UNIVERSIDADE FEDERAL DO PARANÁ

PAOLA ALVES CLAUDINO

CONSUMO DE ALIMENTOS ULTRAPROCESSADOS E RISCO NO DESENVOLVIMENTO DA DOENÇA DE ALZHEIMER: UMA REVISÃO SISTEMÁTICA

CURITIBA

2023

PAOLA ALVES CLAUDINO

CONSUMO DE ALIMENTOS ULTRAPROCESSADOS E RISCO NO DESENVOLVIMENTO DA DOENÇA DE ALZHEIMER: UMA REVISÃO SISTEMÁTICA

Dissertação apresentada ao curso de Pós-Graduação em Alimentação e Nutrição, Setor de Ciências da Saúde, Universidade Federal do Paraná, como requisito parcial à obtenção do título de Mestre em Nutrição.

Orientadora: Profa. Dra. Bárbara Dal Molin Netto

Coorientador: Prof. Dr. Nassib Bezerra Bueno

CURITIBA

2023

Claudino, Paola Alves
Consumo de alimentos ultraprocessados e risco no desenvolvimento da doença de Alzheimer [recurso eletrônico]: uma revisão sistemática / Paola Alves Claudino – Curitiba, 2023.
1 recurso online : PDF

Dissertação (mestrado) – Programa de Pós-Graduação em Alimentação e Nutrição. Setor de Ciências da Saúde, Universidade Federal do Paraná, 2023.

Orientador: Profa. Dra. Bárbara Dal Molin Netto
Coorientador: Prof. Dr. Nassib Bezerra Bueno

1. Ingestão de alimentos. 2. Alimentos industrializados. 3. Doença de Alzheimer. I. Molin Netto, Bárbara Dall. II. Bueno, Nassib Bezerra. III. Universidade Federal do Paraná. IV. Título.

CDD 612.3

Maria da Conceição Kury da Silva CRB 9/1275

TERMO DE APROVAÇÃO

Os membros da Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação ALIMENTAÇÃO E NUTRIÇÃO da Universidade Federal do Paraná foram convocados para realizar a arguição da dissertação de Mestrado de **PAOLA ALVES CLAUDINO** intitulada: **Consumo de alimentos ultraprocessados e risco no desenvolvimento da doença de Alzheimer: uma revisão sistemática.**, sob orientação da Profa. Dra. BARBARA DAL MOLIN NETTO, que após terem inquirido a aluna e realizada a avaliação do trabalho, são de parecer pela sua APROVAÇÃO no rito de defesa.

A outorga do título de mestra está sujeita à homologação pelo colegiado, ao atendimento de todas as indicações e correções solicitadas pela banca e ao pleno atendimento das demandas regimentais do Programa de Pós-Graduação.

CURITIBA, 04 de Agosto de 2023.

Assinatura Eletrônica
09/08/2023 16:34:59.0
BARBARA DAL MOLIN NETTO
Presidente da Banca Examinadora

Assinatura Eletrônica
09/08/2023 13:46:57.0
AMANDA BAGOLIN DO NASCIMENTO
Avaliador Externo (UNIVERSIDADE FEDERAL DE SANTA CATARINA)

Assinatura Eletrônica
15/08/2023 19:00:54.0
DEBORAH CRISTINA LANDI MASQUIO
Avaliador Externo (CENTRO UNIVERSITÁRIO SÃO CAMILO)

AGRADECIMENTOS

À minha família, especialmente aos meus pais Nilton e Everli e ao melhor irmão, Elvis, por tanto amor, cuidado, suporte e investimento em mim. Obrigada por sempre me incentivarem a estudar.

Ao meu namorado, Mateus, por todo amor, amparo, companheirismo e sobretudo, por ser a pessoa que me incentivou a realizar o Mestrado. Obrigada por tornar os meus dias mais felizes, por ser incrível e se fazer presente.

Às professoras do Programa de Pós-Graduação em Alimentação e Nutrição, por todo conhecimento e apoio nessa trajetória.

À minha admirável orientadora, Profa. Dra, Bárbara Dal Molin Netto Cervantes, por me acolher, ensinar e orientar com sabedoria.

Ao meu coorientador, Prof. Dr. Nassib Bezerra Bueno, por todo apoio e orientação.

Aos meus amigos e colegas do Mestrado, por todo companheirismo, auxílio e incentivo em continuar a pesquisa.

À minha amiga, Karoline, pela amizade construída desde a época da graduação. Obrigada pela amizade, momentos compartilhados e por todo apoio ao longo desses anos.

À Universidade Federal do Paraná, pelo ensino gratuito e de excelente qualidade.

À Deus, por sua luz e força ao mostrar o caminho em momentos difíceis e sobretudo, por ter me proporcionado uma família que me ama e apoia os meus sonhos.

“As nuvens mudam sempre de posição, mas são sempre nuvens no céu. Assim devemos ser todo dia, mutantes, porém leais com o que pensamos e sonhamos. Lembre-se, tudo se desmancha no ar, menos os pensamentos”.

Paulo Beleki

RESUMO

Objetivo: Investigar a associação do consumo de alimentos ultraprocessados no risco do desenvolvimento da doença de Alzheimer em adultos e idosos. O protocolo da revisão foi registrado na PROSPERO (CRD42022375944). **Métodos:** Trata-se de uma revisão sistemática relatada conforme o PRISMA. Foram incluídos estudos observacionais, sem restrição de idioma e ano de publicação. Foram excluídos estudos que avaliaram como desfecho apenas outros tipos de demências, não considerando a doença de Alzheimer. A pesquisa foi realizada nas bases Medline, Embase, Lilacs e consulta na literatura cinzenta entre abril e maio de 2023, além de busca por citação nos estudos incluídos. A extração dos dados foi realizada por dois revisores independentes. O risco de viés e qualidade metodológica dos estudos incluídos foram avaliados por meio do checklist do Instituto Joanna Briggs para estudos de coorte. **Resultados:** Um total de 4 estudos envolvendo 614.502 adultos e idosos foram incluídos. Todos os estudos apresentaram desenho de coorte e foram considerados de alta qualidade metodológica. Dos estudos incluídos, 3 estudos evidenciaram associação de risco entre consumo de alimentos ultraprocessados e desenvolvimento da doença de Alzheimer, enquanto 1 estudo apresentou associação de risco apenas com o desenvolvimento de declínio cognitivo. **Discussão:** A associação entre o consumo de AUP no risco de desenvolvimento da DA é um tema recente em estudos científicos, visto que o estudo mais antigo identificado por nossa revisão é de 2017. Dos quatro estudos incluídos, três demonstraram associação significativa do consumo de AUP no risco de desenvolvimento da DA.

Palavras-chaves: alimento ultraprocessado; comida industrializada; fast-food; doença de Alzheimer; demência de Alzheimer.

ABSTRACT

Objective: To investigate the association of the consumption of ultra-processed foods with the risk of developing Alzheimer's disease in adults and the elderly. The review protocol was registered on PROSPERO (CRD42022375944). **Methods:** This is a systematic review reported according to PRISMA guidelines. Observational studies were included without language or publication year restrictions. Studies assessing only other types of dementia as outcomes, not considering Alzheimer's disease, were excluded. The search was carried out in the Medline, Embase, Lilacs databases, and a survey of the gray literature between April and May 2023, in addition to a citation search in the included studies. Data extraction was performed by two independent reviewers. The risk of bias and methodological quality of the included studies were assessed using the Joanna Briggs Institute checklist for cohort studies. **Results:** A total of 4 studies involving 614,502 adults and elderly people were included. All studies had a cohort design and were considered of high methodological quality. Of the included studies, 3 demonstrated a risk association between the consumption of ultra-processed foods and the development of Alzheimer's disease, while 1 study showed a risk association only with the development of cognitive decline. **Discussion:** The association between ultra-processed foods consumption and the risk of developing Alzheimer's disease is a recent topic in scientific studies, given that the oldest study identified by our review dates back to 2017. Of the four included studies, three showed a significant association between ultra-processed foods consumption and the risk of developing Alzheimer's disease.

Keywords: ultraprocessed food; industrialized food; fast-food; Alzheimer disease; Alzheimer's dementia.

LISTA DE FIGURAS

LISTA DE QUADROS

LISTA DE GRÁFICOS

LISTA DE TABELAS

SUMÁRIO

1 INTRODUÇÃO

Com o aumento mundial da expectativa de vida crescem as preocupações com as doenças mais prevalentes entre os idosos, dentre elas a demência. Em 2016, a demência atingiu cerca de 44 milhões de pessoas no mundo, sendo que projeções apontam que esse valor deve aumentar para 135 milhões de casos até 2050 (GBD, 2019; ADI, 2020).

A doença de Alzheimer (DA) é a causa mais comum da demência (ADI, 2020), sendo caracterizada como um processo progressivo de reestruturação fisiopatológica do cérebro, decorrente da deposição e acúmulo extracelular de proteína β-amilóide no parênquima cerebral (Edwards, 2019). Atualmente, tratamentos para retardar a progressão da doença são escassos e o desenvolvimento de novos medicamentos tem sido lento (Cummings *et al.,* 2020).

Evidências na literatura mostram que as intervenções relacionadas à nutrição são fundamentais para a prevenção do declínio cognitivo, visto que a dieta influencia mecanismos diretos e indiretos que podem modificar o risco da DA (Solfrizzi *et al.,* 2018). É importante mencionar que como consequência da transição nutricional, o padrão alimentar foi fortemente modificado nas últimas décadas. Estudos apontam maior disponibilidade e consumo de alimentos de alta densidade energética e baixa concentração de vitaminas e minerais (García *et al.,* 2021)

O fator determinante para esse cenário é o aumento significativo do consumo de alimentos ultraprocessados (AUP) em todo o mundo, sobretudo por serem facilmente acessíveis e práticos. Os AUP representam mais da metade da energia dietética total consumida em países desenvolvidos, como Estados Unidos, Reino Unido e Canadá (Moubarac *et al.,* 2017; Rauber *et al.,* 2018) e entre um quinto do total de energia dietética em países de renda média, como o Brasil, México e Chile (Louzada *et al.,* 2018; Ponce *et al.,* 2018; Cediel *et al.,* 2018) fontes de informação para estimar o consumo de AUP são baseadas em dados dietéticos, podendo ser avaliados por meio de ferramentas como recordatório de 24 horas, questionário de frequência alimentar e diário alimentar (FAO, 2018).

Recentemente publicado, um estudo evidenciou que o consumo de AUP está associado ao maior risco da DA (Li *et al.,* 2022). Existem vários mecanismos biológicos que podem explicar essa associação. Dentre elas, os AUP estão geralmente associados a uma alimentação de baixa qualidade, pois são ricos em açúcar, gordura, sódio e aditivos químicos (Liu *et al.,* 2020). Esse conjunto de características pode promover uma inflamação sistêmica

no organismo e favorecer processos neurogenerativos e fisiopatológicos no cérebro, consequentemente aumentando o risco da DA (Guerville *et al.,* 2017).

Revisões sistemáticas apresentam associação positiva entre consumo de AUP e doenças crônicas não transmissíveis (DCNT), tais como obesidade (Santos *et al.,* 2020), doença cardiovascular (Chen *et al.,* 2020), diabetes mellitus (Moradi *et al.,* 2021), hipertensão arterial sistêmica (Barbosa *et al.,* 2020), câncer (Lane *et al.,* 2021) e depressão (Tian *et al.,* 2020). Apesar de já estar bem estabelecido na literatura que o consumo de AUP eleva o risco para o desenvolvimento de DCNT, a associação no risco da DA tem sido pouco explorada por revisões sistemáticas. Isto posto, o objetivo da presente revisão foi investigar a associação do consumo de alimentos ultraprocessados no risco de desenvolvimento da DA em adultos e idosos.

1.1 OBJETIVOS

1.1.1 Objetivo geral

Compilar e analisar estudos que investigaram a associação do consumo de alimentos ultraprocessados no risco de desenvolvimento da doença de Alzheimer.

1.1.2 Objetivos específicos

a. Elaborar um protocolo de Revisão Sistemática;
b. Identificar nas bases de dados os estudos que investigaram a associação do consumo de alimentos ultraprocessados no risco de desenvolvimento da doença de Alzheimer;
c. Sintetizar as características dos estudos selecionados;
d. Evidenciar os principais achados dos estudos selecionados;
e. Avaliar a qualidade metodológica dos estudos selecionados.

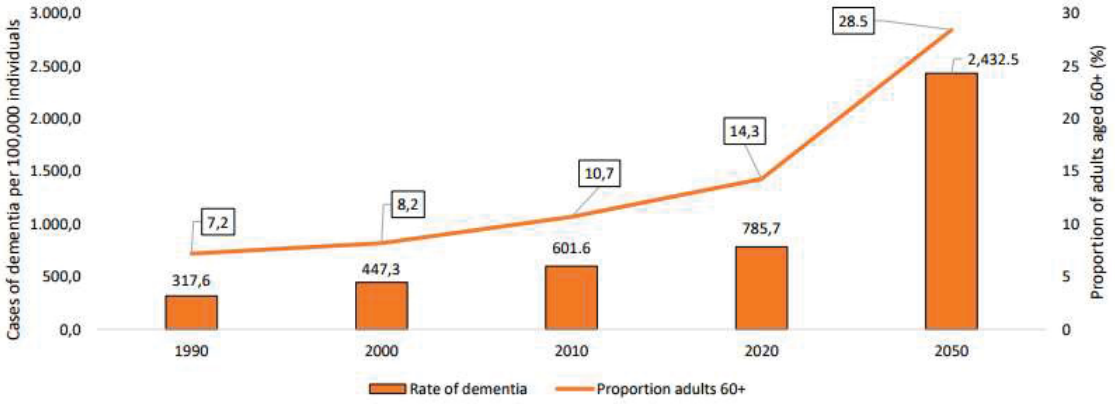
2 REVISÃO DE LITERATURA

2.1 DEMÊNCIA E DOENÇA DE ALZHEIMER – UMA VISÃO EPIDEMIOLÓGICA

Em virtude do crescimento mundial da população idosa e aumento da expectativa de vida, a incidência da DA aumenta a cada ano, prejudicando a qualidade de vida do idoso, visto que é uma das principais doenças relacionadas à redução das atividades básicas de vida diária (Crous-Bou *et al.,* 2017). De acordo com o Relatório Mundial de Alzheimer, em 2015, cerca de 56 milhões de pessoas no mundo apresentavam demência, sendo a DA a causa mais comum (ADI, 2015).

No Brasil, a taxa de internação por demência aumentou 75% de 2010 a 2019. Nenhuma outra doença crônica teve variação superior nesse período (Feter *et al.,* 2020). De acordo com o Gráfico 1, a proporção de pessoas com 60 anos ou mais aumentará em 99% de 2020 a 2050, enquanto os casos de demência por 100.000 indivíduos aumentarão 210%. A expectativa é que o número de pessoas vivendo com demência no Brasil chegue a 5,7 milhões em 2050 (GBD, 2019).

Gráfico 1 - Taxa de demência por 100.000 indivíduos e proporção de idosos com 60 anos ou mais no Brasil de 1990 a 2050

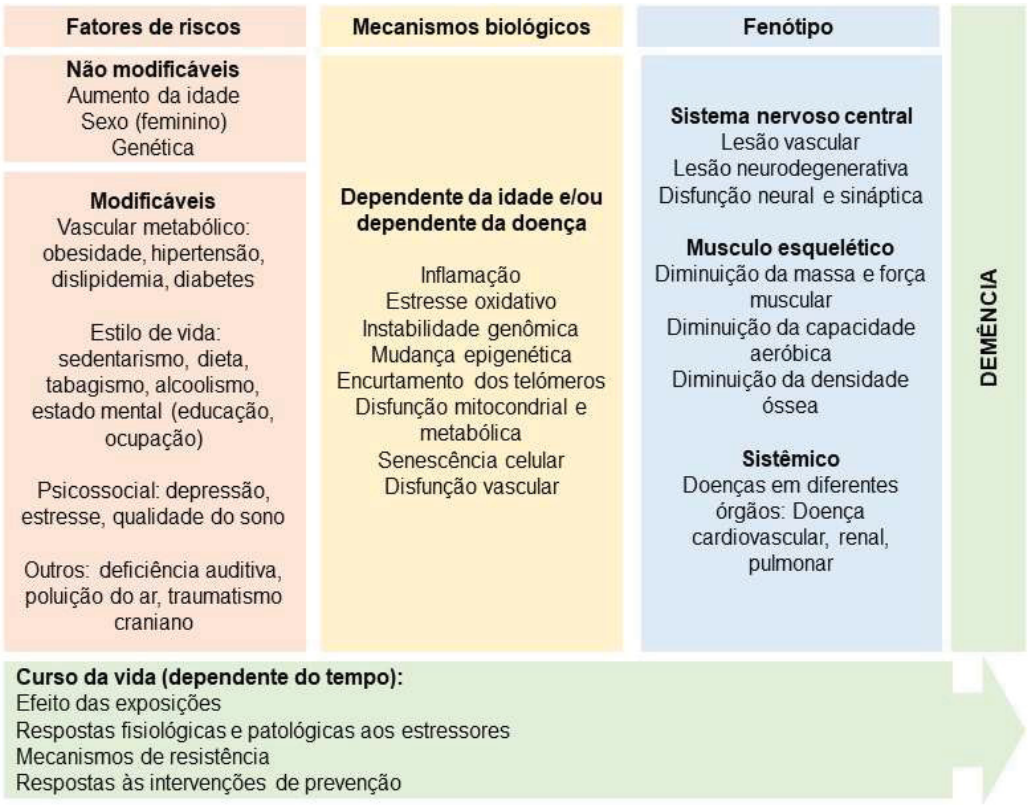


Fonte: GBD, 2019

Apesar dos esforços globais da saúde, a demência ainda é incurável e os tratamentos farmacológicos para controle da progressão da doença são limitados (Szeto; Lewis, 2016). De acordo com a Organização Mundial de Saúde (OMS), em 2016, a demência foi considerada a quarta principal causa não transmissível de morte, sendo responsável por quase dois milhões de mortes em todo o mundo (OMS, 2018).

No início da década de 1990, a idade avançada e os fatores genéticos eram os únicos fatores de risco estabelecidos para a demência, não dando oportunidades para medidas de prevenção (Livingston *et al.,* 2020). No entanto, nas últimas décadas, estudos observacionais forneceram evidências sobre as possibilidades de prevenção da demência, tornando-se evidente que condições multifatoriais e heterogêneas impulsionadas por fatores de riscos genéticos, ambientais, socioeconômicos e fatores de proteção, incluindo fatores vasculares, psicossociais e relacionados ao estilo de vida, podem ser modificáveis e fornecerem possibilidades de prevenção (Lisko *et al.,* 2021) (Figura 1).

Figura 1 - Fatores de riscos comuns e mecanismos biológicos para demência



Fonte: adaptado de Lisko *et al.* (2021)

Há ainda que salientar que fatores de riscos vasculares, como obesidade na meia-idade, dislipidemia e hipertensão arterial sistêmica, estão fortemente associados com o desenvolvimento da demência, sendo que o conjunto desses fatores aumenta o risco de forma ativa (Livingston *et al.,* 2020). Uma meta-análise de estudos observacionais demonstrou que a obesidade na meia-idade aumenta o risco de demência em 33% na fase idosa (Albanese *et al.,* 2017).

2.2 FISIOPATOLOGIA DA DOENÇA DE ALZHEIMER

A DA é um distúrbio de progressão lenta, onde ocorre alterações fisiopatológicas que precedem os sintomas clínicos por muitos anos (Edwards, 2019). Atualmente, a DA é diferenciada entre a de início precoce e tardio. A DA de início precoce apresenta forte componente genético, caracterizada por acometer indivíduos com menos de 60 anos, representando cerca de 1 a 6% dos casos. Já a DA de início tardio é a forma mais comum da doença, a qual acomete indivíduos com mais de 60 anos. Ambas as formas possuem as mesmas características fisiopatológicas, definidas pelo decréscimo progressivo das funções cognitivas (Cacace; Sleegers; Van Broeckhoven, 2016).

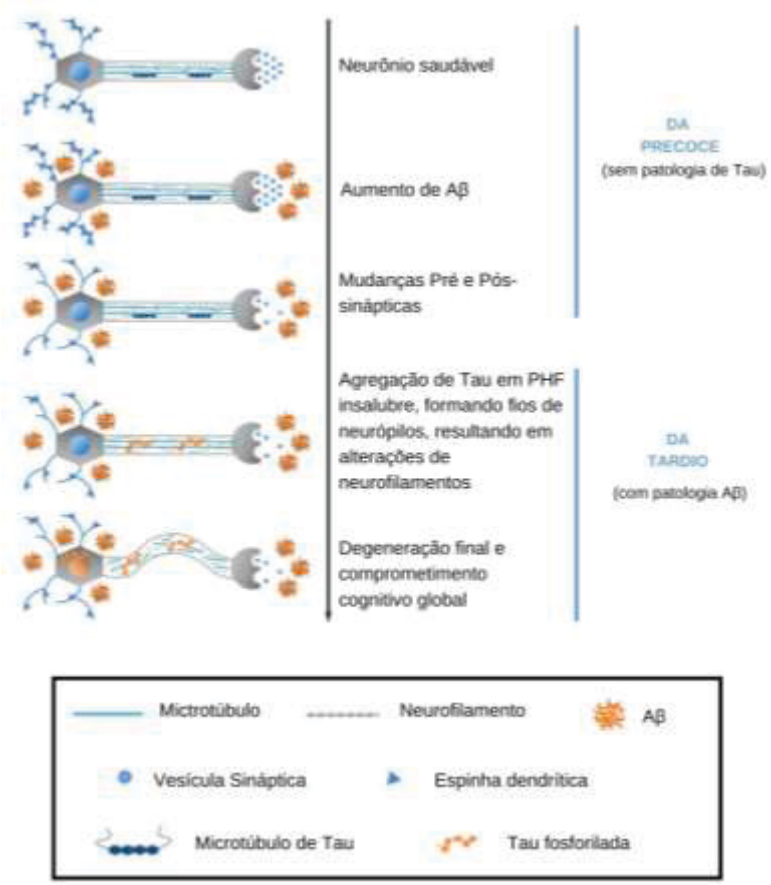
O estágio leve da DA é caracterizado pela perda da memória episódica e semântica, enquanto no estágio moderado o comprometimento cognitivo se torna mais evidente, tendo habilidades de julgamentos, planejamento, organização e raciocínio lógico prejudicadas. Em estágios terminais é observado mudanças notáveis, como alterações do ciclo do sono, alterações comportamentais, inabilidade para falar, andar e realizar atividades de autocuidado (Parnett *et al.,* 2019).

Na literatura descreve-se que o principal gatilho para a DA é o aumento da proteína β-amilóide no sistema nervoso central, que parece desencadear uma cascata de eventos, incluindo o acúmulo de formas tóxicas da proteína Tau (Edwars, 2019). A formação da β-amilóide, é o resultado da digestão da proteína precursora amiloide (PPA), que aparenta ter função fisiológica fundamental com relação aos fenômenos de neuroplasticidade. Observou-se que diversos fragmentos com funções fisiológicas e fisiopatológicas são gerados a partir dessa proteína precursora (Auda; Borrmann, 2018).

Um recente estudo realizado por Edwards (2019), traz uma hipótese que pode explicar a relação entre β-amilóide e proteína Tau. Nos estágios iniciais da DA, conforme os níveis de β-amilóide aumentam, as placas começam a ser depositadas e aumentam progressivamente de tamanho, reduzindo a transmissão glutamatérgica e danificando as sinapses (Pereira *et al.,* 2021). Esse dano às sinapses próximas às placas β-amilóide, inicialmente, produz uma disfunção da rede local que produz uma resposta da microglia, removendo as sinapses danificadas para evitar danos na rede (Cummings *et al.,* 2017). No entanto, conforme mais placas β-amilóide se acumulam, o dano sináptico se torna mais acentuado e se espalha, resultando na fosforilação da Tau, dissociação dos microtúbulos de Tau e formação de amaranhados, desencadeando perda de axônio e neurodegeneração (Hong *et al.,* 2016; Jack *et al.*, 2018). Essa hipótese teve concordância com o encontrado no estudo

de Pereira *et al.* (2021), confirmando que a β-amilóide e proteína Tau têm efeitos tóxicos na função sináptica e na integridade axonal, respectivamente, ligando esses eventos ao longo do curso da DA (Figura 2).

Figura 2 - Efeitos de β-amilóide e Tau na função sináptica e axonal nos estágios iniciais e tardios da DA.



* Em estágios iniciais da doença (aβ-amilóide+Tau- e aβ-amilóide-Tau-), o acúmulo de a β-amilóide em placas reduz o número de espinhas pós sinápticas e o número de vesículas pré-sinápticas, alterando a comunicação sináptica local. Em fases posteriores da doença (aβ-amilóide+Tau+ e aβ-amilóide+Tau-), à medida que as alterações sinápticas se tornam mais pronunciadas, a Tau torna-se fosforilada e agrega-se em filamentos pareados insolúveis (PHF), que formam filamentos de neurópilos e amaranhados neurofibrilares. Essas alterações são seguidas pela dissociação dos neurofilamentos dos microtúbulos, degeneração axonal e comprometimento cognitivo global.
Fonte: adaptado de Pereira *et al*. (2021).

Estudos têm demonstrado um importante papel de alelos apoE na DA. A apoE é uma glicoproteína que desempenha importante papel no cérebro, realizando o transporte de lipídeos para os neurônio por meio da ligação aos receptores apoE da superfície celular envolvidos no metabolismo das lipoproteínas. Evidência na literatura identificaram que a modulação desses receptores da apoE afeta as patologias amiloides e tau (Liu *et al.,* 2016; Rauch *et al.,* 2020). Existem três alelos apoE predominantes, os alelos ε2, ε3 e ε4 que conferem níveis variados de risco de doença. Estudos demonstram que portadores de apoE4

possuem maior risco de desenvolver DA, enquanto que portadores de apoE2 apresentam um menor risco (Halliday et al., 2016; Guen et al., 2022). A compreensão desses mecanismos envolvidos entre apoE4 e DA ajudará a elucidar as vias envolvidas na patogênese da doença e poderá fornecer novas estratégias terapêuticas.

2.3 DIAGNÓSTICO DA DOENÇA DE ALZHEIMER

O diagnóstico clínico da DA é baseado na avaliação minuciosa, especialmente dos domínios cognitivos afetados e do comprometimento funcional do paciente. A DA é um processo patológico progressivo, a qual possui diferentes estágios clínicos, sendo que a demência ocorre em um estágio em que as alterações patológicas já estão difusas. A concepção desse *continuum* cognitivo é importante para a adequada avaliação clínica do paciente (Sevigny *et al.,* 2016).

2.3.1 Anamnese

Segundo o documento da Academia Brasileira de Neurologia (2022), a anamnese detalhada focada nas alterações cognitivas e neuropsiquiátricas mais comum da DA permite diagnosticá-la de forma mais segura, estabelecer seu subtipo e estágio evolutivo, além de diferenciá-la de outras doenças neurodegenerativas. O interrogatório ao paciente e a seu acompanhante deve abranger:

I. Memória episódica: O paciente esquece fatos e datas recentes, itens de compras, compromissos, local onde guarda objeto? Ou fica repetindo as mesmas perguntas ou comentários?
II. Funções executivas: Dificuldades em manter a atenção concentrada, tomar decisões, planejar atividades, resolver problemas cotidianos, fazer compras e lidar com pequenas quantias de dinheiro? Perdeu a motivação e iniciativa? Julga situações inadequadamente?
III. Habilidade visuais-espaciais ou práxicas: Dificuldade para se orientar espacialmente (fora e dentro de casa), vestir-se, pentear-se, barbear-se, usar objetos comuns, reconhecer rostos familiares? Perdeu a destreza com tarefas que antes fazia bem?
IV. Linguagem: Dificuldade para encontrar palavras ao conversar ou nomear objetos e pessoas? Ou para compreender palavras ou frases, explicar as coisas

e fazer-se entendido, apresentando vocabulário pobre e redução da fluência da fala?

2.3.2 Avaliação neuropsicológica

O disgnóstico da DA em sua fase inicial tem maior confiabilidade quando se usam dois subtestes para cada um dos quatro domínios cognitivos afetados pela doença, e maior sensibilidade quando se define score deficitário como >1 desvio padrão – DP – (e não >1.5 ou >2DP) em relação aos valores normativos. Assim, adicionalmente a um teste de escore cognitivo global (MEEM, Mini-Exame do Estado Mental; ou MoCA, Montreal Cognitive Assessment), a avaliação deve abranger o exame da memória episódica, linguagem, funções executivas e visuais-espaciais, com dois subtestes para cada domínio cognitivo (Academia brasileira de neurologia, 2022). Abaixo encontra-se os principais instrumentos recomendados para avaliação cognitiva na DA (Quadro 1).

Quadro 1 - Instrumentos na avaliação cognitiva da DA

Tipos de instrumentos	Principais testes
Testes de rastreios	
Testes breves	Mini-Exame do Estado Mental (MEEM), Montreal Cognitive Assessment (MoCA), Cognitive Abilities Screening Instrument – Short Form (CASI-S), Bateria Breve de Rastreio Cognitivo (BBRC)
Baterias multi-funcionais	Exame Cognitivo de Addenbrooke – versão revisada (ACE-R), Cambridge Cognitive Examination – Revised: CAMCOG-R), Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-COG), Consortium to Establish a Registry for Alzheimer's Disease (CERAD), Mattis Dementia Rating Scale (MDRS)
Avaliação dos diferentes domínios cognitivos	
Memória episódica verbal	Teste de aprendizado auditivo-verbal de Rey (RAVLT), Subteste de aprendizado de palavras da Bateria CERAD
Memória não verbal	Subteste de reconhecimento das figuras da BBRC, Subteste de recordação das figuras geométricas da Bateria CERAD, Figura Complexa de Rey
Linguagem	Fluência verbal (fonêmica e semântica), Teste de nomeação de Boston
Atenção e função executiva	Span ou extensão de dígitos em ordem direta e inversa, Teste do desenho do relógio, Fluência verbal
Habilidades visuais-espaciais	Subteste de cópia das figuras do CERAD / MoCA, Teste do desenho do relógio
Avaliação da funcionalidade	
Atividades instrumentais de vida diária	Functional Activities Questionnaire, Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Direct Assessment of Functional Status-Revised (DAFS-R), Disability Assessment for Dementia (DAD), Activities of Daily Living Questionnaire (ADL-Q), Bayer Activities of Daily Living Scale (B-ADL), AD8 Dementia Screening Interview
Atividades básicas de vida diárias	Katz scale, Functional Activities Questionnaire
Estadiamento da demência	Clinical dementia rating scale (CDR)

Nota: Os escores globais da escala CDR (CDR-EG: 0 ou 0,5 ou 1,0 ou 2,0 ou 3,0) têm a limitação de ser baseados no escore do item Memória, considerando os outros itens como secundários, e subestimando assim informações relevantes de atividades instrumentais que podem estar primária e precocemente afetadas.
Fonte: Academia Brasileira de Neurologia, 2022

2.3.3 Exames Laboratoriais

A lista de exames laboratoriais recomendados deve incluir avaliação hematológica, renal, hepática, perfil lipídico e metabólico (sódio, potássio, cálcio séricos), glicemia de jejum, vitamina B12, TSH, T4 livre, VDRL e, especialmente casos atípicos ou em situações de suspeita clínica, sorologia anti-HIV (Academia brasileira de neurologia, 2022).

2.3.4 Neuroimagem estrutural

A avaliação cerebral por exames de neuroimagem estrutural como tomografia computadorizada (TC) ou ressonância magnética (RM) de crânio é um passo fundamental para o diagnóstico adequado da DA. A RM é o método de escolha por fornecer melhor

resolução anatômica e diferentes técnicas de aquisição que são mais úteis que a TC para diagnósticos diferenciais com outras demências, como as de causa vascular por exemplo (Academia brasileira de neurologia, 2022).

A DA, por ser neurodegenerativa, cursa invariavelmente com atrofia cerebral. O padrão mais comum de alteração volumétrica é o de atrofia de estruturas mesiais temporais (EMTs), como hipocampo e córtex entorrinal, que guarda correlação com a clínica de dificuldade com memória episódica. Porém, pode haver atrofia também em diferentes regiões, sobretudo nas apresentações atípicas e comumente pré-senis, como o que ocorre com as variantes linguística, disexecutiva e/ou comportamental (frontal) e visual-espacial (Sintini *et al.,* 2020).

2.3.5 Diagnóstico assistido por biomarcadores

2.3.5.1 Biomarcadores no líquido cefalorraquidiano

Os biomarcadores liquóricos na DA utilizados para o diagnóstico são o peptídeo Aβ de 42 aminoácidos e a proteína tau em sua composição total e porção fosforilada no resíduo de 181 de treonina (T-tau e P-tau, respectivamente). A assinatura patológica da DA no líquido cefalorraquidiano (LCR) consiste em um padrão determinado pela redução da concentração de Aβ1-42 e aumento das concentrações de T-tau e P-tau (Academia brasileira de neurologia, 2022).

2.3.5.2 Biomarcadores de neuroimagem molecular

Os processos fisiopatológicos relacionados à DA podem ser alternativamente inferidos in vivo por métodos de imagem molecular baseados na emissão de pósitrons (PET), por meio da injeção de diferentes radiotraçadores. Uma das consequências do processo degenerativo progressivo da DA é o hipometabolismo cerebral, que pode ser avaliado por meio do Fluordesoxiglicose (FDG) (Academia brasileira de neurologia, 2022).

O acúmulo de Aβ pode ser avaliado por meio de diversos agentes moleculares com afinidade para o peptídeo Aβ, como o Pittsburgh compound-B (PiB), Flutemetamol, Florbetaben e Florbetapir (Schilling *et al.,* 2016). O acúmulo de proteína tau, outra importante característica patológica da DA, também pode ser avaliada por meio de radiotraçadores específicos, como Flortaucipir (Fleicher *et al.,* 2020). O acúmulo de tau observado nos exames de neuroimagem molecular apresenta importantes correlações clínicas:

o maior acúmulo de tau relaciona-se com a gravidade do declínio cognitivo (Matsuda; Shigemoto; Sato, 2019).

Atualmente, os biomarcadores são utilizados especialmente em cenários de pesquisa. Sob o ponto de vista clínico, a utilização dos biomarcadores é recomendada na avaliação de quadros considerados atípicos, seja pela apresentação clínica inicial não-amnéstica ou em pacientes com início precoce (Academia brasileira de neurologia, 2022).

2.4 ALIMENTOS ULTRAPROCESSADOS – UM VISÃO HISTÓRICA

A substituição de alimentos minimamente processados e preparações culinárias por produtos prontos para consumo está aumentando em todo o mundo, o que têm despertado preocupações para a saúde pública (Monteiro *et al.,* 2019). As mudanças nos padrões alimentares da população têm sido acompanhadas pelo aumento da prevalência da obesidade e outras doenças crônicas (Monteiro *et al.,* 2018).

As tecnologias alimentares são desenvolvidas com a finalidade de preservar e manter os atributos de qualidade dos alimentos, impactando no aumento da vida útil e da biodisponibilidade de nutrientes. No entanto, o processamento dos alimentos também impacta de forma negativa, devido a elevada adição de aditivos químicos e redução no conteúdo de fibras, minerais e vitaminas (Evrendilek, 2018).

O desenvolvimento tecnológico e o aumento da disponibilidade de alimentos altamente processados introduziu o conceito de AUP para classificar esses tipos de produtos (Monteiro *et al.,* 2016). Estudos de base populacional realizados em diferentes países com base em pesquisas de consumo alimentar, conceituam AUP como produtos de alta densidade energética, ricos em açúcares, gorduras e sódio, sendo pobres em fibras, proteínas, vitaminas e minerais (Luiten *et al.,* 2016; Moubarac *et al.,* 2017; Louzada *et al.,* 2018; Cediel *et al.,* 2018).

Nas últimas décadas foram desenvolvidas novas abordagens para o processamento industrial e seu impacto na saúde humana. Revisões sistemáticas destacam cinco sistemas de classificação de alimentos baseados no processamento de alimentos (Moubarac *et al.,* 2014; Crino *et al.,* 2017).

A importância desses sistemas de classificação de alimentos é proporcionar uma nova base para pesquisas experimentais e epidemiológicas, contribuindo para a elaboração de novas diretrizes alimentares e políticas públicas que visem a promoção da saúde (FAO, 2019).

Abaixo encontra-se as características das cinco classificações de alimentos que distinguem os alimentos altamente processados/ultraprocessados dos alimentos processados (Quadro 2).

Quadro 2 - Sistemas de classificação de processamento de alimentos

Sistemas de classificação	Grau de Grupos de Processamento
IARC – Europa (Slimani *et al.,* 2009)	Alimentos não processados
	Alimentos moderadamente processados
	Alimentos altamente processados
NOVA – Brasil (Monteiro *et al.,* 2016)	Alimentos não processados ou minimamente processados (grupo 1)
	Ingredientes culinários processados (grupo 2)
	Alimentos processados (grupo 3)
	Alimentos ultraprocessados (grupo 4)
IFPRI – Guatemala (Asfaw, 2011)	Alimentos não processados
	Alimentos processados primários
	Alimentos altamente processados
IFIC – EUA (Miller; Fulgoni; Keast, 2012).	Alimentos minimamente processados
	Alimentos processados para preservação
	Misturas de ingredietes combinados
	Pronto para consumo processado
	Alimentos/refeições preparados
UNC – EUA (Poti et *al.,* 2015)	Alimentos processados básicos
	Alimentos moderadamente processados
	Alimentos altamente processados

Fonte: Adaptado de Araújo *et al.* (2022)

Na Europa, pesquisadores da Agência Internacional de Pesquisa sobre Câncer (IARC) desenvolveram uma classificação de alimentos ultraprocessados em 2009 (Slimani *et al.,* 2009). No Brasil, pesquisadores do Centro de Estudos Epidemiológicos em Saúde Pública e Nutrição da Faculdade de Saúde Pública da Universidade de São Paulo desenvolveram a Classificação NOVA. A NOVA classifica todos os alimentos e produtos alimentares em quatro grupos, de acordo com a extensão e finalidade do processamento industrial, considerando todos os métodos físicos, biológicos e químicos utilizados (Monteiro *et al.,* 2018) (Figura 3).

Figura 3 - Classificação NOVA

Fonte: adaptado de Monteiro *et al*. (2018)

Em 2011, na Guatemala, foi desenvolvido um sistema de classificação de alimentos pelo Instituto Internacional de Pesquisa em Política Alimentar (IFPRI), o qual teve como base trabalhos anteriores que examinaram a contribuição dos produtos alimentícios processados para o abastecimento de alimentos em países de baixa renda (Asfaw, 2011). Nos Estados Unidos da América (EUA), em 2012, outro sistema de classificação de alimentos foi desenvolvido pela Fundação do Concelho Internacional de Informação Alimentar (IFIC), para determinar a contribuição dos alimentos processados para a ingestão de nutrientes na dieta dos EUA (Miller; Fulgoni; Keast, 2012). Simultaneamente com a pesquisa realizada por Monteiro *et al.* nos EUA em 2015, a Universidade da Carolina do Norte (UNC) desenvolveu um novo sistema de classificação (Poti *et al.,* 2015).

A contribuição média do consumo de AUP na ingestão total de energia pode chegar em até 50% em países desenvolvidos, aumentando cada vez mais em países de renda média sobretudo por serem acessíveis, práticos e de baixo custo (Stelle *et al.,* 2016). Dados da última Pesquisa Nacional de Orçamentos Familiares (2017-2018) referente à população brasileira com dez anos ou mais, revelaram que cerca da metade (49,5%) das calorias totais disponíveis para consumo nos domicílios provém de alimentos in natura ou minimamente processados, 22,3% de ingredientes culinários processados, 9,8% de alimentos processados e 18,4% de AUP (IBGE, 2020).

Evidências sugerem que os AUP estão se tornando cada vez mais acessíveis do que as alternativas saudáveis nos países em desenvolvimento. Um estudo realizado por Maia *et al.* (2020) evidenciou que entre o período de 1995 e 2017 o preço médio dos alimentos in natura ou minimamente processados e ingredientes culinários processados aumentaram continuamente, enquanto que o preço dos AUP aumentou em menor magnitude.

Os AUP vêm dominando o sistema alimentar mundial devido ao marketing agressivo, tempo de prateleira prolongada, hiperpalatabilidade e baixo custo (Monteiro *et al.,* 2015; Langeveld *et al.,* 2020). O cenário de preço identificado no estudo de Maia *et al.,* (2020) certamente intensificará essa tendência de consumo, consequentemente aumentando o risco de DCNT.

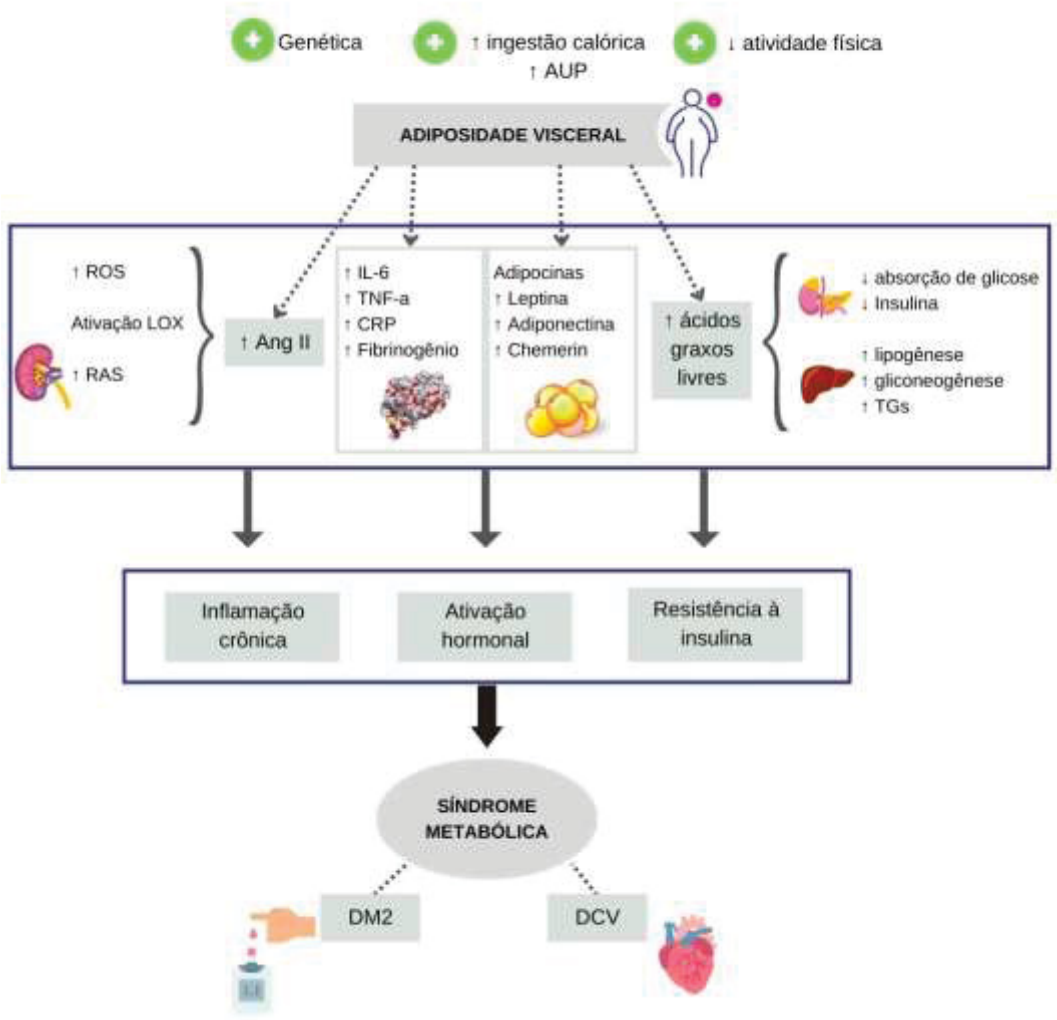
2.5 ALIMENTOS ULTRAPROCESSADOS E RISCO PARA DOENÇAS CRÔNICAS NÃO TRANSMISSÍVEIS

As DCNT são definidas como qualquer condição de saúde de longa duração ou que tem efeitos de longo prazo, não sendo transmissível ou infecciosa em sua etiologia (OMS, 2018) . De acordo com a OMS, as DCNT são responsáveis, mundialmente, por mais de 70% de todas as mortes (OMS, 2018).

A síndrome metabólica (SM) é um conjunto de desregulações metabólicas, incluindo obesidade central, resistência à insulina, dislipidemia aterogênica e hipertensão arterial sistêmica. Além de fatores genéticos e epigenéticos, os fatores de estilo de vida e ambientais foram identificados como os principais contribuintes para o desenvolvimento da SM (Lemieux; Després, 2020).

Um papel causal relacionado à fisiopatologia da SM pode ser atribuído à alta ingestão calórica, visto que a adiposidade visceral tem se mostrado um importante gatilho que ativa a maioria das vias da SM (Pekgor *et al.,* 2019). Na figura 4, podemos observar os principais mecanismos responsáveis pela progressão da SM e sua subsequente transição para doença cardiovascular e diabetes mellitus do tipo 2 (Fahed *et al.,* 2022).

Figura 4 - Mecanismos que destacam a fisiopatologia da SM



Fonte: adaptado de Fahed *et al*. (2022)

Evidências científicas estabelecem uma relação entre má qualidade da dieta e aumento do risco de mortalidade por DCNT (Stein *et al.,* 2019). Uma recente revisão sistemática e meta-análise publicada por Lane *et al.* (2020), evidenciou que o consumo de AUP estava associado a um aumento de 20% a 81% no risco de várias DCNT, e um aumento de 22% a 28% no risco de mortalidade em adultos.

De acordo com estudos observacionais, o aumento no consumo de AUP levam ao deterioramento da qualidade nutricional da dieta (Moubarac *et al.,* 2017; Louzada *et al.,* 2018 Cediel *et al.,* 2018), possuindo relação com o aumento da SM (Nardocci *et al.,* 2019), hipertensão arterial sistêmica (Mendonça *et al.,* 2017), diabetes mellitus (Srour *et al.,* 2020), problemas coronários e doenças cerebrovasculares (Srour *et al.,* 2019).

Tradicionalmente, a prevenção e o manejo das DCNT têm sido limitados e direcionados ao controle de fatores de risco como tabagismo, pressão arterial e obesidade

(BudreviciutE *et al.,* 2020). As atuais pesquisas envolvendo consumo de AUP e DCNT caminham para a vertente de que uma alimentação de baixo valor nutritivo, caracterizada por uma maior quantidade de calorias, açúcares, gorduras e sódio aumenta a prevalência da obesidade e de outras comorbidades (Stein *et al.,* 2019).

2.6 ALIMENTOS ULTRAPROCESSADOS E RISCO PARA DOENÇA DE ALZHEIMER

O desenvolvimento e progressão da demência estão associados a fatores genéticos e ambientais, incluindo estilo de vida e dieta (Ranson *et al.,* 2021). Estudos experimentais e populacionais evidenciam que uma dieta ocidental, rica em AUP, provoca efeitos adversos na função cognitiva (Tabara *et al.,* 2020). Um recente estudo de coorte prospectivo realizado entre 2006 e 2010 com 502.507 adultos, evidenciou que o maior consumo de AUP estava associado ao maior risco de demência, DA e demência vascular. A adição de 10% de AUP na dieta estava associada a um aumento significativo de 13% no risco da DA (Li *et al.,* 2022). Em concordância, outro estudo de coorte prospectivo que acompanhou 803 participantes durante 6 anos apontou que uma dieta saudável, com baixo consumo em AUP, estava associada à redução da incidência de demência, enquanto dietas do tipo ocidental foram associadas ao maior declínio do desempenho cognitivo (García *et al.,* 2022).

Demais estudos de coorte que investigaram a relação entre demência e consumo de AUP específicos vêm demonstrando resultados semelhantes (Barnard; Bunner; Agarwal, 2014; Tabara *et al.,* 2020). O estudo *Framingham Heart* mostrou que uma maior ingestão de bebidas açucaradas e adoçadas artificialmente estavam associados a um maior risco de demência (Pase *et al.,* 2017; Miao *et al.,* 2020). Outro estudo recente do *UK Biobank* evidenciou que o maior consumo de carnes processadas estava associado ao aumento no risco da DA (Zhang *et al.,* 2021). Uma revisão sistemática realizada por Barnard, Bunner e Agarwal (2014) evidenciou que a ingestão de gorduras saturadas e trans estava positivamente associada a um risco maior de desenvolvimento de distúrbios cognitivos de longo prazo, como a DA.

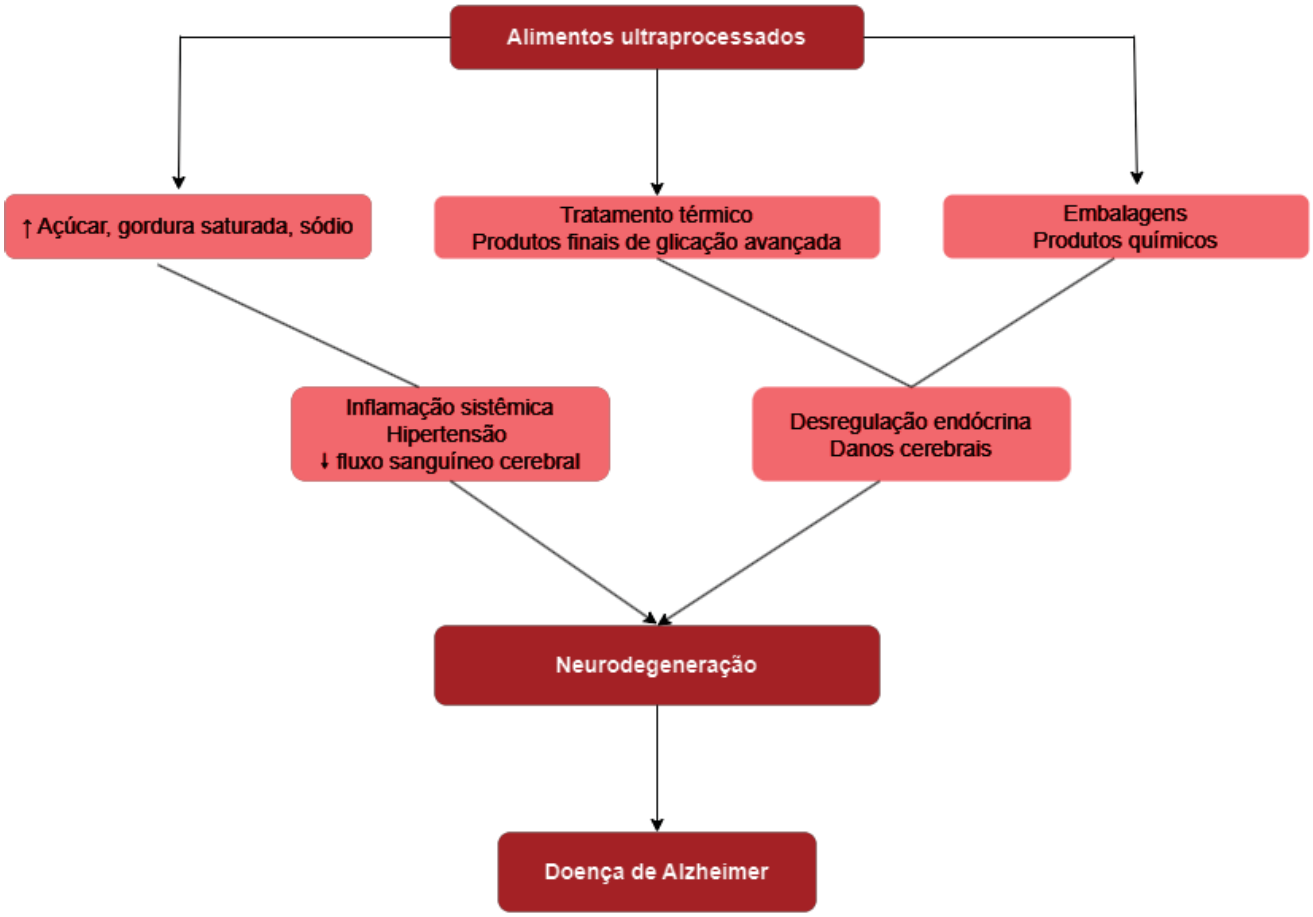
Há vários mecanismos biológicos que podem explicar a associação observada entre consumo de AUP e DA (Figura 5). Primeiramente, os AUP normalmente estão associados a uma dieta de baixa qualidade, com elevado teor de gordura e açúcares (Liu *et al.,* 2020). Esse conjunto de características da dieta rica em AUP podem promover uma inflamação sistêmica que contribui para a progressão da neurodegeneração e patologia vascular do cérebro (Guerville *et al.,* 2017). Além disso, a maioria dos AUP como salgadinhos, embutidos e

temperos industrializados são ricos em sódio. Dietas com alto teor de sódio podem causar hipertensão arterial sistêmica, podendo estar acompanhada por uma diminuição do fluxo sanguíneo cerebral e, potencialmente relacionada com o desenvolvimento de déficit cognitivo e risco para demência (Guo *et al.,* 2017).

Evidências também sugerem que os materiais utilizados para embalar os AUP contêm produtos químicos, como o bisfenol A que pode ocasionar uma desregulação endócrina. Estudos experimentais sugerem que o bisfenol A pode aumentar danos nas células cerebrais e prejudicar a capacidade cognitiva (Zhou *et al.,* 2017).

Em conjunto a isso, o processamento e preparação dos AUP como, o tratamento térmico extensivo utilizado em biscoitos e batata frita, leva à formação de produtos finais de glicação avançada que causam danos vasculares e são expressos nos neurônios e células gliais (Miranda; Agnaf; Outeiro, 2016). Um estudo realizado por Tabara *et al.* (2020) evidenciou que os produtos finais de glicação avançada estão associados ao declínio cognitivo em idosos.

Figura 5 – Mecanismos biológicos envolvidos na relação do consumo de AUP no risco desenvolvimento da DA



Fonte: a autora (2023)

Considerando os resultados encontrados na literatura acerca da associação do consumo de AUP no risco da DA, verifica-se que a qualidade da alimentação parece ser um ponto crucial a ser considerado para a prevenção primária da doença (Kivipelto; Mangialasche; Nngandu, 2018).

3 METODOLOGIA

O presente estudo consiste em uma revisão sistemática da literatura relatada conforme os Itens Preferenciais de Relato para Revisões Sistemáticas e Meta-análises (PRISMA) (Page *et al.,* 2021), sendo seu protocolo registrado no banco de dados do PROSPERO (CRD42022375944).

3.1 CRITÉRIOS DE ELEGIBILIDADE

Os critérios de elegibilidade dos estudos foram determinados com base no acrônimo PECO. A população do estudo incluiu adultos e idosos que, no início do estudo, não tinham Alzheimer ou qualquer outro tipo de demência. A exposição foi o consumo de AUP. O comparador foi considerado a presença de um padrão alimentar saudável composto por alimentos in natura ou minimamente processados, alimentação mais baixa em AUP ou o consumo de outro grupo alimentar. O desfecho avaliado foi a presença ou risco do desenvolvimento da DA.

Definimos AUP conforme classificação pelo sistema NOVA, que inclui produtos como refrigerantes, bebidas lácteas, néctar de frutas, misturas em pó para preparação de bebidas com sabor de frutas, salgadinhos de pacote, doces e chocolates, barras de cereal, sorvetes, panificados embalados, margarinas e outros substitutos de manteiga, bolachas ou biscoitos, misturas para bolos, cereais matinais, tortas, pratos de massa e pizzas pré-preparadas, nuggets de frango e peixe, salsichas, hambúrgueres e outros produtos de carne reconstituída, macarrão instantâneo e misturas em pó para preparação de sopas ou sobremesas (Monteiro, 2019).

Os critérios de inclusão foram estudos observacionais, como estudos transversais e de coorte, prospectivas ou retrospectivas, além de estudos de caso-controle. Não houve restrição de gênero, idioma e ano de publicação. Foram excluídos estudos que avaliaram como desfecho apenas outros tipos de demências, como demência senil, demência vascular,

demência frontotemporal, demência parkisoniana e entre outros, não considerando a DA em suas análises.

3.2 FONTES DE INFORMAÇÃO

Foi realizado uma busca nas bases eletrônicas Medline, Embase e Lilacs, além de uma busca na literatura cinzenta em abril e maio de 2023. A última busca nas bases de dados foi realizada em 03 de junho de 2023. Além da busca eletrônica, os revisores também realizaram uma busca por citação na lista de referências de cada estudo incluído, a fim de identificar estudos potencialmente relevantes que não haviam sido alcançados na busca inicial. Foi contatado o pesquisador principal, via e-mail, dos estudos incluídos que não tinham a versão do texto completo nas bases de dados, a fim de solicitar a disponibilização via e-mail.

3.3 ESTRATÉGIA DE BUSCA

Os termos de pesquisa e estratégia de busca foram desenvolvidos em consulta com um bibliotecário de pesquisa da Universidade Federal do Paraná. Utilizamos os descritos do Medical Subject Heading (MeSH), Descritores em Ciências da Saúde (DeCS) e palavras-chaves de artigos identificados em uma pesquisa anterior. Os descritores foram doença de Alzheimer, demência de Alzheimer, alimento industrializado, alimento processado, alimento ultraprocessado e fast food, combinados com operadores booleanos AND e OR. A estratégia de busca utilizada em cada base de dado encontra-se no Quadro 3.

Quadro 3 - Estratégia de busca utilizada na revisão

Base de dados	Estratégia de busca
Medline	((((((("alzheimer disease"[All Fields]) OR ("alzheimer dementia"[All Fields])) AND ("industrialized foods"[All Fields])) OR ("processed food"[All Fields])) OR ("ultraprocessed food"[All Fields])) OR ("fast foods"[All Fields]))
Embase	('alzheimer disease'/exp OR 'alzheimer disease' OR (alzheimer AND ('disease'/exp OR disease)) OR 'alzheimer dementia':ti,ab,kw) AND 'industrialized foods':ti,ab,kw OR 'processed food':ti,ab,kw OR 'ultraprocessed food':ti,ab,kw OR 'fast foods':ti,ab,kw
Lilacs	(doença de alzheimer) OR (enfermedad de alzheimer) OR (alzheimer disease) OR (demência de alzheimer) OR (alzheimer dementia) OR (demencia de alzheimer) AND (alimentos industrializados) OR (industrialized foods) OR (alimento processado) OR (processed food) OR (alimento ultraprocessado) OR (ultraprocessed food) OR (comida rápida) OR (fast foods)
Google acadêmico	Alzheimer disease OR Alzheimer dementia AND industrialized foods OR processed food OR ultraprocessed food OR fast foods

Fonte: a autora (2023)

3.4 SELEÇÃO DOS ESTUDOS

Após a consulta nas bases de dados, os artigos foram exportados para o software Rayyan®, sendo primeiramente realizada a exclusão das duplicatas. A seleção dos estudos elegíveis foi realizada de forma independente por dois revisores (P.C e S.P). A primeira seleção foi feita por meio da leitura dos títulos e resumos. Em seguida, foi realizado a leitura na íntegra dos estudos pré-selecionados. Por fim, foi realizado a leitura dos títulos e resumos das citações presentes nos estudos incluídos, e leitura do texto na íntegra das citações pré-selecionadas. Para inclusão ou exclusão dos estudos foi exigido o consenso entre os dois revisores, sendo qualquer discrepância resolvida por um terceiro revisor (C.M).

3.5 PROCESSO DE COLETA DE DADOS

Como estratégia para controlar o víeis de medição, a extração dos dados foi realizada de forma independente por dois revisores (P.C e S.P). Os dados extraídos incluíram autoria, ano, local, desenho do estudo, população, método de avaliação dos AUP, ferramenta para avaliar o risco da DA, covariáveis ajustadas, resultados, conclusão e qualidade metodológica. Qualquer discrepância na extração dos dados foi resolvida por um terceiro revisor (C.M).

3.6 AVALIAÇÃO DO RISCO DE VIÉS E QUALIDADE METODOLÓGICA

Para a avaliação do risco de viés e qualidade metodológica dos estudos incluídos, foi utilizado o instrumento do Instituto Joanna Briggs para estudos de coorte (Aromataris; Munn, 2020) (Anexo 2). O instrumento é composto por onze perguntas que foram respondidas com sim, não, não está claro ou não se aplica. As perguntas presentes no instrumento avaliam vieses de seleção, observação e de confusão. O instrumento foi aplicado de forma independente pelos dois revisores (P.C e S.P), e as divergências resolvidas em consenso com um terceiro revisor (C.M). Os estudos foram classificados da seguinte forma: alta qualidade metodológica (≥5 respostas ‘’sim’’), qualidade metodológica moderada (3-4 respostas ‘‘sim’’), ou, baixa qualidade metodológica (0–2 respostas ‘‘sim’’) [23], sendo avaliado de forma descritiva os possíveis vieses identificados em cada estudo. Todos os estudos selecionados, independente da qualidade metodológica, foram submetidos a extração e síntese dos dados.

4 RESULTADOS E DISCUSSÃO

Esta seção apresenta o artigo que foi desenvolvido no formato de "Revisão" e que será submetido à Revista Frontiers in Nutrition. O Anexo 1 apresenta as instruções para o preparo do artigo.

4.1 ARTIGO – CONSUMPTION OF ULTRA-PROCESSED FOODS AND RISK FOR ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW

Paola Alves Claudino[1*], Nassib Bezerra Bueno[2], Sabrina Piloneto[3], Dieniffer Halaiko[4], Leticia Priscila Azevedo de Sousa[5], Cassia Helena Maia[1], Barbara Dal Molin Netto[6*]

[1]Postgraduation Program in Food and Nutrition, Federal University of Paraná.
[2]Postgraduation Program in Nutrition, Federal University of Alagoas.
[3]Nutricionist, graduated from the Pontifical Catholic University of Paraná.
[4]Nutricionist, graduated from the Federal University of Paraná.
[5]Librarian, Federal University of Paraná.
[6]Postgraduation Program in Food and Nutrition, Department of Nutrition, Federal University of Paraná.

*Corresponding author. Lothario Meissner Ave., 632, Jardim Botânico Campus, Curitiba, Paraná. 80.210-170, Brazil. Email: barbaradm@ufpr.br (B. D. M. Netto); paola.claudino@ufpr.br (P.A. Claudino)

Summary

Objective: To investigate the association of the consumption of ultra-processed foods with the risk of developing Alzheimer's disease in adults and the elderly. The review protocol was registered on PROSPERO (CRD42022375944).

Methods: This is a systematic review reported according to PRISMA guidelines. Observational studies were included without language or publication year restrictions. Studies assessing only other types of dementia as outcomes, not considering Alzheimer's disease, were excluded. The research was carried out in the Medline, Embase, Lilacs databases, and a survey of the gray literature between April and May 2023, in addition to citation search in the included studies. Data extraction was performed by two independent reviewers. The risk of bias and methodological quality of the included studies were assessed using the Joanna Briggs Institute checklist for cohort studies.

Results: A total of 4 studies involving 614,502 adults and elderly people were included. All studies had a cohort design and were considered of high methodological quality. Of the included studies, 3 demonstrated a risk association between the consumption of ultra-processed foods and the development of Alzheimer's disease, while 1 study showed a risk association only with the development of cognitive decline.

Discussion: The association between ultra-processed foods consumption and the risk of developing Alzheimer's disease is a recent topic in scientific studies, given that the oldest study identified by our review dates back to 2017. Of the four included studies, three showed a significant association between ultra-processed foods consumption and the risk of developing Alzheimer's disease

Keywords: Ultraprocessed food; Industrialized food; Fast-food; Alzheimer disease; Alzheimer's dementia

INTRODUCTION

With the global increase in life expectancy, concerns about diseases more prevalent among the elderly, such as dementia, are growing. In 2016, dementia affected approximately 44 million people worldwide, with projections indicating this number will rise to 135 million cases by 2050 [1,2].

Alzheimer's disease (AD) is the most common cause of dementia [2], characterized as a progressive physiopathological restructuring of the brain, resulting from the extracellular deposition and accumulation of β-amyloid protein in the cerebral parenchyma [3]. Currently, treatments to slow disease progression are limited, and the development of new drugs has been slow [4].

Evidence in the literature suggests that nutrition-related interventions are crucial for preventing cognitive decline, as diet influences direct and indirect mechanisms that can modify AD risk [5]. It's important to note that due to nutritional transition, dietary patterns have dramatically changed over recent decades. Studies indicate a higher availability and consumption of high-energy-density foods and low concentrations of vitamins and minerals [6].

A significant factor in this scenario is the substantial increase in the consumption of ultra-processed foods (UPF) worldwide, especially because they are easily accessible and convenient. UPFs account for more than half of the total dietary energy consumed in developed countries like the USA, UK, and Canada [7,8], and about a fifth of total dietary energy in middle-income countries such as Brazil, Mexico, and Chile [9,10,11]. Information sources for estimating UPF consumption are based on dietary data, which can be assessed using tools like 24-hour recall, food frequency questionnaires, and food diaries [12].

Recently published, a study showed that the consumption of UPFs is associated with a higher risk of AD [13]. There are several biological mechanisms that can explain this association. Among them, UPFs are typically linked to low-quality diets because they are rich in sugar, fat, sodium, and chemical additives [14]. This set of features can promote systemic inflammation in the body and promote neurodegenerative and physiopathological processes in the brain, consequently increasing the risk of AD [15].

Systematic reviews show a positive association between UPF consumption and non-communicable chronic diseases (NCDs), such as obesity [16], cardiovascular disease [17], diabetes mellitus [18], systemic arterial hypertension [19], cancer [20], and depression [21]. Although it's well-established in the literature that UPF consumption increases the risk for the

development of NCDs, its association with AD risk has been under-explored in systematic reviews. Therefore, the objective of this review was to investigate the association of ultra-processed food consumption with the risk of developing AD in adults and the elderly.

METHODOLOGY

The present study is a systematic literature review reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [22], with its protocol registered in the PROSPERO database (CRD42022375944).

ELIGIBILITY CRITERIA

The eligibility criteria for the studies were determined based on the PECO acronym. The study population included adults and the elderly who, at the beginning of the study, did not have Alzheimer's or any other type of dementia. The exposure was the consumption of UPF. The comparator was considered to be the presence of a healthy dietary pattern composed of unprocessed or minimally processed foods, lower UPF intake, or the consumption of another food group. The outcome assessed was the presence or risk of developing AD.

We defined UPF according to the NOVA classification system, which includes products such as soft drinks, dairy drinks, fruit nectars, powdered mixes for fruit-flavored drinks, packet snacks, candies and chocolates, cereal bars, ice creams, packaged bakery, margarines and other butter substitutes, cookies or biscuits, cake mixes, breakfast cereals, pies, pre-prepared pasta dishes and pizzas, chicken and fish nuggets, sausages, hamburgers and other reconstituted meat products, instant noodles, and powdered mixes for soups or desserts preparation [23].

The inclusion criteria were observational studies, such as cross-sectional and cohort studies, prospective or retrospective, as well as case-control studies. There were no restrictions on type, language, and year of publication. Studies that assessed only other types of dementia as outcomes, such as senile dementia, vascular dementia, frontotemporal dementia, Parkinsonian dementia, and others, without considering AD in their analyses, were excluded.

INFORMATION SOURCES

A search was conducted in the electronic databases Medline, Embase, and Lilacs, as well as a search in the gray literature in April and May of 2023. The last search in the databases was carried out on June 3, 2023. In addition to the electronic search, reviewers also performed a citation search in the reference list of each included study, in order to identify potentially relevant studies that were not captured in the initial search. The principal investigator of the included studies, which did not have the full-text version available in the databases, was contacted via email to request its provision.

SEARCH STRATEGY

The search terms and strategy were developed in consultation with a research librarian from the Federal University of Paraná. We used terms from the Medical Subject Heading (MeSH), Health Sciences Descriptors (HCD), and keywords from articles identified in a previous search. The descriptors were Alzheimer's disease, Alzheimer's dementia, industrialized food, processed food, ultra-processed food, and fast food, combined using the Boolean operators AND and OR. The search strategy used in each database is presented in Table 1.

Table 1 - Search strategy used in the review.

Base de dados	Estratégia de busca
Medline	((((((("alzheimer disease"[All Fields]) OR ("alzheimer dementia"[All Fields])) AND ("industrialized foods"[All Fields])) OR ("processed food"[All Fields])) OR ("ultraprocessed food"[All Fields])) OR ("fast foods"[All Fields]))
Embase	('alzheimer disease'/exp OR 'alzheimer disease' OR (alzheimer AND ('disease'/exp OR disease)) OR 'alzheimer dementia':ti,ab,kw) AND 'industrialized foods':ti,ab,kw OR 'processed food':ti,ab,kw OR 'ultraprocessed food':ti,ab,kw OR 'fast foods':ti,ab,kw
Lilacs	(doença de alzheimer) OR (enfermedad de alzheimer) OR (alzheimer disease) OR (demência de alzheimer) OR (alzheimer dementia) OR (demencia de alzheimer) AND (alimentos industrializados) OR (industrialized foods) OR (alimento processado) OR (processed food) OR (alimento ultraprocessado) OR (ultraprocessed food) OR (comida rápida) OR (fast foods)
Google Scholar	Alzheimer disease OR Alzheimer dementia AND industrialized foods OR processed food OR ultraprocessed food OR fast foods

STUDY SELECTION

After querying the databases, the articles were exported to the Rayyan® software, with duplicates being removed first. The selection of eligible studies was independently carried out by two reviewers (P.C and S.P). The initial selection was made by reading the titles and abstracts. Subsequently, a full-text reading of the pre-selected studies was conducted. Finally, titles and abstracts from citations within the included studies were read, followed by a full-

text reading of the pre-selected citations. The inclusion or exclusion of studies required consensus between the two reviewers, with any discrepancies being resolved by a third reviewer (C.M).

DATA COLLECTION PROCESS

As a strategy to control measurement bias, data extraction was performed independently by two reviewers (P.C and S.P). Extracted data included authorship, year, location, study design, population, method for assessing UPF, tool for assessing AD risk, adjusted covariates, results, conclusion, and methodological quality. Any discrepancies in data extraction were resolved by a third reviewer (C.M).

ASSESSMENT OF RISK OF BIAS AND METHODOLOGICAL QUALITY

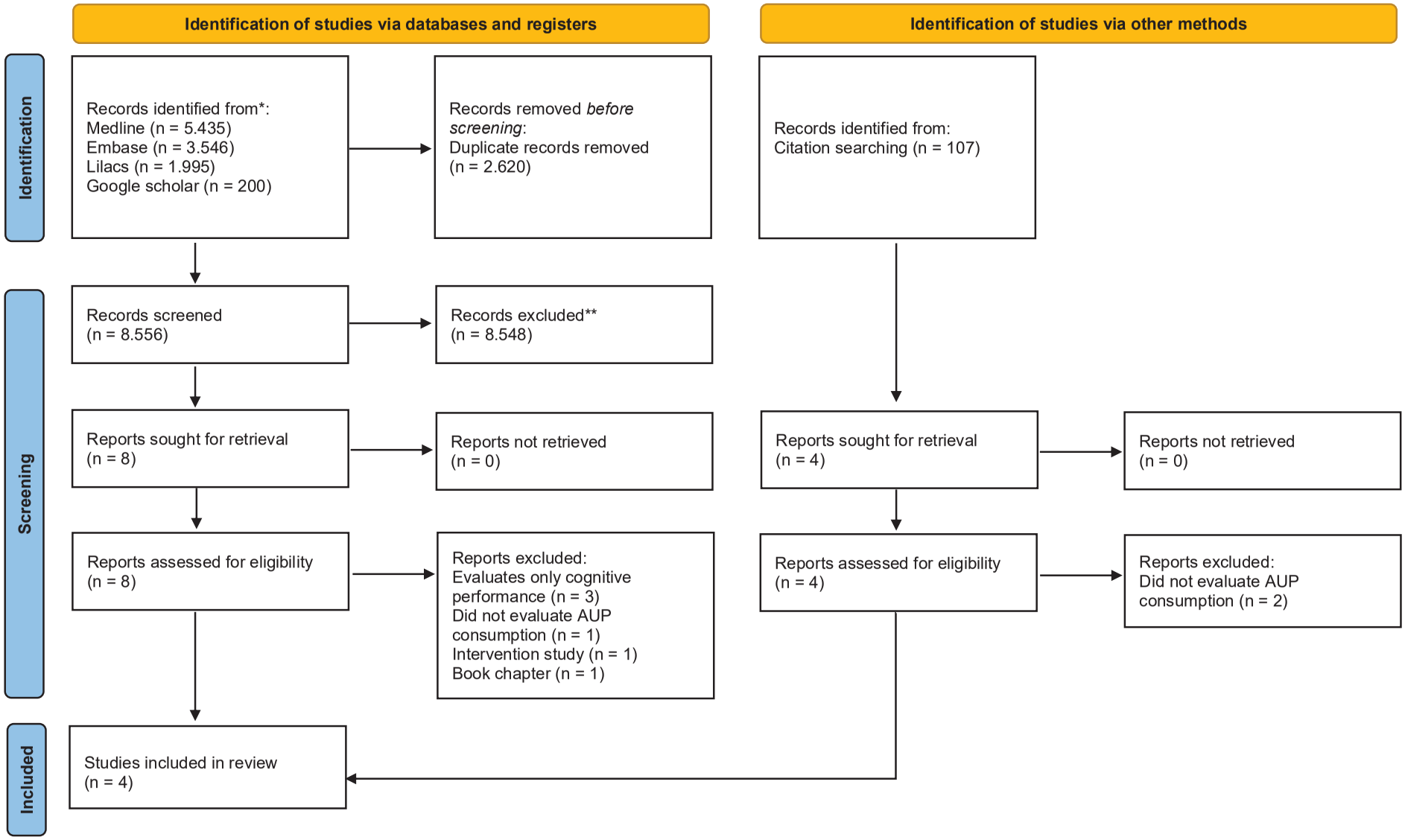
For the assessment of the risk of bias and methodological quality of the included studies, the Joanna Briggs Institute tool for cohort studies was used [24]. The tool consists of eleven questions that were answered with yes, no, unclear, or not applicable. The questions in the tool evaluate selection, observation, and confounding biases. The instrument was independently applied by the two reviewers (P.C and S.P), and discrepancies were resolved in consensus with a third reviewer (C.M). The studies were classified as follows: high methodological quality (≥5 "yes" answers), moderate methodological quality (3-4 "yes" answers), or low methodological quality (0-2 "yes" answers) [24]. The potential biases identified in each study were evaluated descriptively. All selected studies, regardless of methodological quality, were submitted to data extraction and synthesis.

RESULTS

DATABASE SEARCH AND STUDY SELECTION

The initial search yielded 11,176 records. After removing duplicates, 8,556 studies were screened based on title and abstract, with 8 studies retained for full-text evaluation. Considering the eligibility criteria, 2 studies were included in the review. From the included studies, 107 citations were identified in the references; of these, 4 were selected based on title and abstract, with only 2 being included. In total, 4 studies were included in the review. The steps of the study selection process are presented in the Flowchart.

Flowchart of study selection



CHARACTERISTICS OF THE STUDIES

The characteristics of the included studies are described in Table 1. All included studies had a cohort design. The studies were published between 2018 and 2022, they were conducted in the USA [25], United Kingdom [26,13], and Sweden [27]. The duration of the monitoring period in the studies ranged from 8 to 24 years. In total, 614,502 individuals were monitored, with approximately 54.7% being female. The age of the participants ranged from 37 to 73 years.

The studies considered various variables for analysis, such as age, gender, education, smoking, alcohol consumption, caloric intake, family history of dementia, history of stroke, diabetes mellitus, systemic arterial hypertension, cardiovascular disease, atrial fibrillation, sleep duration, lipid parameters, physical activity, Body Mass Index (BMI), waist/hip ratio, and positive result for the APOE4 allele.

Regarding the tools for assessing AD risk, three studies highlighted the use of APOE genotyping [25,26,27]. Other tools used were medical record reviews, neuropsychiatric test batteries, family self-reports, and standard manuals for AD diagnosis.

Considering the methods for evaluating UPF consumption, the study by Pase et al. [25] used a semi-quantitative food frequency questionnaire (FFQ) that included 3 items about sugar-sweetened soft drinks, 4 items about fruit juices, 1 item about non-carbonated sugary beverages, and 3 items about artificially sweetened soft drinks. The FFQ was applied three times during the monitoring period. Zhang et al.'s study [26] used a FFQ covering 47 dietary items, including items related to processed and unprocessed meats, as well as the use of a 24-hour recall (24hR), both applied at the beginning and end of the monitoring. Samuelsson et al.'s study [27] used the FFQ method and photographic records to estimate portion sizes at the start of the monitoring period. Finally, Li et al.'s study [13] used the 24HR method based on a web model, applied four times during the monitoring. Only the study by Li et al. [13] used the NOVA system to classify the UPFs. The included studies evaluated general UPF consumption [13], Western diet consumption containing UPF [27], and specific UPF consumption, such as processed meats [26] and soft drinks [25].

Table 1 - Characteristics of the included studies

Author (Year; Location)	**Study design/ monitoring period**	**Population** Age/sex (M/F)	**UPF** Method of consumption assessment	**Tool** Risk for AD	**Covariates**	**Quality**
Pase et al. [25] USA	Cohort / 10 years Framingham Heart Study (2001-2011)	N = 1.484 Age: ≥ 60 (802/682)	Artificially sweetened soft drinks Sugary drinks Method: FFQ	Diagnostic and Statistical Manual of Mental Disorders, Criteria of the National Institute of Neurological, Communicative Disorders, and Stroke; Association of Disorders Related Criteria for AD, APOE genotyping.	Age, sex, education level, total caloric intake, DGAI, SBP, HBP, CVD, atrial fibrillation, left ventricular hypertrophy, cholesterol levels, DM, alcohol intake, smoking, PA, positivity for APOE4 allele, waist-to-hip ratio	High
Zhang et al. [26] United Kingdom	Cohort / 8 ± 1,1 years UK Biobank (2006-2015)	N = 493.888 Age: 40-69 (269.197/224.691)	Processed meats Method: FFQ / 24HR	Hospital admission and death data, self-report, APOE genotyping.	Region, BMI, PA, smoking, sleep duration, history of CVA, family history of dementia, consumption of vegetables and fruit, fish, tea, coffee, and alcohol.	High
Samuelsson et al. [27] Sweden	Cohort / 24 years Gothenburg (1992-2016)	N = 602 Age: 70 (384/218)	Western dietary pattern including UPF: processed meat, fast food, refined cereals. Method: FFQ/ portion sizes	Neuropsychiatric examination, neuropsychological test battery, APOE genotyping, information from relatives.	Sex, total caloric intake, year of birth, education, PA, smoking, BMI, SAH, DM, serum cholesterol levels	High
Li et al. [13] United Kingdom	Cohort / 12 years UK Biobank (2009-2021)	N = 118.528 Age: 37-73 (65.979/52.549)	Different UPFs: Sugar-sweetened beverages, processed dairy, snacks. Method: 24HR NOVA classification	Hospital admission and death data.	Age, sex, education, smoking, alcohol consumption, PA, BMI, sleep duration, CVD, family history of dementia, total caloric intake	High

Body Mass Index (BMI); Cardiovascular Disease (CVD); Cerebrovascular Accident (CVA); Diabetes Mellitus (DM); Dietary Guidelines Adherence Index (DGAI); Food Frequency Questionnaire (FFQ); Physical Activity (PA); Systemic Arterial Hypertension (SAH); Systolic Blood Pressure (SBP); 24-hour recall (24HR).

Table 2 - Results of the included studies.

Author	Results	Conclusion
Pase et al. [25]	Daily intake of artificially sweetened soft drinks was associated with an ↑ in the risk of AD in models 1 and 2, adjusted for age, sex, caloric intake, education, DGAI, PA, and smoking. However, these associations did not remain significant after adjusting for additional variables, involving SBP, SAH, CVD, atrial fibrillation, left ventricular hypertrophy, lipid profile, DM, waist-to-hip ratio, and positivity for APOE4. Regarding recent beverage intake, daily consumption of artificially sweetened beverages ↑ the risk of dementia only in model 2. Neither fully sweetened drinks nor sweetened soft drinks were associated with dementia risks. DM status was identified as a partial mediator of the association between the intake of artificially sweetened beverages and the risk of AD.	Consumption of artificially sweetened soft drinks was associated with an ↑ risk of AD. Sugar-sweetened beverages were not associated with an ↑ risk of this outcome.
Zhang et al. [26]	Higher consumption of processed meat was associated with an ↑ risk of AD (HR: 1.52 per additional 25 g/day; 95% CI: 1.18, 1.96; P-trend = 0.001). Higher consumption of unprocessed red meat was associated with a ↓ risk of AD (HR: 0.70 per additional 50 g/day; 95% CI: 0.53, 0.92; P-tendency = 0.009). APOE4 carriers had ↑ risks of developing AD by approximately 6 times. For APOE4 carriers, but not for non-carriers, there was a ↓ risk of AD with an increment of 50 g/day of unprocessed red meat	The consumption of processed meat might ↑ the risk of AD incidence, with this risk being even ↑ in individuals with the APOE4 gene. The intake of unprocessed red meat might be associated with a ↓ risk of AD, regardless of the presence of the APOE4 gene.
Samuelsson et al. [27]	There were interactions between dietary patterns and APOE4 status in relation to incident dementia (interaction p-value threshold <0.1), while no evidence of interactions was found between dietary patterns and NAD-PRSs. Those with higher adherence to a healthy dietary pattern had a reduced risk of dementia among ε4 non-carriers (HR: 0.77; 95% CI: 0.61; 0.98), but not among APOE4 carriers (HR: 0.99; CI: 0.81; 1.21).	There is an interaction between the APOE4 status and adherence to dietary patterns in relation to incident dementia. Higher adherence to a Western dietary pattern was associated with an increased risk of dementia among APOE4 carriers, but not among non-carriers. No evidence of interactions was found between dietary patterns and NAD-PRSs.
Li et al. [13]	A suggestive association was observed between the intake of a higher level of UPF and the risk of AD, with an HR of 1.13. Adding 10% UPF to the diet was associated with a significant 13% increase in the risk of AD. Replacing UPF with unprocessed or minimally processed foods was not associated with a ↓ risk of AD. Among the UPF groups, the consumption of ultra-processed meat was associated with an ↑ risk of AD (HR: 2.02; P <0.001).	A higher intake of UPF was associated with a higher risk of AD. Replacing UPF with unprocessed or minimally processed foods was not associated with a decreased risk of AD.

Body Mass Index (BMI); Cardiovascular Disease (CVD); Diabetes Mellitus (DM); Dietary Guidelines Adherence Index (DGAI); Hazard Ratio (HR); Non-APOE AD polygenic risk scores (NAD-PRSs); Percentile (P); Physical Activity (PA); Systemic Arterial Hypertension (SAH); Systolic Blood Pressure (SBP).

CONSUMPTION OF ULTRA-PROCESSED FOODS AND RISK FOR ALZHEIMER'S DISEASE

The results of the included studies are presented in Table 2. The study by Li et al., which evaluated the consumption of UPF using the NOVA classification, showed that higher intake of UPF was associated with an increased risk of AD. However, replacing UPF with unprocessed or minimally processed foods was not associated with a reduced risk of AD [13]. Meanwhile, the study by Samuelson et al. [27], which compared a healthy dietary pattern with a Western-style diet, found that individuals who consumed a Western diet containing UPF and who carried the APOE4 gene only had a higher risk of incident dementia; associations with the risk of AD were not found. The study by Zhang et al. found that the consumption of processed meats was associated with a higher risk of AD, while the consumption of unprocessed red meat appeared to be a protective factor. In this study, it was observed that individuals carrying the APOE4 gene had a 6 times higher risk for the development of AD [26]. Lastly, the study by Pase et al. [25] which compared the consumption of artificially sweetened soft drinks with sugar-sweetened beverages, showed that the consumption of artificially sweetened soft drinks was associated with higher risks for AD. Sugar-sweetened beverages were not associated with an increased risk of AD [25].

METHODOLOGICAL QUALITY AND RISK OF BIAS

The assessment of the methodological quality of the included studies is presented in Table 3. Regarding the risk of bias, the study by Li et al. [13] did not clearly state in the methodology the confounding factors considered for outcome analysis, nor did it specify if there was sample loss during the monitoring period. The study by Zhang et al. [26] also did not clarify the confounding factors, and the studies by Pase et al. [25] and Samuelson et al. [27] did not specify about sample loss during the monitoring period. Despite the presence of these mentioned biases, all studies were considered of high methodological quality according to the JBI critical appraisal checklist for cohort studies.

Table 3 - JBI critical appraisal checklist for cohort studies

Question	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Quality
Samuelsson et al. [27]	NA	NA	Y	Y	Y	Y	Y	Y	LC	LC	Y	Alta
Li et al. (2022) [13]	NA	NA	Y	LC	LC	Y	Y	Y	LC	LC	Y	Alta
Zhang et al. (2021) [26]	NA	NA	Y	LC	LC	Y	Y	Y	Y	NA	Y	Alta
Pase et al. (2018) [25]	NA	NA	Y	Y	Y	Y	Y	Y	LC	LC	Y	Alta

*Yes (S); No (N); Lack of clarity (LC); Not applicable (NA)

DISCUSSION

To the best of our knowledge, this is the first systematic review to investigate the association between UPF consumption and the risk of developing AD. Three studies provided evidence that UPF consumption was significantly associated with a higher risk of AD, while one study showed a risk association only with the development of incident dementia. However, these findings should be interpreted with caution due to the limited number of studies on the topic and the presence of heterogeneity among them. To classify foods according to the purpose and degree of processing, only one study used the NOVA classification [13], introduced in Brazil in 2010, which categorizes foods and food products into four groups: unprocessed or minimally processed foods, processed culinary ingredients, processed foods, and UPF [28]. Another study assessed the consumption of a Western diet characterized as being rich in UPF without using a standard dietary classification system [26]. The other studies specified the type of UPF evaluated, being processed meats [26] and soft drinks and sugary beverages [25].

We observed that the use of different tools to assess dietary intake can be considered a bias for the analysis of the results. 24-hour diet recalls, which were used in 2 studies of our review [13,26], allow the inclusion of any and every reported food item and might better capture food intake by the degree of processing compared to food frequency questionnaires which contain predefined lists of food items [29]. However, studies indicate that at least three repeated 24-hour diet recalls are required to accurately represent habitual food intake [30]. In our review, only the study by Li et al. [13] applied the 24-hour diet recall considering this criterion, while Zhang et al. [26] applied the recall only on two occasions during the monitoring period. Considering that there are currently no validated dietary tools to capture UPF consumption, the development of tools specifically designed to assess the consumption of this food group is of great value to better investigate the association of UPF consumption with health outcomes [20].

Given the importance of considering the synergistic effects of foods, studying dietary patterns rather than isolated foods and nutrients is of great significance [33]. The replacement of minimally processed foods and culinary preparations with ready-to-eat products is increasing worldwide, raising concerns for public health [23]. It's well-established in the literature that changes in population dietary patterns have been accompanied by an increase in the prevalence of obesity and other non-communicable chronic diseases (NCDs) [28]. Previous studies have established a relationship between poor diet quality and increased mortality risk from NCDs [32]. However, to date, no systematic review has specifically investigated the association of UPF consumption with the risk of developing AD.

Of the studies included in our review, Li et al. [13] in a cohort involving 118,528 adults and elderly individuals, found that higher consumption of UPF was associated with a higher risk of AD. The addition of 10% UPF in the diet was associated with a significant 13% increase in the risk of AD [13]. Similar studies that evaluated UPF consumption, but only considering the outcome on cognitive function, showed that a higher percentage of daily energy consumption from UPF was linked to greater cognitive decline in adults and elderly individuals [33,34]. It's important to note that, in our review, only studies assessing the risk of AD were included since the pathophysiological basis of the disease differs from the pathophysiology of cognitive decline and other types of dementia, such as senile dementia, vascular dementia, or dementia in Parkinson's disease. This distinction reduces potential biases in the outcome analysis.

In our sample, the study conducted by Pase et al. [25], which monitored a cohort of 1,484 elderly individuals, showed that the consumption of artificially sweetened beverages increased the risk of AD. On the other hand, no correlation was identified between the consumption of sugar-sweetened beverages and an increased risk of this outcome. Other studies investigating the consumption of artificially sweetened beverages also demonstrated associations with health outcomes, such as a higher risk of cancer [34] and mortality from cardiovascular disease [35], however, results are controversial. More studies assessing the effect of consuming artificially sweetened beverages on health outcomes, including cognitive decline and AD, should be conducted.

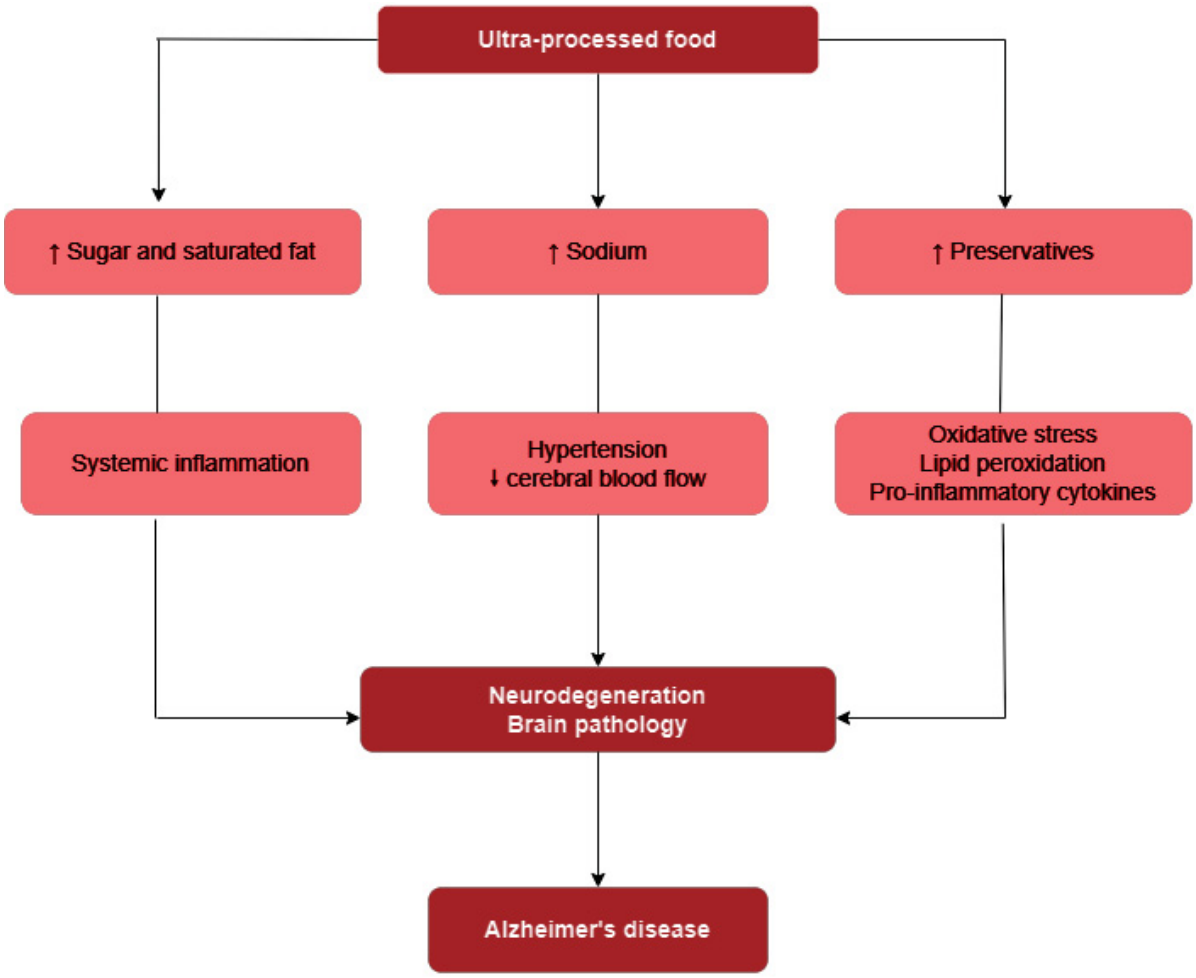
The study conducted by Samuelson et al. [27] followed a cohort of 602 elderly individuals. Although it was the study with the smallest sample, it had a monitoring duration of 24 years, making it the longest cohort when compared to the other studies included in the review. Samuelson et al. [27] found that adherence to a Western dietary pattern containing UPF led to a higher risk in the development of incident dementia only in individuals carrying

the APOE4 allele. No risk association was identified between the Western dietary pattern and the development of AD.

Regarding the study by Zhang et al [26].. that tracked a cohort of 493,888 elderly individuals over 10 years, it was found that an additional consumption of 25g/day of processed meats heightened the risk of AD. Moreover, the AD risk was 6 times greater in individuals carrying the APOE4 allele [26]. In the brain, APOE plays an important role in lipid transport to neurons, binding to APOE receptors on the cell surface involved in lipoprotein metabolism. Research has shown that modulation of these APOE receptors impacts amyloid and tau pathologies [37,38]. There are three predominant APOE alleles, the ε2, ε3, and ε4 alleles, which confer varying degrees of disease risk. APOE4 is a significant genetic risk factor for AD, while APOE2 nearly halves the AD risk and contributes to longevity [39].

All the studies included in our review detail the potential mechanisms involved between the association of UPF consumption and the risk of AD (Figure 1). In general, UPFs are energy-dense, rich in refined carbohydrates, and saturated fatty acids [40]. This combination of features can induce systemic inflammation, contributing to the progression of neurodegeneration and brain pathology [13, 25]. Moreover, most UPFs, such as snacks, processed meats, and processed seasonings, are rich in sodium. High-sodium diets can cause systemic arterial hypertension, potentially accompanied by reduced cerebral blood flow, and possibly linked to the development of cognitive deficits [13, 26]. Upon finding that processed meat consumption was associated with a higher risk of AD, Zhang et al. argue that processed meats, like sausage, hot dogs, and salami, for instance, contain nitrites and N-nitroso compounds, which might lead to oxidative stress, lipid peroxidation, and activation of pro-inflammatory cytokines, among other mechanisms potentially involved in dementia development [26]. Regarding the mechanisms involved in the APOE-diet interaction in relation to the risk of AD, Samuelsson et al. [27] propose that the presence of the APOE4 allele is a risk factor for alterations in lipid and glycolytic metabolism, and when combined with a diet rich in ultra-processed foods, could heighten insulin resistance and inflammatory response, offering links to a greater risk of AD [27].

Figure 1 - Biological mechanisms involved in the association of UPF consumption with the risk of developing AD.



Our review has several strengths. First, this review was the first to explore the association between UPF consumption and the risk of AD. We conducted an extensive literature search, including not only database searches but also grey literature and reference lists. Given that the included studies had a longitudinal design, it's notable that our review showcased robust and impactful results. All the studies included were of high methodological quality.

Limitations should also be acknowledged. Of the four studies included in our review, two significant studies were found through citation search. This leads us to consider that the inclusion of more descriptors related to UPF might have expanded our search. It's also important to note that no quantitative meta-analysis was conducted, an issue we hope will be surpassed in future research.

CONCLUSION

The association between UPF consumption and the risk of developing AD is a recent topic in scientific studies, given that the oldest study identified by our review dates from 2017. Out of the four studies included, three showed a significant association between UPF consumption and the risk of developing AD. Although there have been few studies on the topic so far, the included studies have a longitudinal design with robust results. Our findings reinforce the importance of public strategies aimed at raising awareness among the population about the harmful effects of UPF consumption on cognitive health.

DECLARATION OF COMPETING INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

P.A Claudino contributed to the organization, study selection, data extraction, quality assessment, writing, and editing of the manuscript. S. Piloneto and D. Halaiko contributed to the selection process, data extraction, and quality assessment. C.H Maia acted as the third reviewer. L.P.A Souza assisted in devising the search strategy. B.D.M Netto and N.B Bueno reviewed, edited, and supervised the manuscript. All authors made contributions to the article and approved the submitted version.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ACKNOWLEDGMENTS

We thank the Coordination of the Graduate Program in Food and Nutrition at the Federal University of Paraná for all the support in carrying out this study.

REFERENCES

1. GBD 2019 - Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. Lancet Neurol. 2019, 7, 105-125.
2. Associação internacional da Doença de Alzheimer. Alzheimer's Disease Facts and Figures. Chicago: ADI, 2020.
3. Edwards F. A unifying hypothesis for Alzheimer's disease: from plaques to neurodegeneration. Trends Neurosci. 2019, 42, 310-322.
4. Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K. Alzheimer's disease drug development pipeline: 2020. Alzheimer's Dement. 2020, 6, 1-29.
5. Solfrizzi V, Agosti P, Lozupone M, Custodero C, Schilardi A, Vincenzo V et al. Nutritional intervention as a preventive approach for cognitive related outcomes in cognitively healthy older adults: a systematic review. J Alzheimer's Dis. 2018, 64, 229-254.
6. García M, Gonzalez M, Razquin C, Grima F, Toledo E. Exploratory dietary patterns and cognitive function in the "Seguimiento Universidad de Navarra" (SUN) Prospective Cohort. Eur J Clin Nutr. 2021, 76, 48-55
7. Moubarac J, Batal M, Louzada M, Steele E, Monteiro C. Consumption of ultra-processed foods predicts diet quality in Canada. Appetite. 2017, 108, 512-520.
8. Rauber F, Louzada M, Steele E, Millett C, Monteiro C, Levy R. Ultraprocessed food consumption and chronic noncommunicable diseases-related dietary nutrient profile in the UK (2008–2014). Nutrients. 2018, 10, 1-13.
9. Louzada M, Ricardo C, Steele E, Levy R, Cannon G, Monteiro C. The share of ultra-processed foods determines the overall nutritional quality of diets in Brazil. Public Health Nutr. 2018, 21, 94-102.
10. Ponce J, Pimienta T, Louzada M, Batis B. Energy contribution of NOVA food groups and sociodemographic determinants of ultra-processed food consumption in the Mexican population. Public Health. 2018, 21, 87-93.
11. Cediel G, Reyes M, Louzada M, Steele E, Monteiro C, Corválan et al. Ultraprocessed foods and added sugars in the Chilean diet. Public Health Nutr. 2018, 21, 125-133
12. Food and Agriculture Organization of the United Nations. Dietary Assessment: A Resource Guide to Method Selection and Application in Low Resource Settings**.** Roma: FAO, 2018.
13. Li H, Li S, Yang H, Zhang Y, Zhang S, Ma Y et al. Association of Ultraprocessed Food Consumption With Risk of Dementia: A Prospective Cohort Study. Neurology. 2022, 99, 1056-1066.
14. Liu Y, Gao X, Na M, Etherton P, Mitchell D, Jensen G. Dietary Pattern, Diet Quality, and Dementia: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. J Alzheimers. 2020, 78, 151-168.
15. Guerville M, Leroy A Sinquin A, Laugerette F, Michalski M, Boudry G. Western-diet consumption induces alteration of barrier function mechanisms in the ileum that correlates with metabolic endotoxemia in rats. Am J Physiol Endocrinol Metab. 2017, 313, 107-120.
16. Santos F, Dias M, Mintem G, Oliveira I, Gigante D. Food processing and cardiometabolic risk factors: a systematic review. Rev Saude Publica. 2020, 54, 1-15.
17. Chen X, Zhang Z, Yang H, Qiu P, Wang H, Wang F et al. Consumption of ultra-processed foods and health outcomes: a systematic review of epidemiological studies. Nutr J. 2020, 19, 1-10.

18. Moradi S, Kermani M, Bagheri R, Mohammadi H, Jayedi A, Lane M et al. Ultra-Processed Food Consumption and Adult Diabetes Risk: A Systematic Review and Dose-Response Meta-Analysis. Nutrients. 2021, 13, 1-13.
19. Barbosa S, Sousa L, Silva D, Pimentel J, Evangelista K, Lyra C et al. A Systematic Review on Processed/Ultra-Processed Foods and Arterial Hypertension in Adults and Older People. Nutrientes. 2022, 14, 1-16.
20. Lane M, Davis J, Beattie S, Donoso C, Loughman A, Neil A et al. Ultraprocessed food and chronic noncommunicable diseases: A systematic review and meta-analysis of 43 observational studies. Obes Ver. 2021, 22, 1-19.
21. Tian Y, Deng C, Xie H, Long Q, Yao Y, Deng Y et al. Ultra-processed food intake and risk of depression: a systematic review. Nutr Hosp. 2020, 40**,** 160-176.
22. Page M, Meckenzie J, Bossuyt P, Boutron I, Hoffman T, Mulrow C et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021, 372, 1-6.
23. Monteiro C, Cannon G, Levy R, Moubarac J, Louzada M, Rauber F et al. Ultra-processed foods: what they are and how to identify them. Public Health Nutr. 2019, 22, 936-941.
24. Aromataris E, Munn Z. JBI Manual for Evidence Synthesis. Instituto Joanna Briggs, 2020.
25. Pase M, Himali J, Beiser A, Aparicio H, Satizabal C, Vasan R et al. Sugar- and Artificially Sweetened Beverages and the 396 Risks of Incident Stroke and Dementia: A Prospective Cohort Study. Stroke. 2017, 48**,** 1139-1146.
26. Zhang H, Greenwood D, Risch H, Bunce D, Haridie L, Cade J. Meat consumption and risk of incident dementia: cohort study of 493,888 UK Biobank participants. Am J Clin Nutr. 2021, 114, 175-184.
27. Samuelsson J, Najar J, Wallengren O, Kern S, Wetterberg O, Fassberg M, et al. Interactions between dietary patterns and genetic factors in relation to incident dementia among 70-year-old. Eur J Nutr. 2022, 61, 871-884.
28. Monteiro C, Geoffrey C, Moubarac J, Levy R, Louzada M, Jaime P. The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing. Public Health Nutr. 2018, 21, 5-17.
29. Meneguelli S, Hinkelmann J, Hermsdorff H, Zulet M, Martinez J, Bressan J. Food consumption by degree of processing and cardiometabolic risk: a systematic review. J. Food Sci. Nutr. 2020, 71, 678-692.
30. Levy T, Ramirez S, Pineda E, Nasu L, Carriquiry A, Rivera J. Three 24-Hour Recalls in Comparison with One Improve the Estimates of Energy and Nutrient Intakes in an Urban Mexican Population. J. Nutr. 2016, 146, 1043-1050.
31. Vernooij R, Zeraatkar D, Han M, Dib R, Zworth M, Milio K et al. Patterns of red and processed meat consumption and risk for Cardiometabolic and Cancer outcomes: a systematic review and meta-analysis of cohort studies. Ann Intern Med. 2019, 171, 732-741.
32. Stein D, Benjet C, Gureje O, Lund C, Scott K, Poznyak V et al. Integrating mental health with other non-communicable diseases. BMJ. 2019, 295-364.
33. Gonçalves N, Ferreira N, Khandipur N, Steele E, Levy R, Lotufo P et al. Association Between Consumption of Ultraprocessed Foods and Cognitive Decline. JAMA Neurol. 2022, 80, 142-150.
34. Weinstel G, Vered S, Wagjcman D, Springer R, Heymann A, Sagi S et al. Consumption of Ultra-Processed Food and Cognitive Decline among Older Adults With Type-2 Diabetes. J Gerontol A Biol Sci Med Sci. 2023, 78, 134-142.

35. Debras C, Chazela E, Srour B, Pecollo N, Esseddik Y, Edelenyi, F et al. Artificial sweeteners and cancer risk: Results from the NutriNet-Santé population-based cohort study. PLoS Med. 2022, 19, 1-20.
36. Liu D, Li Z, Shen D, Zhang P, Song W, Zhang W et al. Association of Sugar-Sweetened, Artificially Sweetened, and Unsweetened Coffee Consumption With All-Cause and Cause-Specific Mortality: A Large Prospective Cohort Study. Ann Intern Med. 2022, 175, 909-917.
37. Liu C, Zhao N, Yamaguchi Y, Cirrito J, Kanekiyo T, Holtzman D et al. Neuronal heparan sulfates promote amyloid pathology by modulating brain amyloid-β clearance and aggregation in Alzheimer's disease. Sci Transl Med. 206, 8, 1-25.
38. Rauch J, Luna G, Guzman E, Audouard M, Challis C, Sibih Y et al. LRP1 is a master regulator of tau uptake and spread. Natureza. 2020, 580, 381-385.
39. Guen Y, Belloy M, Boley B, Rojas I, Morales A, Jansen I et al. Association of Rare APOE Missense Variants V236E and R251G With Risk of Alzheimer Disease. JAMA Neurol. 2022, 79, 652-663.
40. Guo C, Wei Z, Huang F, Qin M, Li X, Wang Y al. High salt induced hypertension leads to cognitive defect. Oncotarget. 2017, 8, 95780-95790.

REFERÊNCIAS

Academia Brasileira de Neurologia. **Declínio cognitivo subjetivo, comprometimento cognitivo leve e demência - diagnóstico sindrômico:** recomendações do Departamento Científico de Neurologia Cognitiva e do Envelhecimento da Academia Brasileira de Neurologia. São Paulo, 2022.

ADI – Associação internacional da Doença de Alzheimer. **Alzheimer's Disease Facts and Figures.** Chicago, 2015.

ADI – Associação internacional da Doença de Alzheimer. **Alzheimer's Disease Facts and Figures.** Chicago, 2020.

ALBANESE, Emiliano et al. Body mass index in midlife and dementia: Systematic review and meta-regression analysis of 589,649 men and women followed in longitudinal studies. **Alzheimers Dement,** [s. l], p. 165-178, 2017. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5520956/. Acesso em: 22 dez. 2022.

ARAUJO, T et al. Food Processing: Comparison of Different Food Classification Systems. **Nutrients,** [s. l.], p. 1-14, 2022. Disponível em: https://doi.org/10.3390/nu14040729. Acesso em: 11 jul. 2023.

AROMATARIS, E; MUNN, Z. JBI Manual for Evidence Synthesis. **Instituto Joanna Briggs,** 2020. Disponível em: https://doi.org/10.46658/JBIMES-20-01. Acesso em: 17 marc. 2023.

ASFAW, A. Does consumption of processed foods explain disparities in the body weight of individuals? The case of Guatemala. **Health Econ**, [s. l.], p. 184-195, 2011. Disponível em: https://doi.org/10.1038/ejcn.2009.82. Acesso em: 11 jul. 2023. Acesso em: 11 jul. 2023.

AUDA, Tarifas; BORRMANN, Dieter. Neurochemical Aspects of Alzheimer's Disease and Movement Disturbances: A Theory of β-Amyloid and τ-Protein. **Am J Alzheimers Dis Other Demen,** [s. l.], p. 535-540, 2018. Disponível em: https://pubmed.ncbi.nlm.nih.gov/30045626/. Acesso em: 26 ago. 2023.

BARBOSA, S et al. A Systematic Review on Processed/Ultra-Processed Foods and Arterial Hypertension in Adults and Older People. **Nutrientes**, [s. l.], p. 1-16, 2022. Disponível em: https://doi.org/10.3390/nu14061215. Acesso em: 19 jan. 2023.

BARNARD, D; BUNNER, A.E; AGARWAL, U. Saturated and trans fats and dementia: A systematic review. **Neurobiology of Aging**, [s. l.], p. 65-73, 2014. Disponível em: https://doi.org/10.1016/j.neurobiolaging.2014.02.030. Acesso em: 15 fev. 2023.

BUDREVICIUTE, A et al. Management and Prevention Strategies for Non-communicable Diseases (NCDs) and Their Risk Factors. **Front Public Health,** [s. l.], p. 1-11, 2020. Disponível em: https://pubmed.ncbi.nlm.nih.gov/33324597/. Acesso em: 11 jul. 2023.

CACACE, R; SLEEGERS, K; BROECKHOVEN, C. Molecular genetics of early-onset Alzheimer's disease revisited. **Elsevier**, [s. l.], p. 733-748, 2016. Disponível em: https://doi.org/10.1016/j.jalz.2016.01.012. Acesso em: 04 jan. 2023.

CASTELL, G et al. Contribution of processed foods to the energy, macronutrient and fiber intakes of Mexican children aged 1 to 4 years. **Salud Publica Mex**, [s. l.], p. 345-356, 2007. Disponível em: https://doi.org/10.1590/s0036-36342007000500005. Acesso em: 11 jul. 2023.

CEDIEL, Gustavo et al. Ultraprocessed foods and added sugars in the Chilean diet. **Public Health Nutr,** [s. l.], p. 125-133, 2018. Disponível em: https://doi.org/10.1017/S1368980017001161. Acesso em: 04 jan. 2023.

CHEN, X et al. Consumption of ultra-processed foods and health outcomes: a systematic review of epidemiological studies. **Nutr J**, [s. l.], p. 1-10, 2020. Disponível em: https://doi.org/10.1186/s12937-020-00604-1. Acesso em: 19 jan. 2023.

CRINO, M et al. Systematic Review and Comparison of Classification Frameworks Describing the Degree of Food Processing. **Nutri. Food Technology**, [s. l.], p. 1-12, 2017. Disponível em: https://doi.org/0.16966/2470-6086.138. Acesso em: 11 jul. 2023.

CROUS-BOU, M. Alzheimer's disease prevention: from risk factors to early intervention. **Alzheimers Res Ther**, [s. l.], p. 1-9, 2017. Disponível em: https://doi.org/10.1186/s13195-017-0297-z. Acesso em: 04 jan. 2023.

CUMMINGS, D et al. Neuronal and peripheral pentraxins modify glutamate release and may interact in blood–brain barrier failure. **Cereb Cortex**, [s. l.], p. 3437-3448, 2017. Disponível em: https://doi.org/10.1093/cercor/bhx046. Acesso em: 04 jan. 2023.

CUMMINGS, J et al. Alzheimer's disease drug development pipeline: 2020. **Alzheimer's Dement**, [s. l.], p. 1-29, 2020. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7364858/. Acesso em: 18 jan. 2023.

DEBRAS, C et al. Artificial sweeteners and cancer risk: Results from the NutriNet-Santé population-based cohort study. **PLoS Med**, [s. l.], p. 1-20, 2022. Disponível em: https://doi.org/10.1371/journal.pmed.1003950. Acesso em: 11 jul. 2023.

EDWARDS, F. A unifying hypothesis for Alzheimer's disease: from plaques to neurodegeneration. **Trends Neurosci,** [s. l.], p. 310-322, 2019. Disponível em: https://doi.org/10.1016/j.tins.2019.03.003. Acesso em: 04 jan. 2023.

EVRENDILEK, G. Effects of High-Pressure Processing on Bioavaliability of Food Components. **J. Nutr. Ciência Alimentar,** [s. l.], p. 1-5, 2018. Disponível em: https://doi.org/10.4172/2155-9600.1000676. Acesso em: 11 jul. 2023.

FAHED, M et al. Metabolic Syndrome: Updates on Pathophysiology and Management in 2021. **Int J Mol Sci,** [s. l.], p. 1-38, 2022. Disponível em: https://doi.org/10.3390/ijms23020786. Acesso em: 15 fev. 2023.

FAO - Food and Agriculture Organization of the United Nations. **Dietary Assessment:** A Resource Guide to Method Selection and Application in Low Resource Settings**.** ROMA: FAO, 2018.

FAO - Food and Agriculture Organization of the United Nations. **Sustainable healthy diets:** guiding principles. ROMA: FAO, 2019.

FETER, N. Ten-year trends in hospitalizations due to Alzheimer's disease in Brazil: a national-based study. **Cad Saude Publica.** , [s. l.], p. 1-13, 2020. Disponível em:

https://www.scielo.br/j/csp/a/L4jjqm5BTDW4vs8sFwJRg8m/?lang=en. Acesso em: 18 jan. 2023

FLEISHER, A et al. Positron Emission Tomography Imaging With [18F]flortaucipir and Postmortem Assessment of Alzheimer Disease Neuropathologic Changes. **JAMA Neurol,** [s. l.], p. 829-839, 2020. Disponível em: https://doi.org/10.1001/jamaneurol.2020.0528. Acesso em: 11 jul. 2023.

GARCÍA, M et al. Exploratory dietary patterns and cognitive function in the "Seguimiento Universidad de Navarra" (SUN) Prospective Cohort. **Eur J Clin Nutr,** [s. l.], p. 48-55, 2021. Disponível em: https://doi.org/10.1038/s41430-021-00922-5. Acesso em: 18 jan. 2023.

GBD 2019 - Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. **Lancet Neurol**, [s. l.], p. 105-125, 2022. Disponível em: https://doi.org/10.1016/S2468-2667(21)00249-8. Acesso em: 15 fev. 2023.

GONÇALVES, N et al. Association Between Consumption of Ultraprocessed Foods and Cognitive Decline. **JAMA Neurol**, [s. l.], p. 142-150, 2022. Disponível em: https://pubmed.ncbi.nlm.nih.gov/36469335/Acesso em: 11 jul. 2023.

GUEN, Y et al. Association of Rare APOE Missense Variants V236E and R251G With Risk of Alzheimer Disease. **JAMA Neurol**, [s. l.], p. 652-663, 2022. Disponível em: https://doi.org/10.1001/jamaneurol.2022.1166. Acesso em: 11 jul. 2023.

GUERVILLE, M et al. Western-diet consumption induces alteration of barrier function mechanisms in the ileum that correlates with metabolic endotoxemia in rats**. Am J Physiol Endocrinol Metab**, [s. l.], p. 107-120, 2017. Disponível em: https://doi.org/10.1152/ajpendo.00372.2016. Acesso em: 15 fev. 2023.

GUO, CP al. High salt induced hypertension leads to cognitive defect. 419 **Oncotarget,** [s. l.], p. 95780-95790, 2017. Disponível em: https://doi.org/10.18632/oncotarget.21326. Acesso em: 15 fev. 2023.

HALLIDAY, M et al. Accelerated pericyte degeneration and blood-brain barrier breakdown in apolipoprotein E4 carriers with Alzheimer's disease. **J. Cereb. Blood Flow Metab,** [s. l.], p. 216-227, 2016.Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4758554/. Acesso em: 17 jul. 2023

HONG, S et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. **Science,** [s. l.], p. 718-716, mai. 2016. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5094372/. Acesso em: 04 jan. 2023.

IBGE – Instituto Brasileiro de Geografia e Estatística. **Pesquisa de orçamentos familiares 2017-2018:** avaliação nutricional da disponibilidade domiciliar de alimentos do Brasil. Rio de Janeiro, 2020.

JACK, C et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. **Alzh & Dem,** [s. l.], p. 535-562, 2018. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5958625/. Acesso em: 04 jan. 2023.

KIVIPELTO, M et al. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. **Nat Rev Neurol,** [s. l.], p. 653-666, 2018. Disponível em: https://doi.org/10.1038/s41582-018-0070-3. Acesso em: 15 fev. 2023.

LANE, M et al. Ultraprocessed food and chronic noncommunicable diseases: A systematic review and meta-analysis of 43 observational studies. **Obes Rev**, [s. l.], p. 1-19, 2021. Disponível em: https://doi.org/10.1111/obr.13146. Acesso em: 19 jan. 2023.

LANGEVELD, A et al. The relationship between taste and nutrient content in commercially available foods from the United States. **Public Health Nutr.,** [s. l.], p. 1-7, 2020. Disponível em: https://doi.org/10.1016/j.foodqual.2016.10.012. Acesso em: 15 fev. 2023.

LEMIEUX, I; DESPRÉS, J. Metabolic Syndrome: Past, Present and Future. **Nutrients**, [s. l.], p. 1-7, 2020. Disponível em: https://doi.org/10.3390/nu12113501. Acesso em: 11 jul. 2023.

LEVY, T et al. Three 24-Hour Recalls in Comparison with One Improve the Estimates of Energy and Nutrient Intakes in an Urban Mexican Population. J**. Nutr**, [s. l.], p. 1043-1050, 2016. Disponível em: https://doi.org/10.3945/jn.115.219683. Acesso em: 11 jul. 2023.

LI, H et al. Association of Ultraprocessed Food Consumption With Risk of Dementia: A Prospective Cohort Study. **Neurology,** [s. l.], p. 1056-1066, 2022. Disponível em: https://doi.org/10.1212/WNL.0000000000200871. Acesso em: 04 jan. 2023.

LISKO, I. et al. How can dementia and disability be prevented in older adults: where are we today and where are we going? **The Journal Of Internal Medicine**, [s. l], p. 807-830, 2021. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8248434/pdf/JOIM-289-807.pdf. Acesso em: 22 dez. 2022.

LIU, C et al. Neuronal heparan sulfates promote amyloid pathology by modulating brain amyloid-β clearance and aggregation in Alzheimer's disease. **Sci Transl Med**, [s. l.], p. 1-25, 2016. Disponível em: https://10.1126/scitranslmed.aad3650. Acesso em: 11 jul. 2023.

LIU, D et al. Association of Sugar-Sweetened, Artificially Sweetened, and Unsweetened Coffee Consumption With All-Cause and Cause-Specific Mortality: A Large Prospective Cohort Study. **Ann Intern Med,** [s. l.], p. 909-917, 2022. Disponível em: https://doi.org/10.7326/M21-2977. Acesso em: 11 jul. 2023.

LIU, Y et al. Dietary Pattern, Diet Quality, and Dementia: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. **J Alzheimers,** [s. l.], p. 151-168, 2020. Disponível em: https://doi.org/10.3233/JAD-200499. Acesso em: 15 fev. 2023.

LIVINGSTON, G et al. Dementia prevention, intervention, and care: 2020 report of the lancet commission. **Lancet**, [s. l], p. 413-446, 2020. Disponível em: https://doi.org/10.1016/S0140-6736(20)30367-6. Acesso em: 22 dez. 2022.

LOUZADA, M et al. The share of ultra-processed foods determines the overall nutritional quality of diets in Brazil. **Public Health Nutr,** [s. l.], p. 94-102, 2018. Disponível em: https://doi.org/10.1017/S1368980017001434. Acesso em: 04 jan. 2023.

LUITEN, C et al. Ultraprocessed foods have the worst nutrient profile, yet they are the most available packaged products in a sample of New Zealand supermarkets. **Public Health Nutr,**

[s. l.], p. 530-538, 2016. Disponível em: https://doi.org/10.1017/S1368980015002177. Acesso em: 04 jan. 2023.

MAIA, E et al. What to expect from the price of healthy and unhealthy foods over time? The case from Brazil. **Food Quality and Preference,** [s. l.], p. 579-588, 2020. Disponível em: https://doi.org/10.1017/S1368980019003586. Acesso em: 15 fev. 2023.

MATSUDA, H; SHIGEMOTO, Y; SATO, N. Neuroimaging of Alzheimer's disease: focus on amyloid and tau PET**. Jpn J Radiol,** [s. l.], p. 735-749, 2019. Disponível em: https://doi.org/10.1007/s11604-019-00867-7. Acesso em: 11 jul. 2023.

MENDONÇA, R et al. Ultraprocessed food consumption and the incidence of hypertension in a Mediterranean cohort: the Seguimiento Universidad de Navarra Project. **Am J Hypertens,** [s. l.], p. 358-366, 2017. Disponível em: https://doi.org/10.1093/ajh/hpw137. Acesso em: 04 jan. 2023.

MENEGUELLI, S et al. Food consumption by degree of processing and cardiometabolic risk: a systematic review. **J. Food Sci. nutr**, [s. l.], p. 678-692, 2020. Disponível em: https://doi.org/10.1080/09637486.2020.1725961. Acesso em: 11 jul. 2023.

MIAO, Y et al. Sugar in Beverage and the Risk of Incident Dementia, Alzheimer's Disease and Stroke: A Prospective Cohort Study. **J Prev Alzheimers Dis,** [s. l.], p. 188-193, 2020. Disponível em: https://doi.org/10.14283/jpad.2020.62. Acesso em: 15 fev. 2023.

MILLER, H; FULGONI, V; KEATS, D. Contributions of processed foods to dietary intake in the US from 2003-2008: a report of the Food and Nutrition Science Solutions Joint Task Force of the Academy of Nutrition and Dietetics, American Society for Nutrition, Institute of Food Technologists, and International Food Information Council. **J. Nutri,** [s. l.], p. 2065-2072, 2012. Disponível em: https://doi.org/10.3945/jn.112.164442. Acesso em: 11 jul. 2023.

MIRANDA H, AGNAF O, OUTEIRO T. Glycation in Parkinson's disease and Alzheimer's disease. **Mov Disord,** [s. l.], p. 782-790, 2016. Disponível em: https://doi.org/10.1002/mds.26566. Acesso em: 15 fev. 2023.

MONTEIRO, C et al. Dietary guidelines to nourish humanity and the planet in the twenty-first century. A blueprint from Brazil. **Public Health Nutr,** [s. l.], p. 2311-2322, 2015. Disponível em: https://doi.org/10.1017/S1368980015002165. Acesso em: 04 jan. 2023.

MONTEIRO, C et al. NOVA. A estrela brilha. **World Nutr,** [s. l.], p. 28-38, 2016. Disponível em: https://worldnutritionjournal.org/index.php/wn/article/view/5/4. Acesso em: 04 jan. 2023

MONTEIRO, C et al. The UN Decade of Nutrition, the NOVA food classification and the trouble with ultra-processing. **Public Health Nutr,** [s. l.], p. 5-17, 2018. Disponível em: https://doi.org/10.1017/S1368980017000234. Acesso em: 04 jan. 2023.
MONTEIRO, C et al. Ultra-processed foods: what they are and how to identify them. **Public Health Nutr**, [s. l.], p. 936-941, abr. 2019. Disponível em: https://doi.org/10.1017/S1368980018003762. Acesso em: 04 jan. 2023.

MORADI, S et al. Ultra-Processed Food Consumption and Adult Diabetes Risk: A Systematic Review and Dose-Response Meta-Analysis. **Nutrients**, [s. l.], p. 1-13, 2021. Disponível em: https://doi.org/10.3390/nu13124410. Acesso em: 19 jan. 2023.

MOUBARAC, J et al. Consumption of ultra-processed foods predicts diet quality in Canada. **Appetite,** [s. l.], p. 512-520, 2017. Disponível em: https://doi.org/10.1016/j.appet.2016.11.006. Acesso em: 04 jan. 2023.

MOUBARAC, J et al. Food classification systems based on food processing: significance and implications for policies and actions: a systematic literature review and assessment. **Curr Obes,** [s. l.], p. 256-272, 2014. Disponível em: https://doi.org/10.1007/s13679-014-0092-0. Acesso em: 04 jan. 2023.

NARDOCCI, M et al. Consumption of ultra-processed foods and obesity in Canada. **Can J Public Health,** [s. l.], p. 4-14, 2019. Disponível em: https://doi.org/10.17269/s41997-018-0130-x. Acesso em: 04 jan. 2023.

OMS - Organização Mundial de Saúde. **Global Health Estimates 2016:** Disease burden by Cause, Age, Sex, by 342 Country and by Region, 2000-2016. Geneva: OMS, 2018.

OMS - Organização Mundial de Saúde. **Noncommunicable diseases.** Geneva: OMS, 2018.

PAGE, M et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. **BMJ**, [s. l.], p. 1-6, 2021. Disponível em: https://doi.org/10.1136/bmj.n71. Acesso em: 15 marc. 2023.

PARNETTI, L et al. Prevalence and risk of progression of preclinical Alzheimer's disease stages: a systematic review and meta-analysis. **Alzheimers Res Ther,** [s. l.], p. 11-17, 2019. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6334406/. Acesso em: 04 jan. 2023.

PASE, M et al. Sugar- and Artificially Sweetened Beverages and the 396 Risks of Incident Stroke and Dementia: A Prospective Cohort Study. **Stroke,** [s. l.], p. 1139-1146, 2017. Disponível em: https://doi.org/10.1161/STROKEAHA.116.016027. Acesso em: 15 fev. 2023.

PEKGOR, S et al. The Role of Visceral Adiposity Index Levels in Predicting the Presence of Metabolic Syndrome and Insulin Resistance in Overweight and Obese Patients. **Metab Syndr Relat Disord,** [s. l.], p. 296-302, 2019. Disponível em: https://doi.org/10.1089/met.2019.0005. Acesso em: 15 fev. 2023.

PEREIRA, J et al. Untangling the association of amyloid-β and tau with synaptic and axonal loss in Alzheimer's disease. **Brain,** [s. l.], p. 310-324, 2021. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8210638/. Acesso em: 04 jan. 2023.

PONCE, J et al. Energy contribution of NOVA food groups and sociodemographic determinants of ultra-processed food consumption in the Mexican population. **Public Health,** [s. l.], p. 87-93, 2018. Disponível em: https://doi.org/10.1017/S1368980017002129. Acesso em: 04 jan. 2023.

POTI, J et al. Is the degree of food processing and convenience linked with the nutritional quality of foods purchased by US households? **Am J Clin Nutr,** [s. l.], p. 1251-1262, 2015. Disponível em: https://doi.org/10.3945/ajcn.114.100925. Acesso em: 11 jul. 2023..

RANSON, J et al. Modifiable risk factors for dementia and dementia risk profiling. A user manual for Brain Health Services-part 2 of 6. **Alzheimers Res Ther,** [s. l.], p. 1-12, 2021. Disponível em: https://doi.org/10.1186/s13195-021-00895-4. Acesso em: 11 jul. 2023.

RAUBER, F et al. Ultraprocessed food consumption and chronic noncommunicable diseases-related dietary nutrient profile in the UK (2008–2014). **Nutrients,** [s. l.], p. 1-13, 2018. Disponível em: https://doi.org/10.3390/nu10050587. Acesso em: 04 jan. 2023.

RAUCH, J et al. LRP1 is a master regulator of tau uptake and spread. **Natureza,** [s. l.], p. 381-385, 2020. Disponível em: https://doi.org/10.1038/s41586-020-2156-5. Acesso em: 11 jul. 2023.

SAMUELSSON, J et al. Interactions between dietary patterns and genetic factors in relation to incident dementia among 70-year-old. **Eur J Nutr**, [s. l.], p. 871-884, 2022. Disponível em: https://doi.org/10.1007/s00394-021-02688-9. Acesso em: 11 jul. 2023.

SANTOS, F et al. Food processing and cardiometabolic risk factors: a systematic review. **Rev Saude Publica**, [s. l.], p. 1-15, 2020. Disponível em: https://doi.org/10.11606/s1518-8787.2020054001704. Acesso em: 19 jan. 2023.

SCHILLING, L et al. Imaging Alzheimer's disease pathophysiology with PET. **Dement Neuropsychol**, [s. l.], p. 79-90, 2016. Disponível em: https://doi.org/10.1590/S1980-5764-2016DN1002003. Acesso em: 11 jul. 2023.

SEVIGNY, J et al. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. **Nature**, [s. l.], p. 50-56, 2016. Disponível em: https://doi.org/10.1038/nature19323. Acesso em: 11 jul. 2023..

SILMANI, N et al. Contribution of highly industrially processed foods to the nutrient intakes and patterns of middle-aged populations in the European Prospective Investigation into Cancer and Nutrition study. **Eur. J. Clin. Nutr**, [s. l.], p. 206-225, 2009. Disponível em: https://doi.org/10.1038/ejcn.2009.82. Acesso em: 11 jul. 2023.

SINTINI, I et al. Longitudinal neuroimaging biomarkers differ across Alzheimer's disease phenotypes. **Brain**, [s. l.], p. 2281-2294, 2020. Disponível em: https://doi.org/10.1093/brain/awaa155. Acesso em: 11 jul. 2023..

SOLFRIZZI, V et al. Nutritional intervention as a preventive approach for cognitive related outcomes in cognitively healthy older adults: a systematic review. **J Alzheimer's Dis**, [s. l.], p. 229-254, 2018. Disponível em: https://doi.org/10.3233/JAD-179940. Acesso em: 18 jan. 2023.

SROUR, B et al. Consommation d'aliments ultra-transformés et risque de maladies cardiovasculaires dans la cohorte NutriNet-Santé. **The BMJ**, France, p. 28–30, 2019. Disponível em: https://pubmed.ncbi.nlm.nih.gov/31142457/. Acesso em: 04 jan. 2023.

SROURS, B et al. Ultraprocessed Food Consumption and Risk of Type 2 Diabetes Among Participants of the NutriNet-Santé Prospective Cohort. **Observational Study**, [s. l.], p. 283-291, 2020. Disponível em: https://doi.org/10.1001/jamainternmed.2019.5942. Acesso em: 04 jan. 2023.

STEELE, E et al. Ultra-processed foods and added sugars in the US diet: evidence from a nationally representative cross-sectional study. **BMJ Open**, [s. l.], p. 1-8, 2016. Disponível em: https://doi.org/10.1136/bmjopen-2015-009892. Acesso em: 18 jan. 2023.

STEIN, D et al. Integrating mental health with other non-communicable diseases. **BMJ,** [s. l.], p. 295-364, 2019. Disponível em: https://doi.org/10.1136/bmj.l295. Acesso em: 19 jan. 2023.

SZETO J, SIMON L. Current Treatment Options for Alzheimer's Disease and Parkinson's Disease Dementia. **Curr Neuropharmacol**, [s. l], p. 326-338, 2016. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4876589/. Acesso em: 22 dez. 2022.

TABARA, Y et al. Advanced Glycation End Product Accumulation is Associated with Lower Cognitive Performance in an Older General Population: The Nagahama Study. **J Alzheimers Dis**, [s. l.], p. 741-746, 2020. Disponível em: https://doi.org/ 10.3233/JAD-190878. Acesso em: 04 jan. 2023.

TIAN, Y et al. Ultra-processed food intake and risk of depression: a systematic review. **Nutr Hosp,** [s. l.], p. 160-176, 2020. Disponível em: https://doi.org/ 10.20960/nh.03723. Acesso em: 10 abr. 2023.

VERNOOIJ, R et al. Patterns of red and processed meat consumption and risk for Cardiometabolic and Cancer outcomes: a systematic review and meta-analysis of cohort studies. **Ann Intern Med**, [s. l.], p. 732-741, 2019. Disponível em: https://doi.org/10.7326/M19-1583. Acesso em: 11 jul. 2023.

WEINSTEI, G et al. Consumption of Ultra-Processed Food and Cognitive Decline among Older Adults With Type-2 Diabetes. **J Gerontol A Biol Sci Med Sci**, [s. l.], p. 134-142, 2023. Disponível em: https://pubmed.ncbi.nlm.nih.gov/35305016/. Acesso em: 11 jul. 2023.

ZHANG, H et al. Meat consumption and risk of incident dementia: cohort study of 493,888 UK Biobank participants. **Am J Clin Nutr,** [s. l.], p. 175-184, 2021. Disponível em: https://doi.org/10.1093/ajcn/nqab028. Acesso em: 15 fev. 2023.

ZHOU, Y et al. Neurotoxicity of low bisphenol A (BPA) exposure for 424 young male mice: Implications for children exposed to environmental levels of BPA. **Environ,** [s. l.], p. 40-48, 2017. Disponível em: https://doi.org/10.1016/10.1016/j.envpol.2017.05.043. Acesso em: 15 fev. 2023.

ANEXO

ANEXO 1 – Normas da Revista Frontiers in Nutrition

Author guidelines

General standards
Article type
Frontiers requires authors to select the appropriate article type for their manuscript and to comply with the article type descriptions defined in the journal's 'Article types' page, which can be seen from the 'For authors' menu on every Frontiers journal page. Please pay close attention to the word count limits.

Templates
If working with Word please use our Word templates. If you wish to submit your article as LaTeX, we recommend our LaTeX templates. For LaTeX files, please ensure all relevant manuscript files are uploaded: .tex file, PDF, and .bib file (if the bibliography is not already included in the .tex file).

During the interactive review, authors are encouraged to upload versions using track changes. Editors and reviewers can only download the PDF file of the submitted manuscript.

Manuscript length
Frontiers encourages the authors to closely follow the article word count lengths given in the 'Article types' page of the journals. The manuscript length includes only the main body of the text, footnotes, and all citations within it, and excludes the abstract, section titles, figure and table captions, funding statement, acknowledgments, and references in the bibliography. Please indicate the number of words and the number of figures and tables included in your manuscript on the first page.

Language editing
Frontiers requires manuscripts submitted to meet international English language standards to be considered for publication.

For authors who would like their manuscript to receive language editing or proofreading to improve the clarity of the manuscript and help highlight their research, Frontiers recommends the language-editing services provided by the following external partners.

Note that sending your manuscript for language editing does not imply or guarantee that it will be accepted for publication by a Frontiers journal. Editorial decisions on the scientific content of a manuscript are independent of whether it has received language editing or proofreading by these partner services or other services.

Editage Frontiers is pleased to recommend the language-editing service provided by our external partner Editage to authors who believe their manuscripts would benefit from professional editing. These services may be particularly useful for researchers for whom English is not the primary language. They can help to improve the grammar, syntax, and flow of your manuscript prior to submission. Frontiers authors will receive a 10% discount by visiting the following link: editage.com/frontiers.

The Charlesworth Group Frontiers recommends the Charlesworth Group's author services, who has a long-standing track record in language editing and proofreading. This is a third-party service for which Frontiers authors will receive a 10% discount by visiting the following link: www.cwauthors.com/frontiers.

Language style
The default language style at Frontiers is American English. If you prefer your article to be formatted in British English, please specify this on the first page of your manuscript. For any questions regarding style, Frontiers recommends authors to consult the Chicago Manual of Style.

Search engine optimization (SEO)
There are a few simple ways to maximize your article's discoverability. Follow the steps below to improve the search results of your article:

- include a few of your article's keywords in the title of the article
- do not use long article titles
- pick 5-8 keywords using a mix of generic and more specific terms on the article subject(s)
- use the maximum amount of keywords in the first two sentences of the abstract
- use some of the keywords in level 1 headings.

CrossMark policy
CrossMark is a multi-publisher initiative to provide a standard way for readers to locate the current version of a piece of content. By applying the CrossMark logo Frontiers is committed to maintaining the content it publishes and to alerting readers to changes if and when they occur. Clicking on the CrossMark logo will tell you the current status of a document and may also give you additional publication record information about the document.

Title
The title should be concise, omitting terms that are implicit and, where possible, be a statement of the main result or conclusion presented in the manuscript. Abbreviations should be avoided within the title.
Witty or creative titles are welcome, but only if relevant and within measure. Consider if a title meant to be thought-provoking might be misinterpreted as offensive or alarming. In extreme cases, the editorial office may veto a title and propose an alternative. Authors should avoid:

- titles that are a mere question without giving the answer
- unambitious titles, for example starting with 'Towards,' 'A description of,' 'A characterization of' or 'Preliminary study on'
- vague titles, for example starting with 'Role of', 'Link between', or 'Effect of' that do not specify the role, link, or effect
- including terms that are out of place, for example the taxonomic affiliation apart from species name.

For Corrigenda, General Commentaries, and Editorials, the title of your manuscript should have the following format:

- 'Corrigendum: Title of Original Article'
- General Commentaries: 'Commentary: Title of Original Article' 'Response: Commentary: Title of Original Article'
- 'Editorial: Title of Research Topic'

The running title should be a maximum of five words in length.

Authors and affiliations
All names are listed together and separated by commas. Provide exact and correct author names as these will be indexed in official archives. Affiliations should be keyed to the author's name with superscript numbers and be listed as follows:

- Laboratory, Institute, Department, Organization, City, State abbreviation (only for United States, Canada, and Australia), and Country (without detailed address information such as city zip codes or street names).

Example: Max Maximus1 1 Department of Excellence, International University of Science, New York, NY, United States.

Correspondence
The corresponding author(s) should be marked with an asterisk in the author list. Provide the exact contact email address of the corresponding author(s) in a separate section. Example: Max Maximus* maximus@iuscience.edu
If any authors wish to include a change of address, list the present address(es) below the correspondence details using a unique superscript symbol keyed to the author(s) in the author list.

Equal contributions
The authors who have contributed equally should be marked with a symbol (†) in the author list of the doc/latex and pdf files of the manuscript uploaded at submission.
Please use the appropriate standard statement(s) to indicate equal contributions:

- **Equal contribution:** These authors contributed equally to this work
- **First authorship**: These authors share first authorship

- **Senior authorship:** These authors share senior authorship
- **Last authorship:** These authors share last authorship
- **Equal contribution and first authorship:** These authors contributed equally to this work and share first authorship
- **Equal contribution and senior authorship:** These authors contributed equally to this work and share senior authorship
- **Equal contribution and last authorship:** These authors contributed equally to this work and share last authorship

Example: Max Maximus 1†, John Smith2† and Barbara Smith1 †These authors contributed equally to this work and share first authorship

Consortium/group and collaborative authors
Consortium/group authorship should be listed in the manuscript with the other author(s).

In cases where authorship is retained by the consortium/group, the consortium/group should be listed as an author separated by a comma or 'and'. The consortium/group name will appear in the author list, in the citation, and in the copyright. If provided, the consortium/group members will be listed in a separate section at the end of the article.

For the collaborators of the consortium/group to be indexed in PubMed, they do not have to be inserted in the Frontiers submission system individually. However, in the manuscript itself, provide a section with the name of the consortium/group as the heading followed by the list of collaborators, so they can be tagged accordingly and indexed properly.

Example: John Smith, Barbara Smith and The Collaborative Working Group. In cases where work is presented by the author(s) on behalf of a consortium/group, it should be included in the author list separated with the wording 'for' or 'on behalf of.' The consortium/group will not retain authorship and will only appear in the author list.

Example: John Smith and Barbara Smith on behalf of The Collaborative Working Group.

Abstract
As a primary goal, the abstract should make the general significance and conceptual advance of the work clearly accessible to a broad readership. The abstract should be no longer than a single paragraph and should be structured, for example, according to the IMRAD format. For the specific structure of the abstract, authors should follow the requirements of the article type or journal to which they're submitting. Minimize the use of abbreviations and do not cite references, figures or tables. For clinical trial articles, please include the unique identifier and the URL of the publicly-accessible website on which the trial is registered.

Keywords
All article types require a minimum of five and a maximum of eight keywords.

Text
The entire document should be single-spaced and must contain page and line numbers in order to facilitate the review process. The manuscript should be written using either Word or LaTeX. See above for templates.

Nomenclature
The use of abbreviations should be kept to a minimum. Non-standard abbreviations should be avoided unless they appear at least four times, and must be defined upon first use in the main text. Consider also giving a list of non-standard abbreviations at the end, immediately before the acknowledgments.

Equations should be inserted in editable format from the equation editor.

Italicize gene symbols and use the approved gene nomenclature where it is available. For human genes, please refer to the HUGO Gene Nomenclature Committee (HGNC). New symbols for human genes should be submitted to the HGNC here. Common alternative gene aliases may also be reported, but should not be used alone in place of the HGNC symbol. Nomenclature committees for other species are listed here. Protein products are not italicized.

We encourage the use of Standard International Units in all manuscripts.

Chemical compounds and biomolecules should be referred to using systematic nomenclature, preferably using the recommendations by the International Union of Pure and Applied Chemistry (IUPAC).

Astronomical objects should be referred to using the nomenclature given by the International Astronomical Union (IAU) provided here.

Life Science Identifiers (LSIDs) for ZOOBANK registered names or nomenclatural acts should be listed in the manuscript before the keywords. An LSID is represented as a uniform resource name (URN) with the following format: urn:lsid:<Authority>:<Namespace>:<ObjectID>[:<Version>]

For more information on LSIDs please see the 'Code' section of our polices and publication ethics.

Sections
The manuscript is organized by headings and subheadings. The section headings should be those appropriate for your field and the research itself. You may insert up to 5 heading levels into your manuscript (i.e.,: 3.2.2.1.2 Heading Title).

For Original Research articles, it is recommended to organize your manuscript in the following sections or their equivalents for your field.

Introduction Succinct, with no subheadings.

Materials and methods This section may be divided by subheadings and should contain sufficient detail so that when read in conjunction with cited references, all procedures can be repeated. For experiments reporting results on animal or human subject research, an ethics approval statement should be included in this section (for further information, see the 'Bioethics' section of our polices and publication ethics.)

Results This section may be divided by subheadings. Footnotes should not be used and must be transferred to the main text.

Discussion This section may be divided by subheadings. Discussions should cover the key findings of the study: discuss any prior research related to the subject to place the novelty of the discovery in the appropriate context, discuss the potential shortcomings and limitations on their interpretations, discuss their integration into the current understanding of the problem and how this advances the current views, speculate on the future direction of the research, and freely postulate theories that could be tested in the future.

For further information, please check the descriptions defined in the journal's 'Article types' page, in the 'For authors' menu on every journal page.

Acknowledgments
This is a short text to acknowledge the contributions of specific colleagues, institutions, or agencies that aided the efforts of the authors. Should the content of the manuscript have previously appeared online, such as in a thesis or preprint, this should be mentioned here, in addition to listing the source within the reference list.

Contribution to the field statement
When you submit your manuscript, you will be required to briefly summarize in 200 words your manuscript's contribution to, and position in, the existing literature in your field. This should be written avoiding any technical language or non-standard acronyms. The aim should be to convey the meaning and importance of this research to a non-expert. While Frontiers evaluates articles using objective criteria, rather than impact or novelty, your statement should frame the question(s) you have addressed in your work in the context of the current body of knowledge, providing evidence that the findings – whether positive or negative – contribute to progress in your research discipline. This will help the chief editors to determine whether your manuscript fits within the scope of a specialty as defined in its mission statement; a detailed statement will also facilitate the identification of the editors and reviewers most appropriate to evaluate your work, ultimately expediting your manuscript's initial consideration.

Example statement on: Markram K and Markram H (2010) The Intense World Theory – a unifying theory of the neurobiology of autism. Front. Hum. Neurosci. 4:224. doi: 10.3389/fnhum.2010.00224

Autism spectrum disorders are a group of neurodevelopmental disorders that affect up to 1 in 100 individuals. People with autism display an array of symptoms encompassing emotional processing, sociability, perception and memory, and present as uniquely as the individual. No theory has suggested a single underlying neuropathology to account for these diverse symptoms. The Intense World Theory, proposed here, describes a unifying pathology producing the wide spectrum of manifestations observed in autists. This theory focuses on the neocortex, fundamental for higher cognitive functions, and the limbic system, key for processing emotions and social signals. Drawing on discoveries in animal models and neuroimaging studies in individuals with autism, we propose how a combination of genetics, toxin exposure and/or environmental stress could produce hyper-reactivity and hyper-plasticity in the microcircuits involved with perception, attention, memory and emotionality. These hyper-functioning circuits will eventually come to dominate their neighbors, leading to hyper-sensitivity to incoming stimuli, over-specialization in tasks and a hyper-preference syndrome. We make the case that this theory of enhanced brain function in autism explains many of the varied past results and resolves conflicting findings and views and makes some testable experimental predictions.

Figure and table guidelines

CC-BY license

All figures, tables, and images will be published under a Creative Commons CC-BY license, and permission must be obtained for use of copyrighted material from other sources (including re-published/adapted/modified/partial figures and images from the internet). It is the responsibility of the authors to acquire the licenses, follow any citation instructions requested by third-party rights holders, and cover any supplementary charges.

For additional information, please see the 'Image manipulation' section of our polices and publication ethics.

Figure requirements and style guidelines

Frontiers requires figures to be submitted individually, in the same order as they are referred to in the manuscript; the figures will then be automatically embedded at the end of the submitted manuscript. Kindly ensure that each figure is mentioned in the text and in numerical order.

For figures with more than one panel, panels should be clearly indicated using labels (A), (B), (C), (D), etc. However, do not embed the part labels over any part of the image, these labels will be replaced during typesetting according to Frontiers' journal style. For graphs, there must be a self-explanatory label (including units) along each axis.

For LaTeX files, figures should be included in the provided PDF. In case of acceptance, our production office might require high-resolution files of the figures included in the manuscript in EPS, JPEG or TIF/TIFF format.

To upload more than one figure at a time, save the figures (labeled in order of appearance in the manuscript) in a zip file and upload them as 'Supplementary Material Presentation.'

Please note that figures not in accordance with the guidelines will cause substantial delay during the production process.

Captions

Captions should be preceded by the appropriate label, for example 'Figure 1.' Figure captions should be placed at the end of the manuscript. Figure panels are referred to by bold capital letters in brackets: (A), (B), (C), (D), etc.

Image size and resolution requirements

Figures should be prepared with the PDF layout in mind. Individual figures should not be longer than one page and with a width that corresponds to 1 column (85 mm) or 2 columns (180 mm).

All images must have a resolution of 300 dpi at final size. Check the resolution of your figure by enlarging it to 150%. If the image appears blurry, jagged, or has a stair-stepped effect, the resolution is too low.

The text should be legible and of high quality. The smallest visible text should be no less than eight points in height when viewed at actual size.

Solid lines should not be broken up. Any lines in the graphic should be no smaller than two points wide.

Please note that saving a figure directly as an image file (JPEG, TIF) can greatly affect the resolution of your image. To avoid this, one option is to export the file as PDF, then convert into TIFF or EPS using a graphics software.

Format and color image mode
The following formats are accepted: TIF/TIFF (.tif/.tiff), JPEG (.jpg), and EPS (.eps) (upon acceptance). Images must be submitted in the color mode RGB.

Chemical structures
Chemical structures should be prepared using ChemDraw or a similar program. If working with ChemDraw please use our ChemDraw template. If working with another program please follow the guidelines below.

- Drawing settings: chain angle, 120° bond spacing, 18% width; fixed length, 14.4 pt; bold width, 2.0 pt; line width, 0.6 pt; margin width, 1.6 pt; hash spacing, 2.5 pt. Scale 100% Atom Label settings: font, Arial; size, 8 pt
- Assign all chemical compounds a bold, Arabic numeral in the order in which the compounds are presented in the manuscript text.

Table requirements and style guidelines
Tables should be inserted at the end of the manuscript in an editable format. If you use a word processor, build your table in Word. If you use a LaTeX processor, build your table in LaTeX. An empty line should be left before and after the table.

Table captions must be placed immediately before the table. Captions should be preceded by the appropriate label, for example 'Table 1.' Please use only a single paragraph for the caption.

Kindly ensure that each table is mentioned in the text and in numerical order.

Please note that large tables covering several pages cannot be included in the final PDF for formatting reasons. These tables will be published as supplementary material.

Tables which are not according to the above guidelines will cause substantial delay during the production process.

Accessibility
Frontiers encourages authors to make the figures and visual elements of their articles accessible for the visually impaired. An effective use of color can help people with low visual acuity, or color blindness, understand all the content of an article.

These guidelines are easy to implement and are in accordance with the W3C Web Content Accessibility Guidelines (WCAG 2.1), the standard for web accessibility best practices.

Ensure sufficient contrast between text and its background People who have low visual acuity or color blindness could find it difficult to read text with low contrast background color. Try using colors that provide maximum contrast.

WC3 recommends the following contrast ratio levels:

- Level AA, contrast ratio of at least 4.5:1
- Level AAA, contrast ratio of at least 7:1

You can verify the contrast ratio of your palette with these online ratio checkers:

- WebAIM
- Color Safe

Avoid using red or green indicators More than 99% of color-blind people have a red-green color vision deficiency.

Avoid using only color to communicate information Elements with complex information like charts and graphs can be hard to read when only color is used to distinguish the data. Try to use other visual aspects to communicate information, such as shape, labels, and size. Incorporating patterns into the shape fills also make differences clearer; for an example, please see below:

Supplementary material
Data that are not of primary importance to the text, or which cannot be included in the article because they are too large or the current format does not permit it (such as videos, raw data traces, PowerPoint presentations, etc.), can be uploaded as supplementary material during the submission procedure and will be displayed along with the published article. All supplementary files are deposited to Figshare for permanent storage and receive a DOI.

Supplementary material is not typeset, so please ensure that all information is clearly presented without tracked changes/highlighted text/line numbers, and the appropriate caption is included in the file. To avoid discrepancies between the published article and the supplementary material, please do not add the title, author list, affiliations or correspondence in the supplementary files.

The supplementary material can be uploaded as:

- data sheet (Word, Excel, CSV, CDX, FASTA, PDF or Zip files)
- presentation (PowerPoint, PDF or Zip files)
- image (CDX, EPS, JPEG, PDF, PNG or TIF/TIFF),
- table (Word, Excel, CSV or PDF)
- audio (MP3, WAV or WMA)
- video (AVI, DIVX, FLV, MOV, MP4, MPEG, MPG or WMV).

Technical requirements for supplementary images:

- 300 DPIs
- RGB color mode.

For supplementary material templates (LaTeX and Word), see our supplementary material templates.

References
Frontiers' journals use one of two reference styles, either Harvard (author-date) or Vancouver (numbered). Please check our help center to find the correct style for the journal to which you are submitting.

- All citations in the text, figures or tables must be in the reference list and vice-versa
- The names of the first six authors followed by et al. and the DOI (when available) should be provided
- Given names of authors should be abbreviated to initials (e.g., Smith, J., Lewis, C.S., etc.)
- The reference list should only include articles that are published or accepted
- Unpublished data, submitted manuscripts, or personal communications should be cited within the text only, for article types that allow such inclusions
- For accepted but unpublished works use 'in press' instead of page numbers
- Data sets that have been deposited to an online repository should be included in the reference list. Include the version and unique identifier when available
- Personal communications should be documented by a letter of permission
- Website URLs should be included as footnotes
- Any inclusion of verbatim text must be contained in quotation marks and clearly reference the original source
- Preprints can be cited as long as a DOI or archive URL is available, and the citation clearly mentions that the contribution is a preprint. If a peer-reviewed journal publication for the same preprint exists, the official journal publication is the preferred source. See the preprints section for each reference style below for more information.

Harvard reference style (author-date)
Many Frontiers journals use the Harvard referencing system; to find the correct reference style and resources for the journal you are submitting to, please visit our help center. Reference examples are found below, for more examples of citing other documents and general questions regarding the Harvard reference style, please refer to the Chicago Manual of Style.

In-text citations

- For works by a single author, include the surname, followed by the year
- For works by two authors, include both surnames, followed by the year
- For works by more than two authors, include only the surname of the first author followed by et al., followed by the year

- For humanities and social sciences articles, include the page numbers.

Reference examples
Article in a print journal Sondheimer, N., and Lindquist, S. (2000). Rnq1: an epigenetic modifier of protein function in yeast. Mol. Cell. 5, 163-172.

Article in an online journal Tahimic, C.G.T., Wang, Y., Bikle, D.D. (2013). Anabolic effects of IGF-1 signaling on the skeleton. Front. Endocrinol. 4:6. Doi: 10.3389/fendo.2013.00006

Article or chapter in a book Sorenson, P. W., and Caprio, J. C. (1998). "Chemoreception," in The Physiology of Fishes, ed. D. H. Evans (Boca Raton, FL: CRC Press), 375-405.

Book Cowan, W. M., Jessell, T. M., and Zipursky, S. L. (1997). Molecular and Cellular Approaches to Neural Development. New York: Oxford University Press.

Abstract Hendricks, J., Applebaum, R., and Kunkel, S. (2010). A world apart? Bridging the gap between theory and applied social gerontology. Gerontologist 50, 284-293. Abstract retrieved from Abstracts in Social Gerontology database. (Accession No. 50360869)

Website World Health Organization. (2018). E. coli. https://www.who.int/news-room/fact-sheets/detail/e-coli [Accessed March 15, 2018].

Patent Marshall, S. P. (2000). Method and apparatus for eye tracking and monitoring pupil dilation to evaluate cognitive activity. U.S. Patent No 6,090,051. Washington, DC: U.S. Patent and Trademark Office.

Data Perdiguero P, Venturas M, Cervera MT, Gil L, Collada C. Data from: Massive sequencing of Ulms minor's transcriptome provides new molecular tools for a genus under the constant threat of Dutch elm disease. Dryad Digital Repository. (2015) http://dx.doi.org/10.5061/dryad.ps837

Theses and dissertations Smith, J. (2008) Post-structuralist discourse relative to phenomological pursuits in the deconstructivist arena. [dissertation/master's thesis]. [Chicago (IL)]: University of Chicago

Preprint Smith, J. (2008). Title of the document. Preprint repository name [Preprint]. Available at: https://persistent-url (Accessed March 15, 2018).

Vancouver reference style (numbered)
Many Frontiers journals use the numbered referencing system; to find the correct reference style and resources for the journal you are submitting to, please visit our help center.

Reference examples are found below, for more examples of citing other documents and general questions regarding the Vancouver reference style, please refer to Citing Medicine.

In-text citations
- Please apply the Vancouver system for in-text citations
- In-text citations should be numbered consecutively in order of appearance in the text – identified by Arabic numerals in the parenthesis (use square brackets for physics and mathematics articles).

Reference examples
Article in a print journal Sondheimer N, Lindquist S. Rnq1: an epigenetic modifier of protein function in yeast. Mol Cell (2000) 5:163-72.

Article in an online journal Tahimic CGT, Wang Y, Bikle DD. Anabolic effects of IGF-1 signaling on the skeleton. Front Endocrinol (2013) 4:6. doi: 10.3389/fendo.2013.00006

Article or chapter in a book Sorenson PW, Caprio JC. "Chemoreception". In: Evans DH, editor. The Physiology of Fishes. Boca Raton, FL: CRC Press (1998). p. 375-405.

Book Cowan WM, Jessell TM, Zipursky SL. Molecular and Cellular Approaches to Neural Development. New York: Oxford University Press (1997). 345 p.

Abstract Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, editor. Genetic Programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3–5; Kinsdale, Ireland. Berlin: Springer (2002). p. 182–91.

Website World Health Organization. E. coli (2018). https://www.who.int/news-room/fact-sheets/detail/e-coli [Accessed March 15, 2018].

Patent Pagedas AC, inventor; Ancel Surgical R&D Inc., assignee. Flexible Endoscopic Grasping and Cutting Device and Positioning Tool Assembly. United States patent US 20020103498 (2002).

Data Perdiguero P, Venturas M, Cervera MT, Gil L, Collada C. Data from: Massive sequencing of Ulms minor's transcriptome provides new molecular tools for a genus under the constant threat of Dutch elm disease. Dryad Digital Repository. (2015) http://dx.doi.org/10.5061/dryad.ps837

Theses and dissertations
Smith, J. (2008) Post-structuralist discourse relative to phenomological pursuits in the deconstructivist arena. [dissertation/master's thesis]. [Chicago (IL)]: University of Chicago

Preprint Smith, J. Title of the document. Preprint repository name [Preprint] (2008). Available at: https://persistent-url (Accessed March 15, 2018).

ANEXO 2 - Lista de verificação de avaliação crítica JBI para estudos de coorte

Question
1.Were the two groups similar and recruited from the same population?
2.Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3.Was the exposure measured in a valid and reliable way?
4.Were confounding factors identified?
5.Were strategies to deal with confounding factors stated?
6.Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7.Were the outcomes measured in a valid and reliable way?
8.Was the follow up time reported and sufficient to be long enough for outcomes to occur?
9.Was follow up complete, and if not, were the reasons to loss to follow up described and explored?
10.Were strategies to address incomplete follow up utilized?
11.Was appropriate statistical analysis used?