 2017** [22]	Rats	Control (CTR): chow diet (27.2% mix of animal and soy protein, 3.5% lipid) Malnourished (RBD, regional basic Diet): 8% protein (5:3 vegetal to animal protein), 1% lipid. From 30 days prior mating to PND21,	PND21 Chow diet (Purina, Brazil)	Male PND21, PND90 Cerebral cortex (CC), Cerebellum	1.MDA levels (nmol/mg prot) 2. ROS levels (fluorescence/mg prot) 3. Nitric oxide (nmol nitrite/mg prot) 4. NAD(P)H levels (µM/mg protein) 5. SOD activity (U/mg prot) 6. CAT activity (U/mg prot) 7. GSH levels (µM/mg protein) 8. GSSG levels (µM/mg protein) 9. GSH/GSSG ratio	1. ↑ in RBD group in CC ($p = 0.0369$) at PND21. ↓ in RBD group in cerebellum at PND21 and PND90 ($p<0.0001$). 2. ↑ in RBD group in CC ($p<0.0001$) at PND21 and ↓ at PND90 ($p<0.0001$). ↓ in RBD group in cerebellum ($p<0.0001$) at PND21 and PND90. 3. ↓ in RBD group in CC and cerebellum at PND21 and PND90 ($p<0.0001$). 4. ↓ in RBD group in CC ($p<0.05$) and cerebellum ($p<0.0001$) at PND21.

							5. ↓ in RBD group in CC ($p<0.001$) and ↑ in cerebellum ($p<0.0001$) at PND21. 6. ↑ in RBD group in cerebellum ($p<0.05$) at PND21. 7. ↓ in RBD group in CC and cerebellum at PND21 ($p<0.001$, $p<0.05$) and PND90 ($p<0.05$, $p<0.0001$). 8. ↓ in RBD group in cerebellum at PND21 ($p<0.0001$). ↓ in RBD group in CC ($p<0.05$) and ↑ in cerebellum ($p<0.05$) at PND90. 9. ↑ in RBD group in cerebellum at PND21 and PND90 ($p<0.001$).
Low protein diet	**Brito Alves *et al.*, 2016[18]**	Rats, Wistar	Control (CTR): 17% protein Low-protein (LP): 8% protein Casein as protein source	NA Chow diet (21% protein), Nuvilab, Brazil	Male PND90 Medulla Oblongata (ventral and dorsal)	1. mRNA expression (SOD1, SOD2, CAT, GPx) 2. MDA levels (nmol/mg protein)	1. ↓ in SOD2 and GPx expression in LP group ($p<0.05$). 2. ↑ in ventral and dorsal medulla in LP group ($p<0.05$).

			From conception to PND21			3. SOD and CAT activity (U/mg protein)	3. Both activities ↓ in ventral medulla in LP group ($p<0.05$).
Low protein diet	**De Sousa *et al.*, 2018[17]**	Rats, Wistar	CTR: 17% protein LP: 8% protein Casein as protein source From GD1 to PND21	PND21 Standard chow	Female PND22 and PND122 Brainstems	1. MDA level (µM/mg protein) 2. Carbonyl content (µM/mg protein) 3. SOD activity (U/mg protein). 4.CAT activity (U/mg protein) 5. GPx activity (U/mg protein). 6. GST activity (U/mg protein) 7. Glutathione levels (µM/mg protein) 8. Total thiols content (M/mg protein) 9. Oxidative status (Oxy-score, arbitrary units)	1. PND22: ↑ in LP group ($p<0.01$). PND122: No difference between groups. 2. PND22: ↑ in LP group ($p<0.05$). PND122: ↓ in LP group ($p<0.05$). 3. PND22: ↑ in LP group ($p<0.05$). PND122: No difference between groups. 4. PND22: ↓ in LP group ($p<0.05$). PND122: No difference between groups. 5. PND22: ↓ in LP group ($p<0.001$). PND122: No difference between groups. 6. No difference in both ages.

							7. No difference in reduced glutathione (GSH) content and in GSH/GSSG ratio (oxidized glutathione, GSSG) in both ages. 8. PND22: ↓ in LP group ($p<0.01$). PND122: No difference between groups. 9. PND22: ↓ in LP group ($p<0.001$). PND122: No difference between groups.
Low protein diet	**Ferreira, *et al.*, 2016** [21]	Rats, Wistar	CTR: 17% protein LP: 8% protein Casein as protein source From conception to the end of lactation	-	Male PND22 Brainstem	1. MDA levels (nmol/mg de protein) 2.Carbonyls content (µmol/mg protein) 3.GSH activity (nmol/mg protein) 4.GSH/GSSG (redox status) 5.SOD activity (U/mg prot)	1. No difference between groups. 2. ↑ in LP group ($p \leq 0.01$). 3. ↓ in LP group ($p \leq 0.001$). 4. ↓ in LP group ($p \leq 0.001$). 5. No difference between groups. 6. No difference between groups. 7. No difference between groups.

						6.CAT activity (U/mg prot) 7.GPx activity (U/mg prot) 8. G6PDH activity (U/mg prot) 9.GST activity (U/mg prot) 10. Mitochondrial ROS production (change in fluorescence)	8. No difference between groups. 9. ↓ in LP group ($p \leq 0.001$). 10.↑ in LP group ($p \leq 0.05$).
Low protein diet	**Ferreira *et al.*, 2016** [10]	Rats, Wistar	CTR: 17% protein LP: 8% protein Casein as protein source From conception to the end of lactation	NA Standard chow (Nuvilab CR1-Nuvital®, Brazil)	Male PND100 Brainstem	1. MDA (nmol/mg protein) 2. SOD activity (U/mg protein) 3. CAT activity (U/mg protein) 4. GPx activity (U/mg protein) 5. GST activity (U/mg protein) 6. GR activity (U/mg protein) 7. G6PDH activity (U/mg protein) 8. GSH activity (nmol/mg protein) 9. Redox State	1. ↑ in LP group ($p < 0.01$). 2. ↓ in LP group ($p < 0.001$). 3. ↓ in LP group ($p < 0.01$). 4. ↓ in LP group ($p < 0.001$). 5. ↓ in LP group ($p < 0.01$). 6. ↓ in LP group ($p < 0.05$). 7. ↓ in LP group ($p < 0.001$). 8.↓ in LP group ($p < 0.001$). 9. ↓ in LP group ($p < 0.05$).

Low protein diet	**Ferreira, *et al.*, 2019** [20]	Rats, Wistar	CTR: 17% casein LP: 8% casein From conception to the end of lactation	NA Standard chow (Labina; Purina Agriband)	Male PND150 Brainstem	1. MDA levels (mMol / mg de protein) 2. Carbonyls content (µmol/mg protein) 3. SOD activity (U / mg prot) 4. CAT activity (U / mg prot) 5. GPx activity (U / mg prot) 6. GST activity (U / mg prot) 7. Redox state (GSH/GSSG) 8. Reactive Species production (% of change) 9. Nitrite concentation (µM/mg protein) 10. nNOS expression (arbitrary unit)	1. ↑ in LP group ($p < 0.001$). 2. ↓ in LP group ($p \leq 0.01$). 3. ↓ activity in LP group ($p = 0.05$). 4. No difference between groups. 5. No difference between groups. 6. ↑ in LP group ($p = 0,016$). 7. No difference between groups. 8. ↑ in LP group ($p<0.05$). 9. ↑ in LP group ($p<0.01$). 10. ↑ in LP group ($p<0.05$).
Low protein diet	**Santana *et al.*, 2019** [42]	Rats, Wistar	CTR: 17% protein LP: 8% protein Casein as protein source	PND21 Standard chow (Labina;	Male and female PND30 Brainstem	1.MDA levels (% of CTR group)	1. ↑ in male LP group compared to male CTR group ($p<0.001$).

			From pregnancy to PND21	Purina Agriband, Brazil)		2. Carbonyl content (% of CTR group) 3. Mitochondrial reactive species production (% of CTR group) 4.SOD activity (% of CTR group) 5.CAT activity (% of CTR group) 6.GST activity (% of CTR group) 7.GSH levels (µM/mg protein) 8.GSSG levels µM/mg protein) 9. Redox status	2. ↑ in male LP group compared to male CTR group ($p<0.05$); ↓ in female LP group compared to female CTR group ($p<0.001$). 3. ↑ in male LP group compared to male CTR group ($p<0.01$). 4. No difference in both sexes. 5. ↓ in both sexes in LP groups compared to same sex CTR group (male: $p<0.01$; female: $p<0.001$). 6. ↓ in both sexes in LP groups compared to same sex CTR group ($p<0.01$). 7. No difference in both sexes. 8. ↑ in both sexes in LP groups. compared to same sex CTR group ($p<0.01$). 9. ↓ in both sexes in LP groups compared to same sex CTR

							group (male: $p<0.05$; female: $p<0.01$).
High fat diet	**Curi *et al.*, 2021 (31)**	Mice, Swiss	Control diet (CTR): 11.5% calories from fat High-fat diet (HFD): 45% calories from fat Fat source: soybean oil and lard From 3 weeks before mating to PND21	PND21 CTR diet (Nuvilab, Brazil)	Male PND70 Hippocampus	1.TBARS (µM/mg of prot) 2. Total antioxidant status (µmol Trolox Eq/l) 3. Total oxidant status (µmol H_2O_2 Eq/l) 4. Oxidative stress index (relative units) 5.GSH (nmol/mg prot) 6.GSSG (nmol/mg prot) 7.GSH/GSSG	1. No difference between groups. 2. No difference between groups. 3. No difference between groups. 4. No difference between groups. 5. No difference between groups. 6. No difference between groups. 7. No difference between groups.
High fat diet	**Manousopoulou *et al.*, 2015 (37)**	Mice, C57b1/6	CTR group: 21% calories fat, 17% calories protein, HFD: 45% calories fat, 20% calories protein From 4 weeks before conception until lactation	4 week old Control diet	Male 19 weeks Brain (dissected for frontoparietal cortices)	1.Proteomic analysis	1. Overrepresentation of response to hypoxia/ oxidative stress (FDR corrected P-value = 1.45E-02).

High fat diet	**Proença *et al.*, 2021 [35]**	Rats, Wistar	CTR diet: chow diet (20.5% protein, predominantly soy; 4% fat), (Pragsoluções Biociência, Brazil) HFD: casein (20%), lard (31%), soybean oil (4%) From pregnancy to PND21	PND21 Chow diet (Pragsoluções Biociência, Brazil)	Female PND120 Hippocampus	1.TBARS (nmol/mg protein) 2.Carbonyl content (nmol/mg protein)	1.No significant differences. 2.↑ in HFD group ($p<0.05$).
High fat diet	**Tozuka; Wada; Wada, 2009[43]**	Mice, C57BL/6J	CTR: fatty acids (FA) 3.8 g/100g of diet; 30.1% energy from protein; 10.6% energy from fat. HFD: fatty acids 32.7 g/100g of diet; 19.7% energy from protein; 57.5% energy from fat From 6 week before mating until PND16	PND22 CTR diet	Male PND21, PND70 CC, hippocampus, and cerebellum for western blotting. Fixed brain for immunohistochemistry	1.MDA levels (by immunoblotting) 2. MDA accumulation (by immunohistochemistry) 3. 4-hydroxy-2-hexenal (4-HHE, by immunoblotting)	1. ↑ in HFD group at PND21 in CC, hippocampus, cerebellum. 2. ↑ in HFD group at PND21 in subgranular of zone hippocampal dentate gyrus and in hippocampal progenitor cells. 3. ↑ in HFD group at PND21 in hippocampus
Changes in lipid content	**Machado *et al.*, 2021 [33]**	Rats, Wistar	Soybean Oil (SO): chow diet + 4% soybean oil	PND21 Chow diet (Nuvilab, Brazil)	Male and female PND90	1. Reactive oxygen and nitrogen species	1. ↓ DCFH oxidation in OO groups ($p<0.005$) 2. NS ($p=0.053$)

			Olive Oil (OO): chow diet + 4% olive oil From pregnancy until PND21		Dorsal hippocampus	production (DCFH oxidation) 2. Mitochondrial superoxide production (MitoSOX) 3. SOD (mU /mg prot) 4.CAT (µmol/min/mg prot) 5.GPx (NADPH/min/mg prot)	3.↑ in OO groups ($p<0.001$). 4. ↑ in OO groups ($p<0.001$). 5. ↑ in OO female group ($p<0.05$).
Changes in lipid content	**Mendes-da-Silva *et al.*, 2018 [41]**	Rats, Wistar	CTR group: 7% w/w of soybean oil Safflower group (SG): 7% w/w of safflower oil Casein as protein source From GD14 to PND21	PND21 Standard chow	NA PND65 Brain cortex (right and left cortex separately)	1.MDA levels (nmol/mg protein) 2.SOD activity (U/mg protein) 3.CAT activity (U/mg protein) 4. GST activity (U/mg protein) 5. GSH concentration (µM/mg protein)	1. ↓ in SG group in both sides (right: $p<0.05$; left: $p<0.01$). 2. ↓ in SG group in both hemispheres ($p<0.05$). 3. ↓ in SG group in both hemispheres ($p<0.01$). 4. ↑ in SG group in right hemispheres ($p<0.05$). 5. ↑ in SG group in both hemispheres ($p<0.05$).

Changes in lipid content	**Pase *et al.*, 2015** [34]	Rats, Sprague –Dawley	CTR: standard diet (protein 18.5%, fatty acids 3%, fiber 6%); Olive oil-enriched diet (OOED): 20% olive oil (protein 17%, fatty acids 20%, fiber 3,5%) From pregnancy until PND21	PND21 CTR diet	Fetus: NA GD20 Brain Pups: Male PND21 Brain	1.Reactive Species generation (units of fluorescence) 2.GSH (µM/mg protein)	1. No difference between groups for fetus and pups. 2. ↓ in fetus brain from OOED group ($p<0.005$).
Changes in lipid content	**Queiroz *et al.*, 2019** [40]	Rats, Wistar	CTR: 7% w/w soybean oil Conjugated linoleic acid (CLA 1 group): 7% w/w soybean oil + 1% CLA mix isomers CLA 3 group: 7% w/w soybean oil + 3% CLA mix isomers Casein as protein source From GD7 to PND21	PND21 Chow diet (Purina, Brazil)	Male PND70 Brain	1. MDA levels (nmol/g) 2 Total gluthatione content (nmol/g)	1. ↓ in CLA1 and CLA3 groups compared to CTR group ($p <0,001$). 2. ↑ in CLA1 and CLA3 groups compared to CTR group (CLA1 $p<0,0023$; CLA3 $p<0.0178$).
Multiple modifications	**Bonatto *et al.*, 2006** [19]	Rats, Wistar	Control (CTR): 25% casein	-	NA PND21	1. TBARS level (nmol of MDA	1. ↑ in CTR-MET compared to CTR in cerebellum and

			Control + methionine (CTR-MET): 25% casein + 0.15% l-methionine Low-protein (LP): 8% casein LP + methionine (LP-MET): 8% casein + 0.15% l-methionine From conception to PND21		Cortex, cerebellum	equivalents/mg protein) 2.SOD activity (U/mg protein) 3. CAT activity (U/mg protein)	cortex ($p<0.05$). ↑ in LP compared to CTR in cerebellum ($p<0.05$). ↑ in LP-MET compared to LP in cerebellum and cortex ($p<0.05$). 2. ↓ in LP and LP-MET compared to CTR and CTR-MET, respectively, in cerebellum ($p<0.05$). 3. ↓ in CTR-MET compared to CTR in cerebellum ($p<0.05$). ↑ in LP compared to CTR in cortex ($p<0.05$). ↓ in LP-MET compared to LP in cortex ($p<0.05$).
Multiple modifications	**Liapi *et al.*, 2007** [27]	Rats, Wistar	CTR, I, II, III: Control diet during all periods Choline-deficient (CD)-I: received choline-deficient diet (CDD), obtained from ICN (Costa Mesa, CA,	-	Male and female Experiment I – at birth Experiment II and III – PND21 Brain	1. Total antioxidant status (TAS) (mmol/L)	1. ↓ TAS in all CDD groups in both sexes compared to their respective CTR groups ($p<0.001$).

			USA; catalogue no. 960209) until birth CD-II: received CDD during gestation and CTR diet during lactation CD-III: received CDD during gestation and lactation From mate to birth or PND21 depend on group				
Multiple modifications	**Roy *et al.*, 2012 [36]**	Rats, Wistar	CTR: normal folate (NLfolate), normal B12 (NLB12) NLfolate + B12 deficient (noB12) NLfolate + noB12 + omega 3 supplemented (supp) High folate (Hfolate) + NLB12 Hfolate + noB12 Hfolate + noB12 + omega 3 supp All diets with 18% protein from casein	- -	NA GD20 Brain	1.MDA levels(nmol/ml)	1. ↑ in Hfolate + noB12 group compared to CTR and H folate + NL B12 ($p<0.01$).

			Normal folate: 2mg/kg; High folate: 8mg/kg; Normal B12: 2.5g/kg in 0.1% mannitol; Omega 3 SUPP: 1:1 Omega 3/Omega 6 ratio From GD0 until GD20				
Diet with modifications in vitamins and minerals	**Elfant; Keen, 1987[32]**	Rats, Sprague-Dawley	CTR: 25% (w/w) casein diet with intrinsic 1µg/g vanadium level Vanadium: 25% (w/w) casein diet with 75µg/g vanadium added From GD0 to PND21	-	NA PND21 Brain	1. GSH content (µmoles/g)	1. No difference between groups.
Diet with modifications in vitamins and minerals	**Eyles *et al.*, 2007[44]**	Rats, Sprague-Dawley	CTR: Control diet Vitamin D-deficient: Diet deficient in vitamin D (Dyets Inc., CA, USA) and lighting UV-free	NA Control diet	Male and female 10 weeks age Brain (right hemisphere)	1. Gene array profiling	1. ↓ expression of redox balance-related genes (Sod2, Cat, P4hb, Bcat1) in Vit-D-deficient group.

			From 6 weeks before mate to birth				
Diet with modifications in vitamins and minerals	**Langie *et al.*, 2013 [39]**	Mice, C57BL/J 6	Folate-adequate (CTR): 2 mg folic acid/kg diet Folate-depleted (FD): 0.4 mg folic acid/kg diet From 4 weeks before mating until lactation	PND22-25 Control diet: TD.09506; Harlan Laboratories, USA	Male 6 months Subcortical regions	1. 8-oxo-dG	1. No difference between groups.
Diet with modifications in vitamins and minerals	**Mackenzie *et al.*, 2011[45]**	Rats, Sprague –Dawley	CTR diet: 25 µg Zn/g diet Zn deficient diet (ZDD): 10 µg Zn/g diet From 1 week before breeding until GD19	- -	NA GD19 Brain	1.Total protein thiols (µmol/mg protein)	1. ↓ in ZDD group ($p<0.05$).
Diet with modifications in vitamins and minerals	**Omata *et al.*, 2013 [46]**	Rats, Sprague –Dawley	CTR group: 25 µg Zn/g diet ZDD group: 10 µg Zn/g diet From GD0 to GD19	- -	NA GD19 Brain	1. GSH content (nmol/mg protein) 2. Glutamate cysteine ligase modifier (GCLM) and catalytic (GCLC) levels (GCL/b-tubulin)	1. ↓ in ZDD group compared CTR ($p<0.05$). 2. ↓ in ZDD compared CTR ($p<0.05$). 3. ↓ in ZDD compared CTR ($p<0.05$).

						3. Gclm and Gclc mRNA expression (Gcl/RiboL32)	
Diet with modifications in vitamins and minerals	**Paidi *et al.*, 2014** [25]	Guinea pigs	CTR group: 900mg Vit C/kg diet Vit C deficient group: 100mg Vit C/kg diet From GD6-10 to GD45-56	- -	NA GD45 or GD56 Brain	1.MDA levels (nmol/g tissue) 2.SOD activity (U/g tissue) 3. α-tocopherol (nmol/g tissue) 4. γ-tocopherol (nmol/g tissue) 5. Vit C (nmol/g tissue) 6. Hydroxynonenal (HNE)	1. ↑ in GD56 compared to GD45 for both diet groups ($p<0.0001$); ↑ in Vit C deficient group compared to CTR group at GD56 ($p<0.05$). 2. ↑ in Vit C deficient group in both GD ($p<0.0001$). 3. ↑ in GD56 compared to GD45 for both diet groups ($p<0.0001$). 4. ↑ in Vit C deficient group in GD45 and GD56 ($p<0.05$). 5. ↓ in Vit C deficient group in both GD ($p<0.0001$). 6. ↑ in GD56 compared GD45 ($p<0.0001$).
Diet with modifications in	**Schinella *et al.*, 1999** [26]	Rats, Wistar	CTR: Control diet (15 g of vitE/kg)	- -	Male and female PND18	1.MDA levels (unit of absorbance/g tissue)	1. ↑ in VitE group ($p<0.01$).

vitamins and minerals			VitE: Diet absent in vitamin E Casein as protein source From breeding to PND18		Brain	2.SOD activity (ΔAbsorbance/4min/mg protein) 3.CAT activity (k/mg. protein) 4.Se-GPX activity (U/mg protein)	2. No difference between groups. 3. No CAT activity detected in both groups. 4. No Se-GPX activity detected in both groups.

CAT: Catalase; CDD: Choline-deficient diet; CC: Cerebral cortex; CTR: Control; FD: Folate-depleted; GD: Gestational day; GPx: Glutathione peroxidase; GSH: Glutathione; LP: Low-protein; MDA: Malondialdehyde; MET: Methionine; OOED: Olive oil-enriched diet; PND: postnatal day; RBD: Regional basic diet; SG: Safflower group; SO: Soybean Oil; SOD: Superoxide dismutase; SGGS: Oxidized glutathione; SUPP: supplemented; TBARS: thiobarbituric acid reactive substances; ZDD: Zn deficient diet

Main secondary outcomes results

Secondary outcomes are detailed in Table 3. Diets with modification in lipid observed reduction in velocity of cortical spreading depression [41], increased anhedonia [31], decrease depressive- [33] and anxiety-like behaviors[33,40], and impaired hippocampal neurogenesis[43]. While a multi-deficient diet (Regional Basic Diet) decreased area occupied by myelin layer in the cerebellar parasagittal sections [22].

Table 3 – Secondary outcomes retrieved from articles included in systematic review

Diets	Author, year	Specie/strain	Maternal intervention and experimental groups	Age of weaning and postweaning diet	Sex of pups, age of test	Parameters analyzed	Results
Low protein diet	**Augusto *et al.*, 2017** [22]	Rats	Control (CTR): chow diet (27.2% mix of animal and soy protein, 3.5% lipid) Malnourished (RBD, regional basic Diet): 8% protein (5:3 vegetal to animal protein), 1% lipid. From 30 days prior mating to PND21	PND21 Chow diet (Purina, Brazil)	Male PND21 Lateral Cerebellum	1. Parasagittal section dimension 2. Percentual area occupied by granular, molecular, and myelin layers 3. Myelin basic protein (MBP) immunohistochemistry 2. Calbindin immunohistochemistry	1. ↓ parasagittal section area in RBD group (p=0.0164). 2. ↓ area occupied by myelin layer in RBD group (p=0.005). 3. No differences. 4. ↓ Neuron soma area in RBD group (p=0.04).
High fat diet	**Curi *et al.*, 2021**[31]	Mice, Swiss	Control diet (CTR): 11.5% calories from fat High-fat diet (HFD): 45% calories from fat	PND21 CTR diet (Nuvilab, Brazil)	Male 1.PND62 2.PND65 3.PND66 4. PND70	1.Open field test (OFT) 2.Elevated plus maze test (EPMT) 3.Sucrose preference test (SPT) 4. BDNF expression	1.No differences. 2.↓ number of closed arm entries in HFD (p=0.011).

			Fat source: soybean oil and lard From 3 weeks before mating to PND21				3.↓ sucrose ingestion in HFD ($p = 0.001$). 4. ↓ BDNF expression im hippocampus in HFD ($p<0.0001$).
High fat diet	**Tozuka; Wada; Wada, 2009** [43]	Mice, C57BL/ 6J	CTR: fatty acids 3.8 g/100g of diet; 30.1% energy from protein; 10.6% energy from fat High-fat diet (HFD): fatty acids 32.7 g/100g of diet; 19.7% energy from protein; 57.5% energy from fat From 6 week before mating until PND16	PND22 CTR diet	Fetus (E18) Male PND21, PND49, PND70, PND98	1. 5-bromodeoxyuridine (BrdU) staining 2h after BrdU injection 2. BrdU and Calbindin-D-28K staining 28 days after BrdU injection	1. ↓ number of $BrdU^+$ cell at PND21, and PND70 in HFD. 2. ↓ number of $BrdU^+$ and $Calbindin^+$/ $BrdU^+$ cells at PND49 in HFD.
Changes in lipid content	**Machado *et al.*, 2020** [33]	Rats, Wistar	Soybean Oil (SO): chow diet + 4% soybean oil	PND21 Chow diet (Nuvilab, Brazil)	Male and female 1.PND60 2. PND80-81	1.OFT 2.Forced swimming test 3.SPT	1. ↑ locomotion in female in both diets compared to males ($p=0.002$).

			Olive Oil (OO): chow diet + 4% olive oil. From pregnancy until PND21		3.PND85-87		2. ↑ latency to immobility in males OO group in first day ($p<0.05$); ↑ swimming time, ↓ immobility time, and ↑ latency to immobility in OO groups ($p<0.05$) on second day. 3. No difference between SO and OO groups without maternal separation.
Changes in lipid content	**Mendes-da-Silva *et al.*, 2018** [41]	Rats, Wistar	CTR group: 7% w/w of soybean oil Safflower group (SG): 7% w/w of safflower oil Casein as protein source From GD14 to PND21	PND21 Standard chow	Male 1. PND65	1. Cortical spreading depression (CSD)	1. ↓ CSD velocity in SG ($p<0.05$).
Changes in lipid content	**Queiroz *et al.*, 2019** [40]	Rats, Wistar	CTR: 7% w/w soybean oil	PND21	Male 1.PND35 2.PND42	1. EPMT 2. OFT 3. Light-dark box test	1. ↑ time in open arms in CLA3 compared to

			Conjugated linoleic acid (CLA 1 group): 7% w/w soybean oil + 1% CLA mix isomers CLA 3 group: 7% w/w soybean oil + 3% CLA mix isomers Casein as protein source From GD7 to PND21	Chow diet (Purina, Brazil)	3.PND67		CTR ($p<0.0278$); ↑ entries in open arms in CLA1 compared to CTR ($p<0.0196$); ↑ time in central area in CLA1 and CLA3 compared to CTR ($p<0.0002$). 2. ↑ number of rearing in CLA1 and CLA3 compared to CTR ($p<0.0009$). 3. ↑ transitions and. ↑ movements in the light in CLA1 and CLA3 compared to CTR ($p<0.0001$).

CAT: Catalase; CDD: Choline-deficient diet; CC: Cerebral cortex; CTR: Control; CSD: Cortical spreading depression; EPMT: Elevated plus maze test; GD: Gestational day; GPx: Glutathione peroxidase; GSH: Glutathione; HFD: High fat diet; LP: Low -protein;

MS: Maternal separation; MDA: Malondialdehyde; MET: Methionine; MBP: Myelin basic protein; N: Number; OOED: Olive oil-enriched diet; OFT: Open fiel test; PND: Posnatal day; RBD: Regional basic diet; SG: Safflower group; SPT: Sucrose preference test; SOD: Superoxide dismutase; SGGS: Oxidized glutathione; SUPP: supplemented; TBARS: thiobarbituric acid reactive substance s; ZDD: Zn deficient diet;

DISCUSSION

In the articles retrieved by the systematic review it was possible to observe that perinatal periods (gestation and lactation) are sensible ones to the oxidative balance in the CNS. Different modifications on maternal diet were able to changes components of oxidant and antioxidant system thus interfering in offspring oxidative balance.

Lipid peroxidation is a process in which oxidizing agents damage lipids that have one or more double bonds, especially polyunsaturated fatty acids, producing different aldehydes, including MDA[48]. When using a maternal low-protein (LP) diet, it was observed that some areas of offspring CNS presented increased MDA levels[10,17–20,22,42]. The results were more consistent in male offspring through different ages[10,18,21,22,42] . While females' results varied at early age and did not differ in adulthood[17,42]. It is possible that female offspring have a protective factor against lipid peroxidation explained by the presence of estrogen, which plays a neuroprotective factor, reducing the damage caused by the LP diet[17]. It has already been observed that maternal LP diet can increase MDA levels in other organs, as heart[49], or in the CNS even when LP diet continued after weaning[50].

MDA levels may be increased in response to maternal LP diet because this diet decreases mitochondrial respiratory activity, changing mitochondrial function, which favors increasing in superoxide formation[21]. Moreover, decreased phosphorylation capacity is related to a low activity of citrate synthase (important in the Krebs cycle) and which, when its function is reduced, will affect NADPH levels[21]. It was also observed reduction in NADPH levels in offspring whose mothers ate a multi-deficient diet, which was also reduced in protein content [22]. Mitochondrial dysfunction was presented in offspring from LP diet dams [18,47] associated with increased production of ROS and decreased antioxidant defenses[18]. It is important to note that increased lipid peroxidation is considered toxic and when intensity of oxidative damage exceeds possibilities of cells repair it can induce apoptosis or programmed cell death by necrosis[48] .

Carbonyls are products originating from the oxidation of amino acids caused by ROS and RNS and are considered a good indicator of protein oxidation [51]. Among the studies that evaluated carbonyls in offspring of LP diet dams, it was observed increased levels at young male [42,47] and decreased levels in adult males[20]. In a study with an LP diet in which carbonyls were elevated, it was suggested that this increase

was justified by the composition of specific amino acids, which are sensitive to oxidative damage [47]. The mechanisms of this statement, however, are still unclear. Young females had mixed results for carbonyls content [17,42]. Estrogen levels in adult female offspring may attenuate oxidative damage, as no difference in carbonyl levels were also observed in adult female hearts [52].

Maternal LP diet influences on SOD activity was also widely evaluated in studies. Reduced SOD activity was observed in male adult offspring [10,18,20] while female offspring were not affected [17]. When the evaluation occurred at weaning or right after it, divergent responses were observed [17,19,22,42,47]. This result was also observed in offspring hearts [52]. Although, other studies that used maternal LP diet did not observed differences in SOD activity when the diet was extended after weaning [50] or when the restriction was in the amount of food [53].

Interestingly, all studies that presented decreased SOD activity had increased MDA levels [10,18,20,22]. Another study that evaluated the heart of offspring whose mothers received LP diet observed decreased SOD, CAT and GST activities and elevation of MDA levels [49]. Association between decreased antioxidant defenses (such as SOD activity) and increased levels of oxidant biomarkers (such as MDA) has already been demonstrated in renal patients, with reduction of SOD, GPx and CAT activity in erythrocytes and increased lipid peroxidation, causing hemolysis and anemia [54].

Decreased [10,17–19,42] or no difference [17,20,47] in CAT activity were observed in response to maternal LP diet. CAT is one of the enzymes responsible for inhibiting the accumulation of hydrogen peroxide, converting it to oxygen and water [55]. Cumulative decreased CAT and SOD activities suggest downregulation in antioxidant defense capacity, allowing for greater production of reactive species and lower antioxidant activity in mitochondria [49].

Regarding the non-enzymatic antioxidant systems, GSH levels were reduced in male young or adult offspring from LP diet mothers [10,21,22], while there were no differences in female offspring regardless of age [17,42]. GSH is transformed into GSSG through GPx and the reverse reaction occurs thanks to the action of GR [56]. GSH is the most abundant form found and the GSH/GSSG ratio informs the cellular redox balance [56]. Thus, it is suggested that despite a reduced production of GSH, the redox balance may not be affected in brain in cortex regions [22]. Interestingly GPx was decreased in some studies [10,17,18].

Excess on levels of reactive oxygen and nitrogen species can cause oxidative stress in any neurons; however, the amount of the damage will depend on the susceptibility of each CNS area [13]. In our revision, several studies had shown that maternal LP diet increases ROS and RNS levels depending on the CNS area studied with the brainstem being more sensitive [20,42,47] than hippocampus [33], cerebral cortex or cerebellum [22].

Modification of lipids in maternal diet also brought an impact in oxidative balance in offspring. Diets compositions were more variable than that observed in LP diets. Regarding high-fat diets (HFD), lard was the main ingredient chosen to increased lipids levels [31,35,43] but usually accompanied by other oils as soybean oil [31,35] and safflower oil [43]. One study used HFD with vegetable oil only (olive oil)[34].

When offspring whose dams consumed HFD was evaluated at weaning it was observed increased levels of MDA [43]. This difference was not present at older ages [31,35,43]. High fat content in breast milk underlies the mechanism of increased lipid peroxidation during this phase in offspring [43]. Also, at this age the pups can eat mothers' diet themselves[57]. Differently from MDA levels, carbonyl levels were increased in adult offspring hippocampus from HFD dams[35]. [37]observed that a HFD downregulated some antioxidant protein like superoxide dismutase (Mn) mitochondrial, glutathione peroxidase1, glutathione S-transferase omega-1 that could indicate increased oxidative stress in offspring's brain.

Interestingly, when occurred only modification in lipid source, without increase its quantity, it was observed reduced levels of MDA at young adult offspring[40,41]. These results may be more related to a protective role from diet rich in omega-6 (w-6) fatty acids[40,41] compared to w-9-enriched one[34] that from offspring age. consumption of linoleic acid (w6) is very important for the central nervous system, from pregnancy – transported by the placenta – as well as in childhood, transmitted to offspring through breastfeeding[40].

Maternal diet lipid source also differently affected SOD and CAT activities. W-9 diet rich was responsible to increase SOD and CAT activities in offspring [33], while the opposite was found when a w-6-rich diet was used [41]. Linoleic acid seems to exert an antioxidant effect, preventing the oxidation of fatty acids in offspring CNS[40]. Strengthen this hypothesis, maternal diet rich in w-6 rich increased total glutathione levels[40] and reduced ROS[33], while one rich in w-9 decreased GSH levels in offspring brain [34].

Although diets and methodological parameters were quite different, in general, maternal vitamin- or mineral-depleted or deficient diet increased oxidant biomarkers [25,26,36] and reduced antioxidant agents, as antioxidant enzymatic activity and GSH levels[27,44,46] . These results demonstrate that micronutrient balance in maternal diet is as important as macronutrient ones.

Inadequate maternal nutrition may change cognitive, motor and socio-emotional behavior in offspring[58] . Therefore, we had a secondary objective to study if the oxidative balance changes imposed in offspring CNS by maternal diet modification would influences some brain structure and function. Regarding brain structure, maternal protein-restricted diet induced structural changes in cerebellum and these changes were associate with reduced MDA and ROS levels in this area at weaning, but a more oxidative profile was observed in cerebral cortex at the same age [22]. Decreased velocity of propagation of CSD was observed when safflower oil was the lipid source [41] and it was associated with reduced MDA levels and SOD and CAT activity, but increased GSH levels [41]. Thus, the non-enzymatic antioxidant system also plays an important role in modulating brain excitability through reducing oxidative stress [41]. However, hippocampal neurogenesis was impaired in HFD offspring maybe due to increased peroxidative damage in the region observed by increased MDA levels and accumulation [43]. Lipid peroxidation and oxidative stress could contribute to deficiencies in the postnatal phase, such as decreased cognitive functions, spatial memory learning, contextual memory of fear and anxiety-related behavior [43].

Maternal HFD diet favors hyperactive and anxiety-like behaviors in offspring [7], nevertheless [31] observed reduced entries in closed arm by HFD offspring without changes in times in EPM arms. On the other hand, depressive- [33] and anxiety-like[33,40] behaviors were decreased, and anhedonic-like behavior was not influenced [33] by maternal diet rich in w-6. These results may be related to a protective role of the w-6 expressed reducing levels of lipid peroxides and increasing antioxidant enzymes activities[33,40]. However, changes in anhedonic-like behavior were observed in offspring of HFD mothers [31]. This find was not associate with changes in oxidative stress, but with reduced BDNF expression and reduced hippocampal 5HT1A levels [31]. It is known that serotoninergic pathway is linked to depression and anxiety-like behavior [56,59] and can influence BDNF expression [31]. Vitamin-D deficiency in prenatal environment was associated with abnormally expressed transcript related to schizophrenia and multiple sclerosis including genes linked to oxidative balance and

mitochondrial function [44]. Maternal HFD was associated with increased acetylcholinesterase and carbonyl proteins levels in hippocampus which could play a role in Alzheimer and other dementia diseases [35]. [18] associate increased arterial blood pressure with decreased antioxidant enzymatic and non-enzymatic activity and consequent increasing in lipid peroxidation in medulla oblongata of offspring whose mothers received LP diet. This region has important participation in sympathetic overreaction and neurogenic hypertension[60] . Similarly, maternal LP increased oxidative stress in brainstem that is another brain area related to cardiovascular control[10,20,21]. Hence, changes in oxidative stress in CNS could influence a wide range of neurogenic diseases.

Conclusion

In summary, maternal dietary imbalances during pregnancy and/or lactation modifies oxidative stress biomarkers and antioxidant enzymatic and non-enzymatic systems. Maternal LP, vitamin- or mineral-deficient or HFD diets were in general associated with increased oxidative stress observed mainly by increased lipid peroxidation and reduced antioxidant defense. However, when lipid content in diet was changed, w-6 rich diet was associated with reduced oxidative stress. Nevertheless, offspring sex and age of analysis played an important role in expressed outcomes. Young and adult male offspring seem to be more prone to changes due to maternal diet, while female offspring seemed to be more resistant to changes in adult ages. Those oxidative stress changes were associated with different diseases, ranged from depression, anxiety to schizophrenia, multiple scleroses, dementias, and hypertension.

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6 CONSIDERAÇÕES FINAIS

Desequilíbrios na dieta materna durante a gestação e/ou lactação modifica os níveis de marcadores de estresse oxidativo e a função dos sistemas enzimáticos e não-enzimáticos de defesa antioxidantes. Em geral, dieta materna com redução de proteína (8% de proteína) aumentou o estresse oxidativo, avaliado principalmente pelos níveis de MDA, e reduziu as defesas antioxidantes, principalmente a atividade da SOD e os níveis de GSH. As dietas ricas em gordura (*high-fat diet*) também tiveram padrão similar de influência no balanço oxidativo, favorecendo o aumento do estresse oxidativo. Essas dietas aumentavam o conteúdo de lipídios principalmente com banha animal. Quando a modificação foi na qualidade do lipídio, sem aumento da quantidade, dietas maternas ricas em ômega-6 levaram ao perfil de menor peroxidação lipídica com concomitante redução de atividade de enzimas antioxidantes no SNC da prole. Enquanto nas dietas ricas em ômega-9, não foi observada diferença significativa nos valores de peroxidação lipídica e houve aumento das enzimas antioxidantes. Redução ou ausência de algumas vitaminas, principalmente vitamina C, D, E e B12 também levaram a predominância do sistema oxidante sobre o sistema antioxidante.

Contudo, algumas diferenças entre os artigos foram encontradas e que poderiam estar relacionadas ao sexo e idade de análise dos filhotes. De forma geral, machos jovens e adultos foram mais suscetíveis a mudanças no equilíbrio oxidativo em resposta a modificações da dieta materna. Fêmeas adultas foram mais resistentes a essas mudanças o que poderia sugerir a influência dos hormônios sobre a resposta observada.

As mudanças no balanço oxidativo foram associadas a alterações na estrutura e funcionamento cerebral e alterações de comportamento, memória e aprendizado. Além disso, também houve associação com áreas relacionadas ao controle cardiovascular e respiratório ligando ao desenvolvimento de hipertensão de origem neurogênica. Ademais, outras doenças neurodegenerativas e neuropsiquiátricas como esclerose múltipla, Alzheimer e esquizofrenia também estava associadas às modificações do estresse oxidativo no SNC da prole.

Desta forma, apesar da grande variabilidade metodológica de alteração nutricional da dieta, o tempo de insulto e a estrutura de avaliação influenciando na resposta na prole, há bom escopo científico demonstrando que o ambiente materno

nutricionalmente desequilibrado pode ser a gênese ou ter um papel importante no desenvolvimento de diversas doenças neurogênicas. Entretanto, não foi possível indicar uma associação direta entre alterações no equilíbrio oxidativo, doenças neurogênicas e repercussões secundárias. Nesse mesmo sentido, esse período também pode servir como janela para a utilização de dietas equilibradas e com bom perfil de macro e micronutrientes para atuar na prevenção dessas doenças.

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APÊNDICE A – ESTRATÉGIA DE BUSCA NAS BASES

Pubmed	(Diet OR Dietary supplements OR Nutrients OR Infant Nutrition OR Maternal Nutrition) AND (Pregnancy OR Gestation OR Prenatal Exposure OR Lactation OR Breast Feeding) AND (Oxidative Stress OR Lipid Peroxidation OR Scavenger OR Antioxidants OR Free Radical OR Reactive Oxygen Species) AND (Central nervous system OR Brain OR Brainstem OR Diencephalon OR Prosencephalon OR Hypothalamus OR Hippocampus OR Telencephalon OR Cerebrum OR Mesencephalon OR Cerebellum OR Cerebral cortex OR Basal ganglia OR Amygdala OR Thalamus OR Corpus striatum)
Lilacs	("Diet" OR "Dietary supplements" OR "Nutrients" OR "Infant Nutrition" OR "Maternal Nutrition") AND ("Pregnancy" OR "Gestation" OR "Prenatal Exposure" OR "Lactation" OR "Breast Feeding") AND ("Oxidative Stress" OR "Lipid Peroxidation" OR "Scavenger" OR "Antioxidants" OR "Free Radical" OR "Reactive Oxygen Species") AND ("Central nervous system" OR "Brain" OR "Brainstem" OR "Diencephalon" OR "Prosencephalon" OR "Hypothalamus" OR "Hippocampus" OR "Telencephalon" OR "Cerebrum" OR "Mesencephalon" OR "Cerebellum" OR "Cerebral cortex" OR "Basal ganglia" OR "Amygdala" OR "Thalamus" OR "Corpus striatum")
Scopus	ALL (("diet" OR "Dietary supplements" OR "nutrients" OR "Infant Nutrition" OR "Maternal Nutrition") AND ("pregnancy" OR "gestation" OR "Prenatal Exposure" OR "lactation" OR "breast feeding") AND ("Oxidative Stress" OR "Lipid Peroxidation" OR "scavenger" OR antioxidants OR "Free Radical" OR "Reactive Oxygen Species") AND ("Central nervous system" OR "brain" OR "brainstem" OR "diencephalon" OR " prosencephalon" OR "hypothalamus" OR "hippocampus" OR "telencephalon" OR "cerebrum" OR "mesencephalon" OR "ce rebellum" OR "cerebral" AND "cortex" OR "Basal ganglia" OR "amygdala" OR "thalamus" OR "corpus" AND "s triatum"))
Web of science	(TS=((Diet OR Dietary supplements OR Nutrients OR Infant Nutrition OR Maternal Nutrition) AND (Pregnancy OR Gestation OR Prenatal Exposure OR Lactation OR Breast Feeding) AND (Oxidative Stress OR Lipid Peroxidation OR Scavenger OR

<table>
<tr><td></td><td colspan="2">Antioxidants OR Free Radical OR Reactive Oxygen Species) AND (Central nervous system OR Brain OR Brainstem OR Diencephalon OR Prosencephalon OR Hypothalamus OR Hippocampus OR Telencephalon OR Cerebrum OR Mesencephalon OR Cerebellum OR Cerebral cortex OR Basal ganglia OR Amygdala OR Thalamus OR Corpus striatum)))</td></tr>
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<tr><td></td><td>#2</td><td>Pregnancy OR Prenatal Exposure OR Lactation OR Breast Feeding</td></tr>
<tr><td></td><td>#3</td><td>Oxidative Stress OR Lipid Peroxidation OR Scavenger OR Antioxidant OR Free Radical OR Reactive oxygen metabolite</td></tr>
<tr><td></td><td>#4</td><td>Central nervous system OR Brain OR Brain stem OR Diencephalon OR Forebrain OR Hypothalamus OR Hippocampus OR Telencephalon OR Mesencephalon OR Brain cortex OR Basal ganglion OR Amygdala OR Thalamus OR Corpus striatum</td></tr>
<tr><td></td><td>#5</td><td>#1 and #2 and #3 and #4</td></tr>
</table>

A Embase sugere alteração de algumas palavras para se alcançar um maior número de referências, conforme tabela acima.

APÊNDICE B - FORMULÁRIO DE EXTRAÇÃO DE DADOS

Título do artigo	
DOI	
Autores	
Periódico	
Ano de publicação	
País de correspondência do autor	
População estudada (espécie e linhagem)	
Período da intervenção na dieta materna (gestação/lactação)	
Idade das mães	
Dieta controle	
Dieta manipulada (modificação ocorrida na dieta materna)	
Idade do desmame	
Dieta pós-desmame (depois do período ocorrido)	
Idade da prole na avaliação (10 sem, etc)	
Extração do material (congelado/perfundido)	
Método de eutanásia	
Região do SNC avaliada	
Biomarcadores de estresse oxidativo no cérebro da prole (biomarcadores de peroxidação lipídica e oxidação proteica). *Incluir informações do teste (foi de acordo com protocolo de...)*	
Avaliação do sistema antioxidante (enzimático e não enzimático) SOD (U/mg protein); CAT (U/mg protein; mcg/mL); GSH (mcg/mL; U/mg protein; mol/mg protein (multiples and their submultiples); MDA (mg/mL; mcg/mL; mol/mL (multiples and their submultiples); GPx (U/mg protein; mM/min/mg protein). GST (U/mg protein); GR	

(U/mg protein). ***Incluir informações do teste (foi de acordo com protocolo de...)***	
Produção de espécies reativas. ***Incluir informações do teste (foi de acordo com protocolo de...)***	
Expressão gênica (expressão relativa da proteína-alvo/proteína-endógena; expressão de mRNA: 2-ΔC). ***Incluir informações do teste (foi de acordo com protocolo de...)***	
Resultados de testes de imagens (imuno-histoquímica... e região estudada – qual a área?)	
Idade do teste comportamental	
Metodologia do teste comportamental	
Resultados de testes comportamentais	
Resultados de testes que indiquem doença neurogênica	
Houve interesse de conflito?	
Houve contato com o autor?	
Número de grupos experimentais (incluindo grupo controle e número de animais em cada grupo).	

ANEXO A – PROTOCOLO DE SUBMISSÃO DA REVISÃO SISTEMÁTICA (PROSPERO)

PROSPERO
International prospective register of systematic reviews

NHS
National Institute for Health Research

SYRCLE

Collaborative Approach to Meta Analysis and Review of Animal Data from Experimental Studies
·C·A·M·A·R·A·D·E·S·

Animal review

1. * Review title.

Give the working title of the review. This must be in English. The title should have the interventions or exposures being reviewed and the associated health or social problems.

Maternal diet influences on oxidative stress in offspring's brain and its relation with neurogenic diseases: A systematic review of animal (preclinical) studies.

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

A influência da dieta materna no estresse oxidativo do cérebro da prole e a sua relação com as doenças neurogênicas: uma revisão sistemática em estudos animais

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

01/09/2020

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

01/09/2021

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Natalia Negromonte

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Mrs Negromonte

7. * Named contact email.

Enter the electronic mail address of the named contact.

natalia.souza@ufpe.br

8. * Named contact address.

Enter the full postal address for the named contact.

Universidade Federal de Pernambuco, Centro Academico de Vitoria. Rua Alto do Reservatorio, s/n, Bela Vista - Vitoria de Santo Antao, PE - Brasil, 55608680.

9. Named contact phone number

Enter the telephone number for the named contact, including international dialling code.

04181999047314

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'none' if the review is not affiliated to any organisation.

Universidade Federal de Pernambuco, Centro Academico de Vitoria.

Organisation web address:

www.ufpe.br

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country are now mandatory fields for each person.**

Mrs Natalia Negromonte. Federal University of Pernambuco
Mr Anderson Pedroza. Federal University of Pernambuco
Dr José Antonio-Santos. Federal University of Pernambuco
Dr Claudia Lagranha. Federal University of Pernambuco
Dr Raquel Aragão. Federal University of Pernambuco

12. * Funding sources/sponsors.

Give details of the individuals, organisations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.

Fundação de Amparo à Ciência e Tecnologia de Pernambuco (FACEPE), scholarship number

IBPG-1840-4.05/19.

Grant number(s)

1840-4.05/19

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

[15.1 Review question]

Give details of the question to be addressed by the review, clearly and precisely.

What are the effects of manipulation of maternal diet on oxidative stress in offspring's brain and its relation with neurogenic diseases in rodent and non-rodent mammalian models?

Context and rationale

Provide a brief description of the context and rationale of the review, including information on the relevance of your review for human health (max 250 words).

Animal studies could understand by which mechanisms the maternal diet can predispose the offspring to neurogenic diseases.

16. * Searches.

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full

search strategy is not required, but may be supplied as a link or attachment.

The search will be performed in the databases PubMed, EMBASE, Web of Science, Scopus, LILACS, Cochrane databases. Combination of MeSH descriptors and other entry terms: Diet, Dietary supplements, Nutrients, Infant Nutritional Physiological Phenomena, Maternal Nutritional Physiological Phenomena, Pregnancy, Gestation, Prenatal Exposure Delayed Effects, Lactation, Breast Feeding, Oxidative stress, Lipid Peroxidation, Free Radical Scavengers, Antioxidants, Free Radical, Reactive Oxygen Species will be used to construct Boolean operators. There will be no restriction on language or date of publication. The literature search will be conducted in electronic databases by two independent reviewers. In case of disagreement between the independent reviewers during the search process, a third reviewer will mediate.

17. URL to search strategy.

Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).

Diet, Dietary supplements, Nutrients, Infant Nutritional Physiological Phenomena, Maternal Nutritional Physiological Phenomena, Pregnancy, Gestation, Prenatal Exposure Delayed Effects, Lactation, Breast Feeding, Oxidative stress, Lipid Peroxidation, Free Radical Scavengers, Antioxidants, Free Radical, Reactive Oxygen Species.

PubMed: Diet OR "Dietary supplements" OR Nutrients OR "Infant Nutritional Physiological Phenomena" OR "Maternal Nutritional Physiological Phenomena" AND Pregnancy OR Gestation OR "Prenatal Exposure Delayed Effects" OR Lactation OR "Breast Feeding" AND "Oxidative stress" OR "Lipid Peroxidation" OR "Free Radical Scavengers" OR Antioxidants OR "Free Radical" OR "Reactive Oxygen Species".

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Human disease modelled.

Give a short description of the disease, condition or healthcare domain being modelled.

Oxidative stress in offspring brain.

19. * Animals/population.

Give summary criteria for the animals being studied by the review, e.g. species, sex, details of disease model. Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

Mammals

Exclusion criteria:

Humans, genetically modified animals.

20. * Intervention(s), exposure(s).

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed (e.g. dosage, timing, frequency). Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

Modification in maternal diet (quantity or quality of macro or micronutrients or diet caloric value) during gestation and/or lactation.

Exclusion criteria:

No maternal nutritional intervention during pregnancy and/or lactation. Studies where maternal diet energy content was modified by reducing offer; studies where macronutrient or energy manipulation was performed using beverage drinks (eg. water with glucose) or gavage, studies where offspring received modified diet after weaning.

21. * Comparator(s)/control.

Where relevant, give details of the type(s) of control interventions against which the experimental condition(s) will be compared (e.g. another intervention or a non-exposed control group). Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

Maternal exposure to control diet.

Exclusion criteria:

Offspring of control dams received modified diet after weaning.

22. * Study designs to be included.

Give details of the study designs eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

Controlled studies with a separate control group.

Exclusion criteria:

Studies without a separate control group.

23. Other selection criteria or limitations applied.

Give details of any other inclusion and exclusion criteria, e.g. publication types (reviews, conference abstracts), publication date, or language restrictions.

Inclusion criteria: all languages. Exclusion criteria: not an original primary study. Reviews and meta-analyses

studies will be excluded.

24. Outcome measure(s).

Give detail of the outcome measures to be considered for inclusion in the review. Please include details of both inclusion and exclusion criteria.

Inclusion criteria:

Evaluation of oxidative stress in offspring brain including: biomarkers of lipid peroxidation and protein oxidation, enzymatic and non-enzymatic antioxidant defenses, reactive species production, genes expression.

Exclusion criteria:

Evaluation of oxidative stress except in the offspring's brain. No analyzes in the brain.

25. N/A.

This question does not apply to systematic reviews of animal studies for human health submissions.

26. Study selection and data extraction.

Procedure for study selection

Give the procedure for selecting studies for the review, including the screening phases (title and/or title-abstract and/or full-text), the number of researchers involved, and how discrepancies will be resolved.

Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened independently by two review authors to identify studies that potentially meet the inclusion criteria outlined above. The full text of these potentially eligible studies will be retrieved and independently assessed for eligibility by two review team members. Any disagreement between them over the eligibility of particular studies will be resolved through discussion with a third reviewer.

Prioritise the exclusion criteria

Multiple exclusion criteria may apply to an abstract/paper, which can cause discrepancies between reviewers in the reason for exclusion recorded. To avoid this, it is helpful to prioritize the exclusion criteria (e.g. 1) not an animal study; 2) not a myocardial infarction model, etc.) and record the highest ranking applicable criterion as the reason for exclusion. Please sort the exclusion criteria defined in questions 19 to 24. If applicable, do so for each screening phase.

1. Not an original primary study; 2. No maternal nutritional intervention during pregnancy and/or lactation; 3. No analyzes in the brain.

Methods for data extraction

Describe methods for data extraction, including the number of reviewers performing data extraction, extraction of data from text and/or graphs, whether and how authors of eligible studies will be contacted to provide missing or additional data, etc.

Two reviewers will independently extract data from each article. We first try to extract numerical data from tables, text or figures. In case data are not reported or unclear, we will attempt to contact authors by e-mail (max. 2 attempts). In case an outcome is measured at multiple time points, data from the time point where

efficacy is highest will be included.

Data to be extracted: study design

Specify the data to be extracted related to characteristics of the study design, e.g. controlled versus cross-over, number of experimental groups, etc.

Number of experimental groups (including control group), number of animals in each group.

Data to be extracted: animal model

Specify the data to be extracted related to characteristics of the animal model, e.g. species, sex of the animals, etc.

Population: Species and strain, number of animals, mothers and offspring age.

Data to be extracted: intervention of interest

Specify the data to be extracted related to characteristics of the intervention of interest, e.g. dose, timing, etc.

Intervention: Period of nutritional intervention, dietary characteristics (quantity or quality of macro or micronutrients or diet caloric value) in experimental and control groups, post-weaning diet (if applicable) characteristics.

Data to be extracted: primary outcome(s)

Define the primary outcome measure(s). For each outcome measure, specify in which format data will be extracted, including the eligible units of measurement, and data type (continuous/dichotomous). A description of any other manipulation or transformation of the extracted data that is planned may be included.

SOD (U/mg protein); CAT (U/mg protein; mcg/mL); GSH (mcg/mL; U/mg protein; mol/mg protein (multiples and their submultiples); MDA (mg/mL; mcg/mL; mol/mL (multiples and their submultiples); GPx (U/mg protein; mM/min/mg protein). GST (U/mg protein); GR (U/mg protein).

Data to be extracted: secondary outcome(s)

Define the secondary outcome measure(s). For each outcome measure, specify in which format data will be extracted, including the eligible units of measurement, and data type (continuous/dichotomous). A description of any other manipulation or transformation of the extracted data that is planned may be included.

1) Protein expression: relative expression of target protein / endogenous protein. 2) mRNA expression: 2-?Ct relative expression.

Data to be extracted: other

Specify any other data or study characteristics to be extracted, e.g. bibliographical details, such as author, year and language.

Author and year of publication.

27. Risk of bias and/or quality assessment.

State whether and how risk of bias and/or study quality will be assessed. Assessment tools specific for pre-clinical animal studies include SYRCLE's risk of bias tool and the CAMARADES checklist for study quality

No risk of bias and/or quality assessment planned

No

By use of SYRCLE's risk of bias tool

Yes

By use of SYRCLE's risk of bias tool adapted as follows:

No

By use of the CAMARADES checklist for study quality

No

By use of the CAMARADES checklist for study quality, adapted as follows:

No

Other criteria, namely

No

Method for risk of bias and/or quality assessment

Give the procedure for the risk of bias and/or quality assessment, including the number of reviewers involved, their contribution, and how discrepancies will be resolved.

Two independent researchers will appraise the quality. In case of discrepancies, a third author will mediate.In addition, the kappa index will be calculated to measure the degree of agreement between the first and second reviewers beyond what would be expected by random chance.

28. Strategy for data synthesis.

Planned approach

For each outcome measure, specify whether a quantitative or narrative synthesis is planned and how this decision will be made.

Narrative systematic review without meta-analysis. We will present a descriptive summary of the findings of studies involving the oxidative stress in the brain of offspring, structured around the types and characteristics of maternal diet intervention.

If a meta-analysis is planned, please specify the following:

Effect measure

For each outcome measure, specify the effect measure to be used (e.g. mean difference, odds ratio etc.).

No meta-analysis planned.

Effect models

For each outcome measure, specify the statistical model of analysis (e.g. random-effects or fixed-effect model).

No meta-analysis planned.

Heterogeneity

Specify the statistical methods to assess heterogeneity (e.g. I^2, Q). For further guidance please refer to the

introduction and practical guide to pre-clinical meta-analysis.

No meta-analysis planned.

Other

Specify other details of the meta-analysis methodology (e.g. correction for multiple testing, correction for multiple use of control group).

No meta-analysis planned.

29. * Analysis of subgroups or subsets.

Subgroup analyses

Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.

Subgroup analysis will be based on intervention of population of mammals studies.

Sensitivity

For each outcome measure, specify any sensitivity analyses you propose to perform.

No meta-analysis planned.

Publication bias

Specify whether an assessment of publication bias is planned. If applicable, specify the method for assessment of publication bias.

No meta-analysis planned.

30. * Review type.

Type of review

Animal model review
No

Experimental animal exposure review
No

Pre-clinical animal intervention review
Yes

31. Language.

Select each country individually to add it to the list below, use the bin icon to remove any added in error.
English
Portuguese-Brazil

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Brazil

33. Other registration details.

List other places where the systematic review protocol is registered. The name of the organisation and any unique identification number assigned to the review by that organisation should be included.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one.

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

No

Give brief details of plans for communicating review findings.?

36. * Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line.

Diet, Dietary supplements, Nutrients, Infant Nutritional Physiological Phenomena, Maternal Nutritional Physiological Phenomena, Pregnancy, Gestation, Prenatal Exposure Delayed Effects, Lactation, Breast Feeding, Oxidative stress, Lipid Peroxidation, Free Radical Scavengers, Antioxidants, Free Radical, Reactive Oxygen Species.

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any further information the review team consider relevant to the registration of the review.

40. Details of final report/publication(s) or preprints if available.

This field should be left empty until details of the completed review are available OR you have a link to a preprint. Give the full citation for the preprint or final report or publication of the systematic review.

Give the link to the published review or preprint.

ANEXO B – NORMAS PARA SUBMISSÃO DE ARTIGOS

Instructions for authors

Thank you for choosing to submit your paper to us. These instructions will ensure we have every required so your paper can move through peer review, production and publication smoothly. Ple time to read and follow them as closely as possible, as doing so will ensure your paper matches t requirements.

AUTHOR SERVICES
Supporting Taylor & Francis authors

For general guidance on every stage of the publication process, please visit our Author Services v

EDITING SERVICES
Supporting Taylor & Francis authors

For editing support, including translation and language polishing, explore our Editing Services we

Editorial Manager

This journal uses Editorial Manager to peer review manuscript submissions. Please read the guic Manager authors before making a submission. Complete guidelines for preparing and submittin manuscript to this journal are provided below.

Contents

Nutritional Neuroscience

About the Journal

Nutritional Neuroscience is an international, peer-reviewed journal publishing high-quality, origi
Please see the journal's Aims & Scope for information about its focus and peer-review policy.

Please note that this journal only publishes manuscripts in English.

Nutritional Neuroscience accepts the following types of article: Research Papers, Review Articles
Studies.

Open Access

You have the option to publish open access in this journal via our Open Select publishing progı
open access means that your article will be free to access online immediately on publication, ir
visibility, readership and impact of your research. Articles published Open Select with Taylor &
receive 95% more citations* and over 7 times as many downloads** compared to those that a
published Open Select.

Your research funder or your institution may require you to publish your article open access. V
Services website to find out more about open access policies and how you can comply with the

You will be asked to pay an article publishing charge (APC) to make your article open access an
often be covered by your institution or funder. Use our APC finder to view the APC for this jour

Please visit our Author Services website if you would like more information about our Open Se

*Citations received up to 9th June 2021 for articles published in 2016-2020 in journals listed in
Science®. Data obtained on 9th June 2021, from Digital Science's Dimensions platform, availab
https://app.dimensions.ai
**Usage in 2018-2020 for articles published in 2016-2020.

Peer Review and Ethics

Peer Review and Ethics

Taylor & Francis is committed to peer-review integrity and upholding the highest standards of review. Once your paper has been assessed for suitability by the editor, it will then be double blind peer reviewed by independent, anonymous expert referees. If you have shared an earlier version of your Author's Original Manuscript on a preprint server, please be aware that anonymity cannot be guaranteed. Further information on our preprints policy and citation requirements can be found on our Preprints Author Services page. Find out more about what to expect during peer review and read our guidance on publishing ethics.

Preparing Your Paper

All authors submitting to medicine, biomedicine, health sciences, allied and public health journals should conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, prepared by the International Committee of Medical Journal Editors (ICMJE).

Structure

Your paper should be compiled in the following order: title page; abstract; keywords; main text introduction, materials and methods, results, discussion; acknowledgments; declaration of interest statement; references; appendices (as appropriate); table(s) with caption(s) (on individual pages); figures; figure captions (as a list).

Word Limits

Please include a word count for your paper.

A typical paper for this journal should be no more than 6000 words, inclusive of:

- Abstract
- Tables
- References
- Figure or table captions

Style Guidelines

Please refer to these quick style guidelines when preparing your paper, rather than any published articles or a sample copy.

Any spelling style is acceptable so long as it is consistent within the manuscript.

Please use single quotation marks, except where 'a quotation is "within" a quotation'.

Please note that long quotations should be indented without quotation marks.

Research Papers should contain a maximum of 6000 words and 6 to 8 illustrations. We recommend that the article contains no more than 25 references. The article should be divided into the following sections. Long articles may require subheadings within some sections to clarify their content.

Nutritional Neuroscience

1. Introduction

The introduction should provide an appropriate background to the article, drawing on relevant literature and explaining the research question to be addressed. Authors should avoid obviously partisan selection and quotation of literature.

2. Methods

The methods section should demonstrate a clear and documented design or strategy directed towards a specific research question. This section should describe and account for:

· the study design

· the criteria for selecting the sample and recruitment to the study

· data collection

· data analysis

· details of interventions (if applicable)

This section should also include details of approval from a named research ethics committee. Please consult the publishing ethics section of these Instructions for more information.

Authors submitting randomized, controlled trials (RCTs) should refer to the CONSORT statement. These guidelines provide a set of recommendations comprising a list of items to report and a patient flow diagram.

3. Results

The results section should contain all the information required by readers to assess the validity of the conclusions. This section should include

· a description of the sample included in the study and its characteristics

· for quantitative studies, include details of the response rates and numbers lost to follow up

· analysis should be clear and systematic

· results of statistical tests should be reported with measures of central tendency (mean, median) and error estimates (e.g. s.e.m.)

· no more than 6 tables should be included.

4. Discussion

The discussion section should be structured and we recommend that this covers the following sections, using sub headings:

· summary of main findings

· the strengths and limitations of the study

· how and why it agrees with existing literature, in particular including any papers published since the study was designed and carried out

· the implications for future research or clinical practice

Review Articles

Review Articles should be a maximum of 7500 words and have up to 6 to 8 figures.

Case Studies

Case Studies should not exceed 2500 words and can contain a maximum of 4 figures.

Formatting and Templates

Papers may be submitted in Word or LaTeX formats. Figures should be saved separately from the text. To assist you in preparing your paper, we provide formatting template(s).

Word templates are available for this journal. Please save the template to your hard drive, ready for use.

If you are not able to use the template via the links (or if you have any other template queries) please contact us here.

References

Please use this reference guide when preparing your paper.

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Checklist: What to Include

1. **Author details.** Please ensure everyone meeting the International Committee of Medical Journal Editors (ICMJE) requirements for authorship is included as an author of your paper. Please ensure all listed authors meet the Taylor & Francis authorship criteria. All authors of a manuscript should include their full name and affiliation on the cover page of the manuscript. Where available, please also include ORCiDs and social media handles (Facebook, Twitter or LinkedIn). One author will need to be identified as the corresponding author, with their email address normally displayed in the article PDF (depending on the journal) and the online article. Authors' affiliations are the affiliations where the research was conducted. If any of the named co-authors moves affiliation during the peer-review process, the new affiliation can be given as a footnote. Please note that no changes to affiliation can be made after your paper is accepted. Read more on authorship.

2. Should contain an unstructured abstract of 250 words. Read tips on writing your abstract.
3. **Graphical abstract** (optional). This is an image to give readers a clear idea of the content of your article. It should be a maximum width of 525 pixels. If your image is narrower than 525 pixels, please place it on a white background 525 pixels wide to ensure the dimensions are maintained. Save the graphical abstract as a .jpg, .png, or .tiff. Please do not embed it in the manuscript file but save it as a separate file, labelled GraphicalAbstract1.
4. You can opt to include a **video abstract** with your article. Find out how these can help your work reach a wider audience, and what to think about when filming.
5. No more than 8 **keywords**. Read making your article more discoverable, including information on choosing a title and search engine optimization.
6. **Funding details.** Please supply all details required by your funding and grant-awarding bodies as follows:
   For single agency grants
   This work was supported by the [Funding Agency] under Grant [number xxxx].
   For multiple agency grants
   This work was supported by the [Funding Agency #1] under Grant [number xxxx]; [Funding Agency #2] under Grant [number xxxx]; and [Funding Agency #3] under Grant [number xxxx].
7. **Disclosure statement.** This is to acknowledge any financial or non-financial interest that has arisen from the direct applications of your research. If there are no relevant competing interests to declare please state this within the article, for example: *The authors report there are no competing interests to declare*. Further guidance on what is a conflict of interest and how to disclose it.
8. **Biographical note.** Please supply a short biographical note for each author. This could be adapted from your departmental website or academic networking profile and should be relatively brief (e.g. no more than 200 words).
9. **Data availability statement.** If there is a data set associated with the paper, please provide information about where the data supporting the results or analyses presented in the paper can be found. Where applicable, this should include the hyperlink, DOI or other persistent identifier associated with the data set(s). Templates are also available to support authors.
10. **Data deposition.** If you choose to share or make the data underlying the study open, please deposit your data in a recognized data repository prior to or at the time of submission. You will be asked to provide the DOI, pre-reserved DOI, or other persistent identifier for the data set.
11. **Supplemental online material.** Supplemental material can be a video, dataset, fileset, sound file or anything which supports (and is pertinent to) your paper. We publish supplemental material online via Figshare. Find out more about supplemental material and how to submit it with your article.
12. **Figures.** Figures should be high quality (1200 dpi for line art, 600 dpi for grayscale and 300 dpi for colour, at the correct size). Figures should be supplied in one of our preferred file formats: EPS, PS, JPEG, TIFF, or Microsoft Word (DOC or DOCX) files are acceptable for figures that have been drawn in Word. For information relating to other file types, please consult our Submission of electronic artwork document.
13. **Tables.** Tables should present new information rather than duplicating what is in the text. Readers should be able to interpret the table without reference to the text. Please supply editable files.
14. **Equations.** If you are submitting your manuscript as a Word document, please ensure that equations are editable. More information about mathematical symbols and equations.
15. **Units.** Please use SI units (non-italicized).

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Disclosure Statement

Please include a disclosure statement, using the subheading "Disclosure of interest." If you have no interests to declare, please state this (suggested wording: *The authors report no conflict of interest*). For all NIH/Welcome-funded papers, the grant number(s) must be included in the declaration of interest statement. Read more on declaring conflicts of interest.

Clinical Trials Registry

In order to be published in a Taylor & Francis journal, all clinical trials must have been registered in a public repository, ideally at the beginning of the research process (prior to participant recruitment). Trial registration numbers should be included in the abstract, with full details in the methods section. Clinical trials should be registered prospectively – i.e. before participant recruitment. However, for clinical trials that have not been registered prospectively, Taylor & Francis journals requires retrospective registration to ensure the transparent and complete dissemination of all clinical trial results which ultimately impact human health. Authors of retrospectively registered trials must be prepared to provide further information to the journal editorial office if requested. The clinical trial registry should be publicly accessible (at no charge), open to all prospective registrants, and managed by a not-for-profit organization. For a list of registries that meet these requirements, please visit the WHO International Clinical Trials Registry Platform (ICTRP). The registration of all clinical trials facilitates the sharing of information among clinicians, researchers, and patients, enhances public confidence in research, and is in accordance with the ICMJE guidelines.

Complying with Ethics of Experimentation

Please ensure that all research reported in submitted papers has been conducted in an ethical and responsible manner, and is in full compliance with all relevant codes of experimentation and legislation. All original research papers involving humans, animals, plants, biological material, protected or non-public datasets, collections or sites, must include a written statement in the Methods section, confirming ethical approval has been obtained from the appropriate local ethics committee or Institutional Review Board and that where relevant, informed consent has been obtained. For animal studies, approval must have been obtained from the local or institutional animal use and care committee. All research studies on humans (individuals, samples, or data) must have been performed in accordance with the principles stated in the Declaration of Helsinki. In settings where ethics approval for non-interventional studies (e.g. surveys) is not required, authors must include a statement to explain this. In settings where there are no ethics committees in place to provide ethical approval, authors are advised to contact the Editor to discuss further. Detailed

guidance on ethics considerations and mandatory declarations can be found in our Editorial Policies section on Research Ethics.

Consent

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