A.C.CAMARGO CANCER CENTER
FUNDAÇÃO ANTÔNIO PRUDENTE

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RELAÇÃO ENTRE O CONSUMO ALIMENTAR E ADENOCARCINOMA GÁSTRICO NO BRASIL

Tese de Doutorado, apresentada à Fundação Antônio Prudente como requisito para obtenção do título de Doutor em Ciências da Saúde. Área de concentração: Oncologia.
Orientador (a): Dra. Maria Paula Curado
Coorientador (a): Dra. Valdete Regina Guandalini

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"Em cada prato há histórias, culturas e escolhas —
mas também, às vezes, silenciosas ameaças.
Entender isso exige coragem, e transformar isso em
ciência é um ato de cuidado."

Autor(a) desconhecido(a)

RESUMO

Silva ARCS. **Relação entre o consumo de alimentar e adenocarcinoma gástrico no Brasil**. [Tese - Doutorado]. São Paulo: Fundação Antônio Prudente; 2025.

Introdução: O câncer gástrico (CG) é a quinta neoplasia mais incidente e a quinta principal causa de mortalidade por câncer no mundo, sendo o adenocarcinoma gástrico (AdG) responsável por aproximadamente 90% dos casos. Evidências indicam que a dieta pode influenciar de forma significativa o processo de carcinogênese gástrica, atuando como fator de risco ou proteção. No entanto, há escassez de estudos que investiguem, de forma abrangente, a relação entre o consumo alimentar e o risco de AdG na população brasileira. **Objetivo:** Analisar a associação entre o consumo alimentar — considerando o potencial inflamatório da dieta, os padrões alimentares e seus fatores mediadores — e o risco de AdG, além de realizar uma metanálise sobre a associação entre ingestão de cálcio e risco de CG. **Metodologia:** Esta tese foi estruturada em três artigos científicos. O primeiro consistiu em um estudo caso-controle de base hospitalar, conduzido em três capitais brasileiras, com o objetivo de avaliar a associação da dieta pró-inflamatória, por meio do do Índice Inflamatório da Dieta ajustado por Energia (E-IID), e o risco de AdG. O segundo, também um estudo caso-controle, foi realizado em quatro capitais, visando identificar padrões alimentares e avaliar o papel mediador de nutrientes na associação entre esses padrões e o risco de AdG. Em ambos os estudos, as informações foram obtidas por meio de questionários epidemiológicos semiestruturados e de frequência alimentar, entre 2016 e 2023. As associações foram estimadas por regressões logísticas, com Odds Ratio e intervalos de confiança de 95% (IC 95%). O terceiro artigo corresponde a uma revisão sistemática com metanálise sobre a ingestão de cálcio e o risco de CG. A busca foi realizada nas bases PubMed, Scopus, EMBASE, LILACS e Web of Science, incluindo estudos de coorte e caso-controle publicados até 19 de agosto de 2024. A qualidade metodológica foi avaliada pela Escala de Newcastle–Ottawa, e o viés de publicação pelos testes de Egger e Begg. As estimativas de risco relativo e IC 95% foram agrupadas por modelo de efeitos aleatórios, com análise adicional de dose-resposta. **Resultados:** O primeiro artigo demonstrou que dietas com maior potencial inflamatório, segundo o E-IID, estiveram

associadas a maior risco de AdG, especialmente em tumores da cárdia e do subtipo histológico difuso. O segundo identificou que padrões alimentares não saudáveis aumentaram o risco de AdG, mediado por açúcares adicionados, enquanto padrões saudáveis reduziram esse risco, com o sódio como principal nutriente mediador. A metanálise incluiu 13 estudos com 1.610.992 participantes e revelou uma associação inversa não significativa entre ingestão de cálcio e risco de CG. A análise de dose-resposta indicou redução de 10% no risco a cada 300 mg/dia de cálcio, com efeito protetor para ingestões acima de 400 mg/dia. **Conclusão:** Os achados desta tese indicam que o potencial inflamatório da dieta e os padrões alimentares estão associados ao risco de AdG e uma tendência de efeito protetor da ingestão de cálcio. Tais descobertas contribuem para o entendimento dos fatores dietéticos envolvidos na carcinogênese gástrica e reforçam a importância da alimentação como alvo estratégico de ações preventivas para CG.

Palavras-chave: Câncer gástrico. Dieta pró-inflamatória. Padrões alimentares. Análise de mediação. Ingestão de cálcio. Metanálise.

ABSTRACT

Silva ARCS. **Association between dietary intake and gastric adenocarcinoma in Brazil**. [Tese - Doutorado]. São Paulo: Fundação Antônio Prudente; 2025.

Introduction: Gastric cancer (GC) is the fifth most commonly diagnosed malignancy and the fifth leading cause of cancer-related mortality worldwide, with gastric adenocarcinoma (GA) accounting for approximately 90% of all cases. Evidence suggests that diet may significantly influence the gastric carcinogenesis process, acting as either a risk or protective factor. However, few comprehensive studies have investigated the relationship between dietary intake and the risk of GA in the Brazilian population. **Objective:** To analyze the association between dietary intake—considering the inflammatory potential of the diet, dietary patterns, and their mediating factors—and the risk of GA, as well as to conduct a meta-analysis on the association between calcium intake and GC risk. **Methods:** This thesis comprises three scientific articles. The first was a hospital-based case–control study conducted in three Brazilian capitals, aimed at evaluating the association between pro-inflammatory diets, assessed using the Energy-Adjusted Dietary Inflammatory Index (E-DII), and the risk of GA. The second, also a case–control study, was carried out in four capitals to identify dietary patterns and assess the mediating role of nutrients in the association between these patterns and GA risk. In both studies, data were collected between 2016 and 2023 using semi-structured epidemiological questionnaires and food frequency questionnaires. Associations were estimated using logistic regression models, with odds ratios and 95% confidence intervals (95% CI). The third article consists of a systematic review and meta-analysis examining calcium intake and the risk of GC. The literature search was conducted in PubMed, Scopus, EMBASE, LILACS, and Web of Science, including cohort and case–control studies published up to August 19, 2024. Methodological quality was assessed using the Newcastle–Ottawa Scale, and publication bias was evaluated using Egger's and Begg's tests. Relative risk estimates and 95% CIs were pooled using random-effects models, with an additional dose–response analysis. **Results:** The first article showed that diets with higher inflammatory potential, as indicated by the E-DII, were associated with an increased risk of GA, particularly for cardia tumors and the diffuse histological subtype. The second article

identified that unhealthy dietary patterns increased the risk of GA, mediated by added sugars, whereas healthy patterns were associated with reduced risk, with sodium acting as the main mediating nutrient. The meta-analysis included 13 studies with a total of 1,610,992 participants and revealed a non-significant inverse association between calcium intake and GC risk. Dose–response analysis indicated a 10% reduction in risk per 300 mg/day increase in calcium intake, with a protective effect observed at intakes above 400 mg/day. **Conclusion:** The findings of this thesis indicate that the inflammatory potential of the diet and dietary patterns are associated with the risk of GA and suggest a potential protective effect of calcium intake. These results contribute to a better understanding of the dietary factors involved in gastric carcinogenesis and highlight the importance of diet as a strategic target for GC prevention efforts.

Keywords: Gastric cancer. Pro-inflammatory diet. Dietary patterns. Mediation analysis. Calcium intake. Meta-analysis.

SUMÁRIO

1 INTRODUÇÃO

1.1 Panorama epidemiológico do câncer gástrico

Nas últimas décadas, as taxas de incidência e mortalidade por câncer gástrico (CG) apresentaram uma tendência de queda, refletindo avanços no diagnóstico, prevenção e controle dos fatores de risco[1]. No entanto, o CG continua sendo o quinto tipo de câncer mais incidente e a quinta principal causa de morte por câncer no mundo[1,2]. As estimativas indicam que os casos poderão crescer 62% até 2040, atingindo um total de 1,77 milhão[1]. Sua distribuição é heterogênea, com variações expressivas entre diferentes regiões geográficas e grupos populacionais, evidenciando a influência de determinantes ambientais, dietéticos e genéticos[3,4].

O CG em estágio inicial apresenta-se de forma assintomática ou manifesta sinais clínicos inespecíficos, o que contribui para o diagnóstico tardio e, consequentemente, o atraso do tratamento. Como resultado, grande parte dos casos são identificados em fases avançadas da doença, o que compromete significativamente o prognóstico[5,6]. Estima-se que a taxa de sobrevida em cinco anos ultrapasse 90% nos casos diagnosticados precocemente, mas esse índice pode cair para menos de 20% quando o CG atinge estágios intermediários ou avançados[6].

Nas Américas, há uma tendência crescente na incidência de CG, atribuída ao envelhecimento da população e ao aumento de grupos de alto risco[7]. No Brasil, estima-se que 21.480 novos casos ocorram no triênio 2023-2025, tornando o CG o quinto câncer mais frequentemente diagnosticado no país. No ano de 2021, o CG foi responsável por 14.259 mortes registradas no Brasil, representando 6,2% de todas as mortes relacionadas ao câncer e os homens correspondendo a 63% dessas mortes[8].

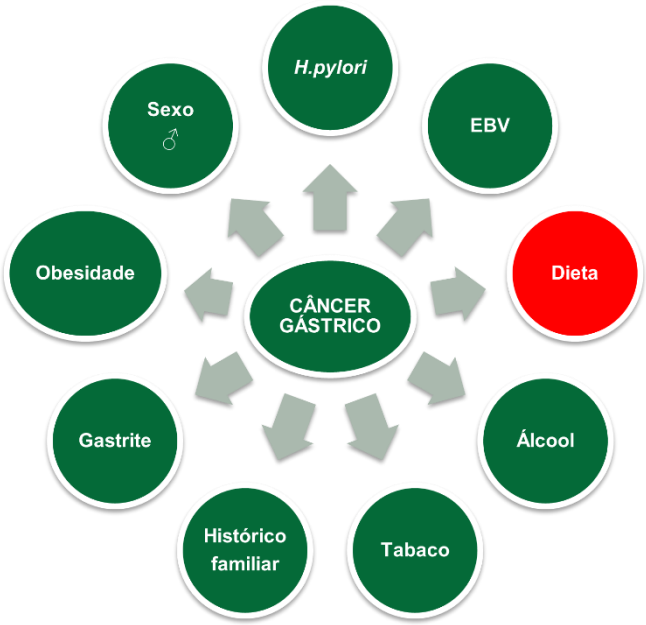
A distribuição da carga de CG no Brasil apresenta diferenças regionais. As estimativas para o triênio apontam cerca de 8.950 novos casos na região Sudeste, 5.680 no Nordeste, 1.830 no Norte e 1.430 no Centro-Oeste, evidenciando variações significativas entre as regiões. Embora o maior número absoluto de casos se concentre no Sudeste, devido à maior população, as maiores taxas ajustadas de incidência ocorrem nas regiões Norte (8,65/100 mil) e Nordeste (7,47/100 mil). Entre os homens, a Região Norte apresenta uma estimativa maior de casos entre os tumores mais incidentes, além de taxas de mortalidade proporcionalmente elevada[8].

1.2 As características e os principais fatores de risco

O tipo histológico predominante do CG é o adenocarcinoma gástrico (AdG), responsável por cerca de 90% dos casos. O AdG pode ser classificado de acordo com a localização anatômica — em regiões da cárdia ou não cárdia (fundo, corpo e piloro) — e, segundo a classificação histológica de Laurén, em subtipos difuso, intestinal ou misto[6,9–11].

Os fatores de risco para CG podem ser classificados como elementos modificáveis e não modificáveis. Os fatores de risco modificáveis incluem escolhas de estilo de vida, como dieta, tabagismo e consumo de álcool, consumo prolongado de inibidores de bomba de prótons, que podem ser alteradas para reduzir o risco[9,12]. Os fatores de risco não modificáveis incluem predisposições genéticas, histórico familiar, idade e certas condições clínicas como diabetes e gastrite[9]. Outros fatores de riscos modificáveis e não modificáveis[6,9,13] estão descritos na Figura 1.

Figura 1 – Principais fatores de risco para câncer gástrico.



Fonte: Autoria própria.

Legenda: EBV: Vírus Epstein–Barr.

A infecção por *Helicobacter pylori* (*H. pylori*) é o principal fator de risco para AdG em região não-cárdia (maior incidência), sendo classificada como um carcinógeno do Grupo I pela Agência Internacional de Pesquisa sobre o Câncer (IARC)[14,15]. Em relação a dieta, as carnes processadas (isto é, salsicha, linguiça,

bacon e presunto) também foram classificadas como carcinógeno do Grupo I pela IARC em 2015[16].

1.3 O papel da dieta na etiologia do adenocarcinoma gástrico

A dieta pode desempenhar um papel crucial no risco de AdG, podendo tanto potencializar quanto mitigar os processos inflamatórios iniciados, por exemplo, pela infecção por *H. pylori*[14,17]. O impacto da dieta no risco de AdG envolve múltiplos mecanismos, incluindo a modulação do microbiota intestinal, o estresse oxidativo e o equilíbrio energético[18–20]. A exposição prolongada a componentes dietéticos agressivos—como o consumo excessivo de sal, as carnes defumadas e processadas, os nitritos e nitratos, as dietas ricas em gorduras saturadas e açúcares refinados—pode contribuir para a inflamação da mucosa gástrica e o desenvolvimento de lesões pré-malignas a longo prazo. Por outro lado, elementos dietéticos protetores como os ácidos graxos poli-insaturados (AGPIs), as frutas, os vegetais, as fibras e os grãos integrais podem auxiliar na redução do risco de CG[21–23].

Historicamente, as pesquisas dietéticas têm se concentrado em nutrientes isolados ou grupos de alimentos; no entanto, essas abordagens não captam completamente a complexidade das interações dietéticas[24,25]. As Diretrizes Dietéticas dos Estados Unidos para 2020–2025 sugerem uma mudança para a análise dos padrões alimentares globais em vez de se concentrar apenas em componentes dietéticos individuais. Essa perspectiva reconhece que as pessoas consomem combinações de alimentos e nutrientes que, em conjunto, influenciam os resultados de saúde[26]. Estudos recentes destacam que padrões alimentares "Ocidentais/Não Saudáveis"—caracterizados por alta ingestão de carnes processadas, carboidratos refinados, gorduras e álcool—estão associados a um maior risco de AdG, enquanto padrões alimentares "Prudentes/Saudáveis"—ricos em frutas, vegetais e alimentos integrais—correlacionam-se com um risco reduzido[27,28].

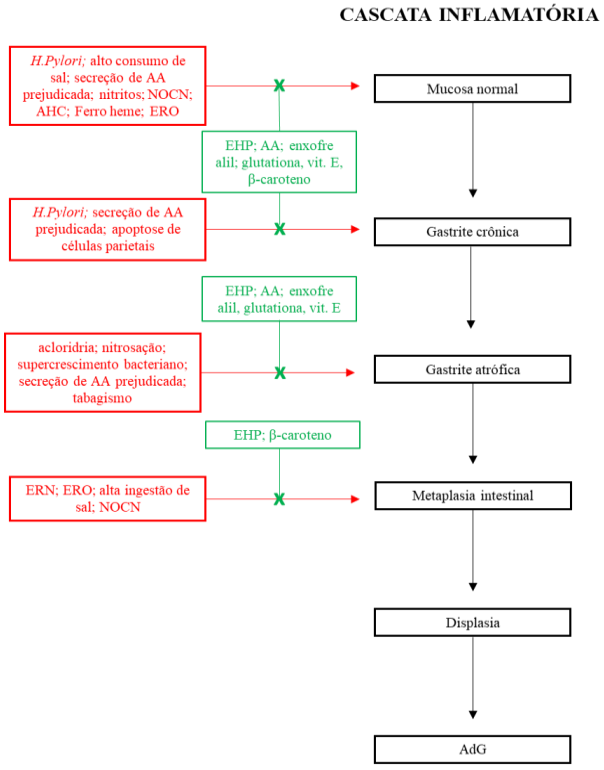
Nesse contexto, o conceito de "dieta pró-inflamatória" tem se destacado, referindo-se a padrões alimentares que promovem a liberação de mediadores pró-inflamatórios, exacerbando a inflamação crônica e aumentando potencialmente o risco de câncer[18,19,29]. A cascata inflamatória de Toh e Wilson[17] descreve como a inflamação crônica induzida por *H. pylori* ou a exposição a outros fatores de risco levam à progressão do CG. A liberação de citocinas pró-inflamatórias causa estresse oxidativo,

danos ao DNA e alterações epigenéticas, favorecendo a transição para adenocarcinoma. Fatores dietéticos e genéticos podem modular esse processo e influenciar o risco de CG (Figura 2)[17].

O Índice Inflamatório da Dieta (IID®) é uma ferramenta utilizada para quantificar o potencial inflamatório de uma dieta[18]. É composto por 45 parâmetros alimentares (isto é, macronutrientes, incluindo categorias específicas de ácidos graxos, carboidratos e proteínas; micronutrientes, incluindo vitaminas e minerais; flavonoides; e alimentos integrais, incluindo ervas e especiarias) em relação a seis biomarcadores inflamatórios—ou seja, interleucinas (IL)-1b, -4, -6, -10, fator de necrose tumoral-alfa (TNF-α) e proteína C reativa (PCR)[18].

Meta-análises estabeleceram uma ligação entre escores elevados do IID e CG em populações europeias e asiáticas, enquanto o IID ajustado por energia (E-IID™) também foi associado a vários tipos de câncer, incluindo próstata, mama e glioma[30–34].

Figura 2 – Cascata inflamatória moderna de Correa da carcinogênese gástrica do tipo intestinal.



Fonte: Adaptada de Toh e Wilson[17].

Legenda: Fatores agressores estão em vermelho; Fatores protetores estão em verde. AA: ácido ascórbico; AHC: amina heterocíclica; ERO: espécie reativa de oxigênio; EHP: erradicação do *H.pylori*;

ERN: espécie reativa de nitrogênio; NOCN: nitrosaminas e outros compostos nitrosos; AdG: adenocarcinoma gástrico.

A capacidade protetora dos micronutrientes contra o risco de câncer tornou-se relevante para pesquisa mundial. Entre os micronutrientes, destaca-se o cálcio que é um mineral essencial para a vida humana, pois mantém a arquitetura esquelética e dos tecidos, além de desempenhar papéis importantes na coagulação e no controle do comportamento celular[35].

A sinalização do cálcio nas vias de controle celular pode ser crucial para o desenvolvimento do câncer. Canais e bombas de Ca2+ são potenciais alvos terapêuticos para o tratamento do câncer[36]. Isso sugere que a ingestão dietética de cálcio pode, até certo ponto, afetar as células cancerígenas. Embora os mecanismos subjacentes a esses efeitos não sejam totalmente compreendidos, a ativação do receptor sensor de cálcio (CaSR) tem sido proposta como um fator supressor de tumor[37,38].

O relatório do *World Cancer Research Fund International* de 2025 indicou que o consumo de cálcio auxilia na proteção contra o câncer colorretal[39]; além de evidências indicarem também o efeito protetor para cânceres de pulmão, de próstata e de mama. No entanto, a associação entre o consumo de cálcio e o risco de CG é limitada e apresenta resultados inconclusivos[40].

2 JUSTIFICATIVA

Diante das evidências crescentes sobre o papel da dieta na carcinogênese gástrica, torna-se fundamental investigar padrões alimentares, seus mediadores e o papel do potencial inflamatório na relação entre dieta e AdG. Esses aspectos ainda são pouco explorados na América Latina, especialmente no Brasil, onde os hábitos alimentares variam regionalmente e diferem dos padrões observados em outros países.

Dessa forma, ampliar o conhecimento sobre essas associações, incluindo a ingestão de cálcio, não apenas contribui para o avanço científico, mas também fornece subsídios essenciais para a formulação de políticas públicas de prevenção e promoção da saúde, com potencial impacto na redução da carga da doença na população

3 OBJETIVOS

3.1 Geral

Analisar a relação entre o consumo alimentar e o risco de AdG, e o papel da ingestão de cálcio no CG.

3.2 Específicos

– Avaliar a associação entre dieta pró-inflamatória e o risco de AdG;

– Identificar padrões alimentares na população brasileira e investigar sua relação causal com o risco de AdG;

– Investigar a associação entre o consumo de cálcio e o CG por meio de revisão sistemática com metanálise.

4 MÉTODOS

A presente tese foi elaborada no formato de três artigos científicos:

- **Artigo 1:** *"Association between Dietary Inflammatory Index and Gastric Adenocarcinoma: A Multicenter Case-Control Study in Brazil"*
- **Artigo 2:** *"Exploring the link between dietary patterns and gastric adenocarcinoma in Brazil: a mediation analysis"*
- **Artigo 3:** *"Calcium intake and gastric cancer risk: A systematic review and dose–response meta-analysis of observational studies"*

4.1 Artigos 1 e 2

4.1.1 Desenho e população do estudo

O projeto "Epidemiologia e genômica dos adenocarcinomas gástricos no Brasil" sigla *GE4GAC-Brazil*, é um estudo caso-controle multicêntrico de base hospitalar, realizado em cinco capitais de diferentes regiões do Brasil[41]. Resumidamente, todos os casos diagnosticados com AdG foram confirmados por histologia e codificado de acordo com a Classificação Internacional de Doenças para Oncologia (C16). Dois grupos de controles foram utilizados: O grupo Controle I incluiu participantes com queixas gástricas que realizaram endoscopia, com diagnóstico negativo para CG ou lesão pré-maligna. O grupo Controle II foi composto por participantes hospitalares sem diagnóstico de câncer ou queixas gástricas, recrutados em clínicas não oncológicas e em Programas de Prevenção do Câncer.

Os critérios de exclusão dos participantes foram: histórico prévio de malignidade, exceto câncer de pele não melanoma; participantes com mobilidade comprometida devido a doença ou condições mentais e cognitivas que os impedissem de compreender as perguntas dos entrevistadores; e casos diagnosticados com AdG há mais de dois anos antes da entrevista ou aqueles com câncer em estágio avançado (isto é, estágio terminal sem proposta terapêutica). Adicionalmente, para ambos os estudos, os participantes que apresentaram uma ingestão energética implausível de < 500 ou > 5000 kcal por dia[42] foram excluídos.

O estudo foi aprovado pelo Comitê de Ética em Pesquisa em Seres Humanos da Fundação Antônio Prudente – A.C.Camargo Cancer Center, bem como pelos comitês de ética locais dos centros participantes, estando registrado na Plataforma Brasil, vinculada ao Conselho Nacional de Saúde do Brasil (parecer nº 4708881 –

fevereiro de 2016, registro CAAE: 53166915.9.1001.5432). Todos os participantes forneceram consentimento informado por escrito para a coleta e armazenamento de dados. O número de capitais e de participantes incluídos em cada estudo foram:

– **Artigo 1:** Este estudo utilizou um banco de dados de três capitais brasileiras com coleta de dados completa: São Paulo (SP), Belém (PA) e Goiânia (GO). O recrutamento foi conduzido de abril de 2016 a setembro de 2022. Os controles foram pareados por sexo e idade (± 5 anos, na faixa etária de 18 a 75 anos). Em Goiânia, o pareamento não foi realizado. No total, participaram 1645 participantes (492 casos, 377 controle I e 776 controle II).

– **Artigo 2:** Este estudo utilizou um banco de dados de quatro capitais brasileiras com coleta de dados completa: São Paulo (SP), Belém (PA), Goiânia (GO) e Fortaleza (CE). O recrutamento foi realizado de abril de 2016 a novembro de 2023. Em Goiânia e Fortaleza, o pareamento não foi realizado. No total, participaram 1751 participantes (600 casos, 377 controle I e 774 controle II).

4.1.2 Coleta de dados

As entrevistas presenciais foram realizadas por pessoal treinado, utilizando um questionário epidemiológico estruturado online na plataforma REDCap®. Os dados anonimados foram registrados na plataforma por centro participante. Foram coletadas informações sobre sexo (feminino ou masculino), idade (em anos), escolaridade (≤ 8 anos = analfabeto até ensino fundamental, 9 a 12 anos = ensino médio e ≥ 13 anos = ensino superior) e hábitos de vida (ou seja, consumo de álcool e tabagismo). Para calcular o consumo de álcool (g/dia), foi utilizado o método proposto por Boffetta e Garfinkel[43], e classificado como sem consumo, baixo consumo (≤ 12 g/dia) ou consumo moderado/alto (> 12 g/dia)[44]. O tabagismo foi calculado em maços/ano[45], com as classificações—sem consumo, baixo consumo (≤ 10 maços/ano) ou consumo intermediário/alto (> 10 maços/ano)[44].

Informações sobre a presença de úlcera péptica (sim ou não), dados clínicos e histórico familiar de câncer em parentes de primeiro grau (sim ou não), consumo de inibidores de bombas de prótons/antagonistas do receptor H2 (IBP/H2RA), antiácidos, aspirina, outros anti-inflamatórios não-esteroidais (AINE) e diabetes (sim ou não) também foram coletadas. Além disso, de acordo com as diretrizes da Organização Mundial da Saúde, foram aferidos o peso (kg) e a altura (m) para o cálculo do índice

de massa corporal (IMC, kg/m²) e posterior classificação do IMC (< 18,5, 18,5–24,9, 25–29,9, ≥ 30 kg/m²)[46].

Para os casos, foram coletadas informações clínicas sobre a localização anatômica (cárdia ou não cárdia), o subtipo histológico do tumor (difuso, intestinal ou misto)[11] e o *status* da infecção por *H. pylori* (positivo ou negativo) a partir dos prontuários eletrônicos, sendo que o *status* da infecção também foi coletado para os indivíduos do grupo controle I com base nos laudos da endoscopia gástrica.

4.1.3 Avaliação do consumo alimentar

Para avaliar o consumo alimentar foi utilizado um questionário de frequência alimentar (QFA) validado, contendo 130 itens alimentares[47]. O QFA foi relacionado ao consumo usual dos alimentos durante o último ano. Cada item foi coletado com base na frequência e no tamanho da porção: (1) frequência de consumo alimentar—variando de 1 a 10 vezes por dia, semanalmente, mensalmente ou anualmente e (2) tamanho da porção ingerida—pequena, média ou grande (cada alimento tinha sua porção em gramas e sua equivalência em fatias, colheres e/ou xícaras/copos). O consumo de cada item foi calculado em gramas por dia.

A ingestão de nutrientes foi determinada utilizando o *software Nutrition Data System for Research*—NDSR® versão 2021 (Minneapolis, MN, EUA). Para calcular o consumo de alimentos específicos e preparações regionais, foi utilizado a Tabela Brasileira de Composição de Alimentos (TBCA) versão 7.2, disponível em <http://www.fcf.usp.br/tbca>[48]. Os nutrientes foram ajustados pela energia utilizando o método de densidade por 1000 kcal[49].

4.2 Índice Inflamatório da Dieta (Artigo 1)

O potencial inflamatório da dieta foi calculado com base no IID®, que foi desenvolvido para quantificar o potencial inflamatório das dietas individuais em uma escala que vai do maximamente anti-inflamatório (escore mais negativo) ao maximamente pró-inflamatório (escore mais positivo). O desenvolvimento do IID foi descrito em detalhes por Shivappa et al.[18]. Resumidamente, o algoritmo de pontuação do IID foi baseado em uma revisão cuidadosa da literatura, por meio da qual 1943 artigos identificaram 45 parâmetros alimentares (ou seja, macronutrientes, incluindo categorias específicas de ácidos graxos, carboidratos e proteínas; micronutrientes,

incluindo vitaminas e minerais; flavonoides; e alimentos integrais, incluindo ervas e especiarias) em relação a seis biomarcadores inflamatórios—ou seja, interleucinas (IL)-1b, -4, -6, -10, fator de necrose tumoral-alfa (TNF-α) e proteína C reativa (PCR) (Tabela 1).

Tabela 1 – Parâmetros alimentares que compõe o IID®, pontuações do efeito inflamatório e valores de consumo do banco de dados global.

Parâmetro alimentar	Número ponderado de artigos	Pontuação bruta do efeito inflamatório	Pontuação geral do efeito inflamatório	Média global da ingestão média (unid./d)	Desvio padrão
Álcool (g)	417	-0.278	-0.278	13.98	3.72
Vitamina B12 (µg)	122	0.205	0.106	5.15	2.70
Vitamina B6 (µg)	227	-0.379	-0.365	1.47	0.74
β-Caroteno (µg)	401	-0.584	-0.584	3718	1720
Cafeina (g)	209	-0.124	-0.110	8.05	6.67
Carboidrato (g)	211	0.109	0.097	272.2	40.0
Colesterol (mg)	75	0.347	0.110	279.4	51.2
Energia (kcal)	245	0.180	0.180	2056	338
Eugenol (µg)	38	-0.868	-0.140	0.01	0.08
Gordura total (g)	443	0.298	0.298	71.4	19.4
Fibra (g)	261	-0.663	-0.663	18.8	4.9
Ácido fólico (µg)	217	-0.207	-0.190	273.0	70.7
Alho (g)	277	-0.412	-0.412	4.35	2.90
Gengibre (g)	182	-0.588	-0.453	59.0	63.2
Ferro (mg)	619	0.032	0.032	13.35	3.71
Magnésio (mg)	351	-0.484	-0.484	310.1	139.4
MUFA (g)	106	-0.019	-0.009	27.0	6.1
Niacina (mg)	58	-1.000	-0.246	25.90	11.77
Ácido graxo n-3 (g)	2588	-0.436	-0.436	1.06	1.06
Ácido graxo n-6 (g)	924	-0.159	-0.159	10.80	7.50
Cebola (g)	143	-0.490	-0.301	35.9	18.4
Proteína (g)	102	0.049	0.021	79.4	13.9
AGPIs (g)	4002	-0.337	-0.337	13.88	3.76
Riboflavina (mg)	22	-0.727	-0.068	1.70	0.79
Açafrão (g)	33	-1.000	-0.140	0.37	1.78
Gordura saturada (g)	205	0.429	0.373	28.6	8.0
Selênio (µg)	372	-0.191	-0.191	67.0	25.1
Tiamina (mg)	65	-0.354	-0.098	1.70	0.66
Gordura trans (g)	125	0.432	0.229	3.15	3.75
Cúrcuma (mg)	814	-0.785	-0.785	533.6	754.3
Vitamina A (RE)	663	-0.401	-0.401	983.9	518.6
Vitamina C (mg)	733	-0.424	-0.424	118.2	43.46
Vitamina D (µg)	996	-0.446	-0.446	6.26	2.21

Vitamina E (mg)	1495	-0.419	-0.419	8.73	1.49
Zinco (mg)	1036	-0.313	-0.313	9.84	2.19
Chá verde/preto (g)	735	-0.536	-0.536	1.69	1.53
Flavano-3-ol (mg)	521	-0.415	-0.415	95.8	85.9
Flavonas (mg)	318	-0.616	-0.616	1.55	0.07
Flavonol (mg)	887	-0.467	-0.467	17.70	6.79
Flavonoides (mg)	65	-0.908	-0.250	11.70	3.82
Antocianidinas (mg)	69	-0.449	-0.131	18.05	21.14
Isoflavonas (mg)	484	-0.593	-0.593	1.20	0.20
Pimenta (g)	78	-0.397	-0.131	10.00	7.07
Orégano/ tomilho (mg)	24	-1.000	-0.102	0.33	0.99
Alecrim (mg)	9	-0.333	-0.013	1.00	15.00

Legenda: RE: equivalente de retinol.
Fonte: Shivappa et al.[18]

Os valores dos parâmetros alimentares foram transformados em escores z utilizando um banco de dados comparativo global, composto por dados de 11 países, subtraindo a média do banco de dados global do valor autorrelatado do indivíduo e dividindo pelo desvio-padrão. Esses escores foram então convertidos em proporções (ou seja, com valores variando de 0 a 1) e centralizados em zero, dobrando cada um e subtraindo 1. Essas proporções centralizadas foram então multiplicadas pelos respectivos coeficientes (escores de efeito inflamatório específicos para cada parâmetro alimentar) para obter os escores IID para cada parâmetro alimentar. Estes foram somados para obter o escore total do IID.

Os escores IID ajustados pela energia (E-IID^{TM}) foram calculados utilizando o método de densidade, calculando o IID por 1000 kcal. Esse procedimento utilizou a mesma metodologia para pontuação, mas depende de um banco de dados global comparativo ajustado para energia[50,51].

Esses escores IID e E-IID têm um intervalo potencial de aproximadamente −9 a +8, ou seja, de minimamente a maximamente pró-inflamatório, respectivamente. O IID e o E-IID são pontuados de maneira semelhante e escalados de forma idêntica; portanto, os escores são comparáveis entre os estudos[51].

Para este estudo, 30 dos 45 parâmetros alimentares foram usados para calcular o escore geral do IID de um indivíduo, incluindo energia, carboidratos, proteínas, gorduras totais, colesterol, ácidos graxos saturados (AGS), ácidos graxos monoinsaturados (AGMIs), AGPIs, ácidos graxos *trans* (AGTs), fibras, vitaminas A, C, D, E, tiamina, riboflavina, niacina, vitamina B6, vitamina B12, magnésio, ferro, selênio,

zinco, cafeína, β-caroteno, ácido fólico, ômega-3, ômega-6, cebola e pimenta. Para o E-DII, foi utilizado o método de densidade para ajustar a ingestão total de energia para todos os componentes alimentares; portanto, 29 parâmetros foram usados para este cálculo. Nesse estudo, suplementos nutricionais não foram incluídos no cálculo do IID ou do E-IID. A decisão de usar o E-IID foi baseada na análise da adequação do modelo, realizada pelo teste de qualidade de ajuste Hosmer–Lemeshow.

Os quartis foram determinados com base nos escores E-IID dos controles (controle I e do controle II) separadamente; o quartil 1 incluiu os participantes com o menor potencial inflamatório dietético, os quartis 2 e 3 foram intermediários, e o quartil 4 incluiu os participantes com o maior potencial inflamatório dietético.

4.3 Padrões alimentares (Artigo 2)

Os 130 itens alimentares listados no QFA foram agrupados em 31 grupos alimentares com base nas semelhanças dos perfis de nutrientes e uso culinário.

Foi realizado uma análise fatorial exploratória para extrair padrões dietéticos potencialmente ligados ao AdG a partir dos 31 grupos alimentares. Inicialmente, esses dados de consumo alimentar foram registrados em gramas por dia, porém apresentaram uma distribuição assimétrica à direita e inflação de zeros. Assim, os dados foram categorizados em variáveis ordinais com quatro categorias baseadas nos tercis calculados entre os consumidores: (1) sem consumo, (2) < 1º tercil, (3) ≥ 1º e < 2º tercil, e (4) ≥ 2º tercil. Em seguida, foi realizado uma análise fatorial exploratória utilizando uma matriz de correlação policórica calculada a partir dos 31 grupos alimentares. Foi optado pela matriz de correlação policórica em vez da matriz de correlação de Pearson, pois esta última assume variáveis contínuas que seguem uma distribuição normal multivariada.

Foi avaliado a adequação da matriz de correlação policórica utilizando o teste de esfericidade de Bartlett, onde um resultado significativo indica que a matriz é adequada para a análise fatorial. Além disso, foi considerado a medida geral de adequação amostral Kaiser–Meyer–Olkin (KMO), sendo que um valor superior a 0,80 indica adequação para a análise fatorial. A solução do fator principal foi usada como método de fatoração. Para determinar o número de fatores a serem retidos, foi considerado o gráfico de declive (*scree plot graph)*, o critério do autovalor (*eigenvalue*) > 1 e a interpretabilidade dos fatores retidos.

As cargas fatoriais foram obtidas por meio da rotação varimax, e os grupos alimentares foram atribuídos aos fatores com base na sua maior contribuição. Os nomes dos fatores rotacionados foram derivados das variáveis com as correlações mais fortes. A análise fatorial foi realizada utilizando a função "*fa*" do pacote R "*psych*"

Para avaliar a associação entre os padrões alimentares e o risco de AdG, os participantes foram categorizados em quatro grupos com base nos quartis dos escores fatoriais dos controles.

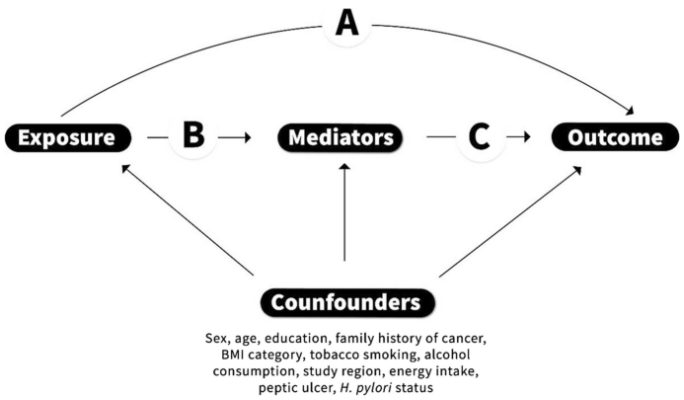
4.3.1 Análise de mediação

Para explorar o papel de nutrientes específicos dentro do padrão dietético, foi realizado uma análise de mediação para decompor o efeito total do padrão dietético em efeito direto e efeito indireto mediado por um conjunto de nutrientes previamente definidos. Este conjunto incluiu ingestões de AGS (% de kcal), açúcares adicionados (% de kcal), fibra total (g/1000 kcal) e sódio (g/1000 kcal). O consumo desses nutrientes está presente na dieta dos brasileiros, que tendem a ter uma alta ingestão de AGS, açúcares adicionados e sódio, e uma baixa ingestão de fibra[52–54]. As variáveis de exposição nesta análise foram os escores fatoriais (em valores contínuos) relacionados aos dois padrões alimentares identificados na análise fatorial.

A análise de mediação utilizou a técnica descrita por Yu e Li[55], implementada no pacote R *"mma"*. Essa técnica permite a consideração simultânea de múltiplos mediadores de diferentes tipos, possibilitando a separação dos efeitos indiretos dos mediadores individuais do efeito total.

O pacote *mma* inclui uma função para identificar mediadores, ou seja, variáveis significativamente associadas tanto ao preditor quanto ao desfecho. Variáveis que não atenderam a ambas as condições foram consideradas covariáveis. Para identificar mediadores, definimos os valores de alfa para associação em 0,1. O gráfico acíclico direcionado (DAG), que representa o modelo causal hipotético, está ilustrado na Figura 3. Modelos lineares gerais foram usados para ajustar os relacionamentos entre as variáveis e estimar os efeitos de mediação, que foram apresentados como *odds ratio* (OR) e intervalos de confiança de 95% (IC 95%). A OR para os efeitos indiretos indica o efeito dos padrões alimentares no risco de AdG transmitido pelo mediador.

Figura 3 – Gráfico acíclico direcionado: relação dos padrões alimentares com o risco de adenocarcinoma gástrico e decomposição do efeito.



Fonte: Silva et al.[56]

Legenda: A seta “A” representa o efeito direto (ED) dos padrões alimentares sobre o risco de adenocarcinoma gástrico, enquanto os caminhos “B + C” representam o efeito indireto (EI), mediado pelo sódio, açúcares adicionados, fibras e ácidos graxos saturados. A soma do ED e do EI resulta no efeito total.

A porcentagem mediada (PM) foi calculada como a razão entre o efeito indireto e o efeito total, ambos na escala logarítmica, e depois multiplicada por 100. As inferências sobre os efeitos de mediação foram realizadas utilizando o método *bootstrap* com 500 reamostragens.

Foram realizadas análises de mediação separadas utilizando o grupo controle I ou II. Para o controle I, foi empregado modelos de regressão com um conjunto completo de covariáveis, incluindo também ajustes para úlcera péptica e infecção por *H. pylori*.

4.4 Análises estatísticas

As variáveis contínuas foram expressas como mediana e percentis (P_{25}, P_{75}). As variáveis categóricas foram expressas em frequências absolutas (n) e relativas (%). O teste de Kolmogorov–Smirnov foi aplicado para verificar a normalidade das variáveis contínuas e as diferenças foram avaliadas utilizando o teste de Kruskal–Wallis com o teste *pós-hoc* de Dunn–Bonferroni. Para as variáveis categóricas, foram aplicados os testes χ^2 de Pearson ou o teste exato de Fisher.

Para associação entre E-DII e AdG, as ORs e IC 95% foram estimadas por regressão logística binária. Os modelos finais foram avaliados utilizando o teste de qualidade de ajuste Hosmer–Lemeshow. As associações entre os escores E-IID e a localização anatômica (cárdia ou não cárdia) e entre o escore E-DII e o subtipo histológico (difuso ou intestinal) foram estimadas por regressão logística multinomial. Para ambos os tipos de regressão logística, ajustes foram feitos para múltiplas variáveis em diferentes modelos.

Ao considerar os casos e os indivíduos do controle I, dois modelos foram testados: modelo 1—sexo, idade, estado civil, escolaridade, etnia autorrelatada, histórico familiar de câncer em parentes de primeiro grau, região estudada, uso de IBPs/H2RAs, antiácidos, aspirina, outros AINEs, suplementos nutricionais, classificação de IMC, tabagismo, consumo de álcool, diabetes e consumo de sódio (g/dia); modelo 2—modelo 1 + úlcera péptica e status de *H. pylori*. Ao analisar casos e indivíduos do controle II, foi selecionado o modelo 1. O quartil 1 (a dieta mais anti-inflamatória) foi utilizado como referência para ambas as análises.

O teste para tendência linear foi realizado ajustando o escore E-IID como uma variável contínua; os resultados desse modelo podem ser interpretados como o efeito nos desfechos de AdG para cada incremento de 1 ponto no escore do E-IID.

Para avaliar a associação entre padrões alimentares e AdG, também foram estimados ORs e seus respectivos IC 95% para cada grupo utilizando modelos de regressão logística binária. O grupo com o menor escore fatorial foi usado como referência. Os modelos foram ajustados para as seguintes covariáveis: sexo, idade (contínua), escolaridade, histórico familiar de câncer, categoria de IMC, tabagismo, consumo de álcool, região de estudo e ingestão de energia (contínua). Para o controle I, também foi feito ajuste para úlcera péptica e status de *H. pylori*. Além disso, realizamos testes para tendência linear, regredindo a OR no ponto médio dos limites que definem os grupos de escore fatorial.

Todos os testes foram bilaterais, e o nível de significância (α) foi de 5%. As análises foram realizadas utilizando o *software* IBM SPSS® Statistics versão 25.0 (Nova Iorque, NY, EUA) (Artigo 1) e o *software* STATA© 17.0 (College Station, TX, USA) (Artigo 2).

4.5 Revisão sistemática com metanálise (Artigo 3)

A revisão sistemática com metanálise foi conduzida de acordo com as diretrizes PRISMA[57] e recomendações da Colaboração Cochrane[58], com protocolo registrado na plataforma PROSPERO (CRD42024550664).

A busca da literatura foi realizada nas bases PubMed, Scopus, EMBASE, LILACS e *Web of Science* até agosto de 2024, sem restrições de idioma. Dois revisores independentes selecionaram os estudos e extraíram os dados de forma padronizada, resolvendo divergências por consenso.

Foram incluídos estudos observacionais (coorte e caso-controle) que avaliaram a ingestão de cálcio por meio de questionários validados e relataram ORs ou risco relativo (RR) com IC 95% para CG confirmado histologicamente. A qualidade metodológica foi avaliada pela Escala de Newcastle–Ottawa, classificando os estudos como de alta, moderada ou baixa qualidade[59,60].

As análises foram conduzidas no Stata 17.0, utilizando modelos de efeitos aleatórios para estimar as associações entre ingestão dietética, suplementar ou total de cálcio e risco de CG. As ORs ajustadas (maior *versus* menor ingestão de cálcio) foram consideradas aproximações dos RRs, e os resultados foram relatados como RRs[61].

A ordem de seleção das ORs para a meta-análise seguiu a seguinte hierarquia: cálcio total, cálcio dietético, suplementos de cálcio, ambos os sexos (masculino, feminino), ambos os subtipos histológicos (difuso, intestinal e misto) e localização anatômica (cárdia, não cárdia). Quando isso não era possível, foram selecionadas as ORs para cálcio dietético, sexo masculino, subtipo difuso e localização não cárdia, devido à maior taxa de incidência relativa[14,62,63].

A heterogeneidade foi examinada pelos testes Q de Cochran e I^2 [64], e o viés de publicação pelos testes de Begg e Egger[65,66].

Também foi realizada análise de dose-resposta linear e não linear, segundo os métodos de Greenland & Longnecker (1992)[67] e Orsini et al. (2006)[68], expressando os resultados como RRs para cada incremento de 300 mg/dia de cálcio[69].

5 DESENVOLVIMENTO

5.1 Artigo 1 – *Association between Dietary Inflammatory Index and Gastric Adenocarcinoma: A Multicenter Case-Control Study in Brazil* (publicado em *Nutrients*, 2023)

Este artigo foi publicado em acesso aberto no periódico *Nutrients* (Fator de Impacto: 5.0) no ano de 2023 [70] (Apêndice A).

nutrients MDPI

Article

Association between Dietary Inflammatory Index and Gastric Adenocarcinoma: A Multicenter Case-Control Study in Brazil

Alex Richard Costa Silva [1], Valdete Regina Guandalini [2,3], Taísa Sabrina Silva Pereira [4], Longgang Zhao [5,6], Michael D. Wirth [5,6,7], James R. Hébert [5,6], Gisele Aparecida Fernandes [1,8], Paulo Pimentel de Assumpção [9], Mônica Santiago Barbosa [10] and Maria Paula Curado [1,8,*]

DOI: https://doi.org/10.3390/nu15132867.

5.2 Artigo 2 – *Exploring the Link between Dietary Patterns and Gastric Adenocarcinoma in Brazil: A Mediation Analysis* (publicado em *BMC Medicine*, 2024)

Este artigo foi publicado em acesso aberto no periódico *BMC Medicine* (Fator de Impacto: 8.3) em 2024 [56] (Apêndice B).

Silva *et al. BMC Medicine* (2024) 22:562
https://doi.org/10.1186/s12916-024-03785-2

BMC Medicine

RESEARCH Open Access

Exploring the link between dietary patterns and gastric adenocarcinoma in Brazil: a mediation analysis

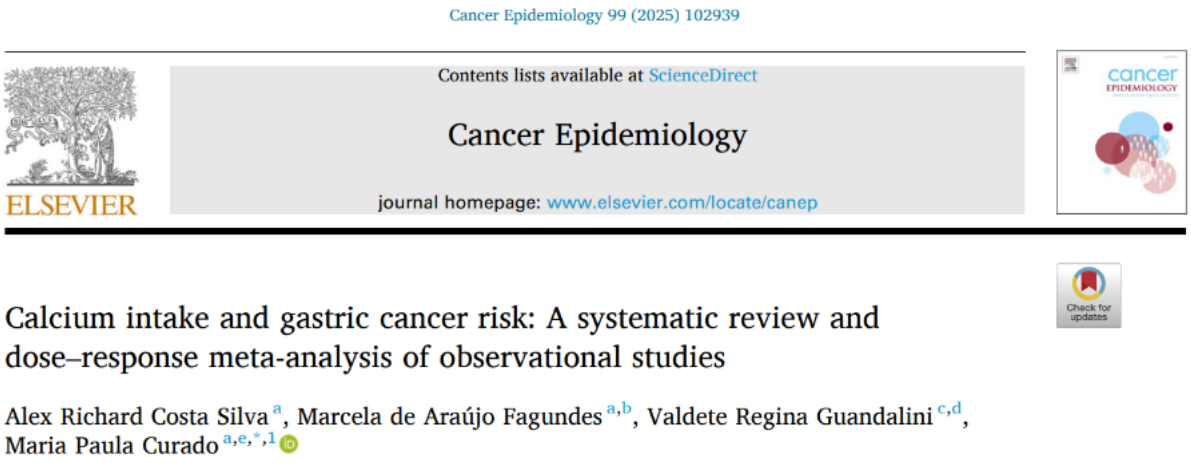
Alex Richard Costa Silva[1], Gianfranco Alicandro[2,3], Valdete Regina Guandalini[4,5], Patrícia Paula da Fonseca Grili[4], Paulo Pimentel Assumpção[6], Mônica Santiago Barbosa[7], Rosane Oliveira de Sant'Ana[8,9], Felipe José Fernández Coimbra[1,10] and Maria Paula Curado[1,11*]

DOI: https://doi.org/10.1186/s12916-024-03785-2.

Os resultados deste estudo obtiveram ampla divulgação na mídia científica e em veículos de comunicação de alcance nacional, evidenciando a relevância do tema para a saúde pública e a nutrição preventiva. As principais conclusões foram destacadas em diferentes portais e revistas, como na plataforma do Ministério da Saúde – Bibliosus, na *Veja Saúde*, na *Folha de S.Paulo*, na *Revista Galileu*, no *Cubo Jornalismo*, no *Conexão Planeta*, no *Estadão* e no *Metrópoles*. Essa ampla repercussão contribuiu para disseminar o conhecimento científico produzido e reforçar a importância das evidências sobre os efeitos do consumo excessivo de sal e açúcares adicionados na etiologia do AdG.

5.3 Artigo 3 – *Calcium Intake and Gastric Cancer Risk: A Systematic Review and Dose-Response Meta-Analysis of Observational Studies* (publicado em *Cancer Epidemiology*, 2025)

Este artigo foi publicado no periódico *Cancer Epidemiology* (Fator de Impacto: 2.3) em 2025 [71]. Em razão da publicação em acesso fechado, o manuscrito completo não foi incluso nesta tese e o resumo está disponível no Apêndice C.


Cancer Epidemiology 99 (2025) 102939

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Calcium intake and gastric cancer risk: A systematic review and dose–response meta-analysis of observational studies

Alex Richard Costa Silva [a], Marcela de Araújo Fagundes [a,b], Valdete Regina Guandalini [c,d], Maria Paula Curado [a,e,*,1]

DOI: https://doi.org/10.1016/j.canep.2025.102939.

6 CONSIDERAÇÕES FINAIS

Os resultados desta tese ressaltam a complexidade da relação entre dieta e AdG. O primeiro estudo mostrou que dietas com maior potencial inflamatório estiveram associadas a risco aumentado de AdG em diferentes regiões anatômicas e tipos histológicos. Ainda assim, o índice utilizado precisa ser aprimorado com a inclusão de nutrientes relevantes, como o sódio que desempenha um papel importante na carcinogênese gástrica, além da necessidade de aprofundar investigações sobre componentes pró e anti-inflamatórios da dieta brasileira.

O segundo estudo evidenciou que um padrão alimentar saudável, caracterizado pelo consumo de frutas e vegetais, esteve relacionado a menor risco de AdG, enquanto padrões não saudáveis, ricos em carnes processadas, bebidas adoçadas e *fast-food*, aumentaram esse risco. O sódio e os açúcares adicionados desempenharam papel mediador importante nessas associações, auxiliando a explicar parte dos mecanismos biológicos envolvidos.

O terceiro estudo indicou um possível efeito protetor do cálcio, com redução de risco observada em subgrupos específicos, como mulheres, populações asiáticas e casos de AdG não-cárdia. No entanto, a heterogeneidade entre estudos e limitações na mensuração da ingestão recomendam cautela na interpretação, reforçando a necessidade de explorar como o cálcio interage com outros fatores dietéticos e ambientais.

De maneira geral, os achados desta tese oferecem contribuições relevantes para a vigilância epidemiológica e para a formulação de políticas de saúde pública, ao identificar padrões alimentares e nutrientes associados ao risco de AdG. Essas evidências podem orientar estratégias de prevenção adaptadas à realidade brasileira, considerando a heterogeneidade alimentar e desigualdades regionais no acesso a alimentos saudáveis.

Como perspectivas futuras, destaca-se a importância de estudos longitudinais e ensaios clínicos que avaliem intervenções dietéticas capazes de modular a inflamação, reduzir o consumo de sódio e açúcares adicionados e adequação do consumo de cálcio. Pesquisas integradas que incluam microbiota, polimorfismos genéticos, marcadores inflamatórios e outros fatores ambientais poderão ampliar a compreensão da carcinogênese gástrica e subsidiar estratégias preventivas personalizadas.

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Association between Dietary Inflammatory Index and Gastric Adenocarcinoma: A Multicenter Case-Control Study in Brazil

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Abstract: Background: Few studies have evaluated the association between diet-related inflammation and gastric adenocarcinoma (GA) and evidence is scarce in Brazil. This study evaluated the association between a pro-inflammatory diet and GA. Methods: A multicenter case–control study was conducted in Brazil. A total of 1645 participants—492 cases, 377 endoscopy controls, and 776 hospital controls—were included. Energy-adjusted Dietary Inflammatory Index (E-DII^{TM}) scores were derived from a validated food frequency questionnaire. We used binary and multinomial logistic regression models for the analysis of total GA, and its subtypes (cardia and non-cardia, intestinal, and diffuse histological subtypes). Results: In cases versus endoscopy controls, a pro-inflammatory diet, estimated by higher E-DII scores, was associated with a higher risk GA (OR_{Q4vsQ1}: 2.60, 1.16–5.70), of non-cardia GA (OR: 2.90, 1.06–7.82), and diffuse subtype (OR: 3.93, 1.59–9.70). In cases versus hospital controls, higher E-DII scores were associated with a higher risk of GA (OR: 2.70, 1.60–4.54), of cardia GA (OR: 3.31, 1.32–8.24), non-cardia GA (OR: 2.97, 1.64–5.39), and both intestinal (OR: 2.82, 1.38–5.74) and diffuse GA (OR: 2.50, 1.54–5.11) subtypes. Conclusions: This study provides evidence that a pro-inflammatory diet is associated with an increased risk of GA in Brazil. E-DII requires the inclusion of sodium due to its importance in carcinogenesis.

Keywords: gastric cancer; energy-adjusted dietary inflammatory index; pro-inflammatory diet; Brazilian population; Latin American population; endoscopy; risk factor

1. Introduction

Gastric cancer (GC) was the fifth most common cancer and ranked fourth in cancer deaths throughout the globe in 2020, with estimates of 1.1 million new cases and 770,000 deaths [1]. In Brazil, the estimated incidence for the three-year period 2023–2025 is

21,480 new cases, which will make it the fifth most frequently diagnosed cancer in Brazil [2]. In 2020, there were 13,850 recorded deaths from GC in Brazil, comprising 6.1% of all cancer deaths and ranking fifth among leading causes of cancer death, of which 63% of deaths were among men [2].

The most frequent histological type of GC is gastric adenocarcinoma (GA), which accounts for 90% of all cases [3]. *Helicobacter pylori (H. pylori)* infection is the main risk factor for non-cardia GA; it accounts for 90% of cases and was identified as a Group I carcinogen by the International Agency for Research on Cancer in 1994, which reconfirmed this classification in 2009 [4,5]. Diet is an associated factor that can act by both potentiating and inhibiting the inflammatory process caused by the infection. In addition to H. pylori infection, prolonged exposure to various dietary factors that are considered aggressive to the gastric mucosa (e.g., alcohol, salt, smoked foods, processed meats, etc.) can lead to inflammation and premalignant lesions [4,6].

Diet is a key modifiable target for reducing the risk of chronic non-communicable diseases such as cancer. Thus, dietary factors remain one of the main drivers of the global burden of these diseases. Diet can affect risk through multiple mechanisms of action, including modulation of the gut microbiome, oxidative stress, and energy balance. Potential pro- or anti-inflammatory properties of dietary patterns, in addition to individual dietary components, underlie all these mechanisms [7–9]. Most studies on diet and GA have evaluated a single nutrient or a group of isolated foods, which may not reflect the full effect of diet-related inflammation associated with cancer, as individuals consume combinations of foods and nutrients. The United States (US) 2020–2025 Dietary Guidelines emphasizes the value of focusing on overall dietary patterns instead of looking exclusively at a single dietary component [10]. The concept of a "pro-inflammatory diet" has thus emerged, having been defined as foods and nutrients that can stimulate the release of pro-inflammatory mediators, contributing to or exacerbating chronic inflammation [7,8,11].

To assess the inflammatory potential of a diet, the most widely used tool is the Dietary Inflammatory Index (DII®), which was specifically designed to assess and provide quantitative information about the inflammatory potential of an individual's diet [7]. Recent meta-analyses have shown an association between DII and GA in European and Asian populations, supporting the hypothesis that pro-inflammatory diets increase the risk of GA [12,13]. The energy-adjusted DII (E-DII™), which was developed to account for differences in energy intake that could influence inflammation, also has been evaluated in different types of cancer, including prostate [14], breast [15], and glioma [16], and a more pro-inflammatory diet has been found to be associated with a higher risk of developing these cancers.

While some studies have investigated the link between the inflammatory potential of diet and GA, there are relatively few studies focusing on Latin American populations, and even fewer related to the Brazilian population. Given the mounting evidence of the role played by diet in the regulation of inflammation and carcinogenesis, there is a need for further research in this area. Therefore, the objective of this study is to investigate the association between pro-inflammatory diets and GA in a multicenter case–control study conducted in Brazil.

2. Materials and Methods

2.1. Study Population and Design

GE4GAC-Brazil is a large, hospital-based, multicenter case–control study carried out in five capitals of different Brazilian regions [17]. Briefly, all cases were diagnosed with GA, confirmed by histology and coded according to the International Classification of Diseases in Oncology (C16). Two control groups were used. Control I group included participants with gastric complaints who underwent endoscopy, with a negative diagnosis for GC or a premalignant lesion. Control II group was composed of hospital participants without a diagnosis of cancer or gastric complaints and who were recruited from non-oncology clinics and from Cancer Prevention Programs. The exclusion criteria for participants were previous

malignancy, except for non-melanoma skin cancer; participants with impaired mobility due to illness or mental and cognitive conditions that prevented them from understanding the questions asked by the interviewers; and cases that had been diagnosed with GA more than two years prior to the interview or those with advanced cancer (i.e., terminal stage with no feasible chance of survival). The study was approved by the Committee on Ethics in Human Research of Antônio Prudente Foundation—A.C. Camargo Cancer Center, as well as the local ethics committees of the study centers, under registration on the Brazil platform linked to the National Health Council of Brazil (grant nº 4708881–February 2016, registration CAAE: 53166915.9.1001.5432). All participants provided written informed consent for data collection and storage.

This study used a database from three Brazilian capitals with complete data collection, São Paulo (São Paulo state; southeastern region/metropolitan), Belém (Pará state; northern region/Amazon Rainforest), and Goiânia (Goiás state; central-western region/agrobusiness). Recruitment was conducted from April 2016 to September 2022. Controls were matched on sex and age (i.e., ±5 years in the range of 18 to 75 years). In the central-western region, pairing was not performed. All participants provided written informed consent for data collection and storage.

Participants who had an implausible energy intake of <500 and >5000 kcal per day were excluded from this study. A total of 1645 participants: 492 cases, 377 control I, and 776 control II, were included in the study (Figure 1).

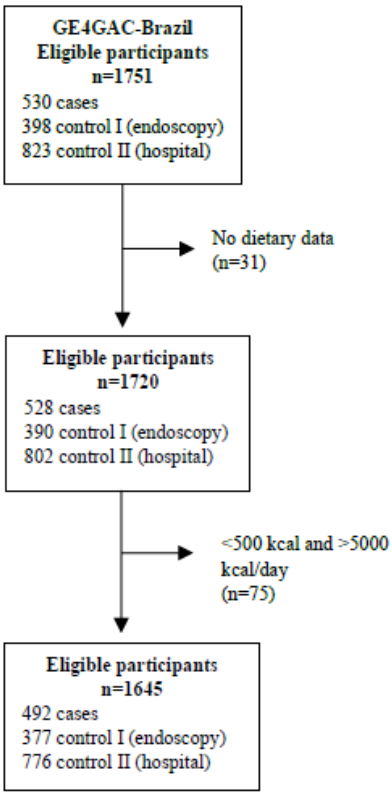

Figure 1. Flow chart of study population selection.

2.2. Data Collection

Face-to-face interviews were conducted at baseline by trained personnel using an online structured epidemiological questionnaire on the REDCap® platform. Anonymized data were recorded on the platform at participating centers. We collected data on sex, age, marital status, schooling, self-reported ethnicity, and lifestyle habits (i.e., alcohol consumption and tobacco smoking). To calculate alcohol consumption (g/day), we used a previously reported method [18,19], while tobacco smoking was calculated in packs/year [19,20]. Information was collected on the presence of comorbidities, such as peptic ulcer and diabetes

mellitus, that are associated with GA [19,21,22], and clinical data/family history of cancer in first-degree relatives. Information about the use of drugs aimed at controlling gastric acidity, treating gastroesophageal reflux, such as proton pump inhibitors (PPIs) and H2-receptor antagonists (H2Ras), antacids, aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs) were collected [23–25]. Additionally, in accordance with the guidelines of the World Health Organization (WHO), we measured weight (kg) and height (m) for the calculation of body mass index (BMI, kg/m^2), and BMI classification (underweight/malnutrition: <18.5 (adults) and <21.9 (older adults); normal weight: 18.5 - < 25 (adults) and 22–27 (older adults); overweight: 25 - < 30 and 27.1 - < 30 (older adults); or obesity: ≥30 (adults and older adults) [26,27].

For cases, clinical information on anatomical location (cardia or non-cardia), tumor histological subtype (diffuse, intestinal, or mixed) [28], and status of *H. pylori* infection (positive or negative) were collected from medical records, the latter also having been collected for control I individuals based on gastric endoscopy reports.

2.3. Dietary Assessment

An adapted food frequency questionnaire (FFQ) applied here includes >120 food items previously validated for a population with cancer [29]. Moreover, typical foods and preparations from the three Brazilian capitals in this study were added [30]. The FFQ asked about the food consumption patterns of the cases and both control groups in the prior twelve months. Each item was collected based on the frequency and portion size: (1) frequency of food consumption—ranging from 1 to 10 times daily, weekly, monthly, or yearly; and (2) size of the portion ingested—small, medium, or large (each food had its portion in grams and its equivalent in slices, spoons, and/or cups/glasses). Consumption of each item was calculated in grams per day. In addition, information on the consumption of nutritional supplements (yes/no) was collected.

Nutrient intake by cases and controls was determined using the Nutrition Data System for Research software—NDSR® version 2021 (Minneapolis, MN, USA). To calculate the consumption of specific foods and preparations for the Brazilian regions evaluated here, we used the Brazilian Food Composition Table (TBCA) version 7.2 available at <http://www.fcf.usp.br/tbca> accessed on 2 January 2023 [31].

2.4. Assessing Dietary Inflammatory Potential

The inflammatory potential of the diet was calculated based on the DII, which was developed to quantify the inflammatory potential of individuals' diets on a scale from maximally anti-inflammatory (most negative score) to maximally pro-inflammatory (most positive score). The development of the DII has been described in detail elsewhere [7]. Briefly, the DII scoring algorithm was based on a careful review of the literature through which 1943 articles identified 45 food parameters (i.e., macronutrients including specific categories of fatty acids, carbohydrate, and proteins; macronutrients including vitamins and minerals; flavonoids; and whole food items including herbs and spices) as having sufficiently robust literature in relation to six inflammatory biomarkers—i.e., interleukins (IL)-1b,-4,-6,-10, tumor-necrosis factor-alpha (TNF-α), and C-reactive protein (CRP). Self-report values for 30 of these food parameters were available from the FFQ. These were translated into z-scores using a global comparative database consisting of data from 11 countries by subtracting the mean of the global database from the individual's self-report value and then dividing by the standard deviation. These scores were then converted to proportions (i.e., with values ranging from 0 to 1) and centered on zero by doubling each and subtracting 1. These centered proportions were then multiplied by their respective coefficients (overall food parameter-specific inflammatory effect scores) to obtain DII scores for each food parameter. These were summed to obtain the overall DII score. Energy-adjusted DII (E-DII™) scores were calculated using the density approach by calculating DII per 1000 kcal consumption. This employed the same procedure for scoring but relies on an energy-adjusted global comparison database [32,33]. These DII and E-DII scores

have a potential range from approximately −9 to +8; i.e., from minimally to maximally pro-inflammatory, respectively. The DII and E-DII are scored similarly and scaled identically; so, the scores are comparable across studies [33].

For this study, 30 of the 45 food parameters were used to calculate an individual's overall DII score, including energy, carbohydrates, proteins, total fats, cholesterol, saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), polyunsaturated fatty acids (PUFAs), trans fatty acids (TFAs), fiber, vitamins A, C, D, E, thiamin, riboflavin, niacin, vitamin B6, vitamin B12, magnesium, iron, selenium, zinc, caffeine, β-carotene, folic acid, omega-3, omega-6, onion, and pepper. For the E-DII, we used a density method to adjust for total energy intake for all dietary components; so, 29 parameters were used for computation. In this study, nutritional supplements were not included in the DII or E-DII calculation. The decision to use the E-DII was based on model goodness of fit analyzed by Hosmer–Lemeshow goodness-of-fit test.

2.5. Statistical Analyses

Continuous variables were expressed as median and percentiles (P_{25}, P_{75}). Categorical variables were expressed in absolute (n) and relative (%) frequencies. The Kolmogorov–Smirnov test was applied to verify the normality of continuous variables and differences were evaluated using the Kruskal–Wallis test with Dunn–Bonferroni post hoc test. For categorical variables, the Pearson χ^2 or Fisher's Exact tests was applied. Quartiles were determined based on the E-DII scores of the controls (control I and control II) separately; quartile 1 included participants with the lowest dietary inflammatory potential, quartiles 2 and 3 are intermediate, and quartile 4 included participants with the highest dietary inflammatory potential.

The odds ratios (ORs) and respective 95% confidence intervals (CI) for the association between E-DII and GA in cases and controls were estimated by binary logistic regression. The final models were evaluated using the Hosmer–Lemeshow goodness-of-fit test. Associations between E-DII score and anatomical location (cardia or non-cardia) and E-DII score and histological subtype (diffuse or intestinal) were estimated by multinomial logistic regression. For both types of logistic regression, adjustments were made for multiple variables in different models.

When considering cases and control I individuals, two models were tested, model 1—sex, age, marital status, education, self-reported ethnicity, family history of cancer in first-degree relatives, region studied, PPIs/H2RAs, antacids, aspirin, other NSAIDs, nutritional supplement, BMI (categories), tobacco smoking, alcohol consumption, diabetes, and sodium consumption (g/day); model 2—model 1 + peptic ulcer and *H. pylori* status. When analyzing cases and control II individuals, model 1 was selected. Quartile 1 (the most anti-inflammatory diet) was used as a reference for both analyses.

The test for the linear trend was conducted by fitting the E-DII score as a continuous variable; the results from that model can be interpreted as the effect on GA outcomes for each 1-point-increment in E-DII score.

All tests were two-sided, and the significance level (α) was 5%. Analyses were performed using the software IBM SPSS® Statistics version 25.0 (New York, NY, USA).

3. Results

When compared with the two control groups, the cases group comprised mostly males (59.6%), individuals with a median age of 58 years, self-declared brown skin (50.6%), and with schooling ≤ 8 years (47.2%). About 61.6% of the cases had a family history of cancer in first-degree relatives, 43.1% showed intermediate/high tobacco smoking, and 37.4% reported intermediate/high alcohol consumption. In addition, 9.1% had diabetes, 8.3% peptic ulcer disease, and 22.6% had tested positive for *H. pylori* infection. In terms of drug use, 45.8% of cases consumed PPIs/H2RAs, 14.9% antacids, and 11.4% other NSAIDs; about 30% were overweight or obese. The cases had a median energy intake of 2193 kcal and sodium intake of 2.2 g/day, and values were higher than those in the control

groups ($p < 0.001$). Most (77.7%) cases had GA located in the non-cardia region and 50.1% were classified as diffuse type. The overall E-DII score in this study ranged from −5.55 (maximum anti-inflammatory score) to +4.60 (maximum pro-inflammatory score). The cases group had higher median score (−0.45) when compared with both controls (−0.73 for control I and −0.83 for control II) ($p < 0.001$) (Table 1).

Table 1. Sociodemographic, clinical, and nutritional characteristics of cases and controls, GE4GAC-Brazil (2016–2022).

Variables	GE4GAC-Brazil (*n* = 1645)			*p*-Value [1]
	Cases (*n* = 492)	Control I (*n* = 377)	Control II (*n* = 776)	
	Median (P_{25}, P_{75}) or *n* (%)			
Sex				0.002
Female	199 (40.4)	182 (48.3)	398 (51.3)	
Male	293 (59.6)	195 (51.7)	378 (48.7)	
Age (years)	58 (49, 65) [a]	57 (44, 64) [b]	55 (44, 64) [b]	0.001
Self-reported ethnicity				
White	181 (36.8)	180 (47.7)	287 (37.0)	<0.001
Brown	249 (50.6)	134 (35.5)	320 (41.3)	
Black	44 (8.9)	43 (11.4)	110 (14.2)	
Others	18 (3.7)	20 (5.3)	58 (7.5)	
Schooling (years) †				<0.001
≤8	232 (47.2)	96 (25.5)	172 (22.2)	
9–12	159 (32.3)	163 (43.2)	412 (53.1)	
≥13	101 (20.5)	118 (31.3)	192 (24.7)	
Marital status				0.13
Married	353 (71.7)	247 (65.5)	523 (67.4)	
Single	71 (14.4)	66 (17.5)	147 (18.9)	
Others	68 (13.8)	64 (17.0)	106 (13.7)	
Family history of cancer in first-degree relatives				<0.001
No	188 (38.4)	159 (42.3)	391 (50.5)	
Yes	302 (61.6)	217 (57.7)	383 (49.5)	
Tobacco smoking §				<0.001
No	198 (40.5)	227 (60.5)	495 (64.1)	
Low	80 (16.4)	67 (17.9)	106 (13.7)	
Intermediate/High	211 (43.1)	81 (21.6)	171 (22.2)	
Alcohol consumption ¥				<0.001
No	230 (47.2)	180 (48.5)	508 (66.7)	
Low	75 (15.4)	55 (14.8)	64 (8.4)	
Intermediate/High	182 (37.4)	136 (36.7)	190 (24.9)	
Diabetes				0.003
No	447 (90.9)	327 (86.7)	721 (92.9)	
Yes	45 (9.1)	50 (13.3)	55 (7.1)	
Peptic ulcer				0.04
No	451 (91.7)	359 (95.2)	-	
Yes	41 (8.3)	18 (4.3)	-	
H. pylori status *				0.04
Negative	230 (77.4)	226 (70.0)	-	
Positive	67 (22.6)	97 (30.0)	-	
PPIs/H2RAs				<0.001
No	265 (54.2)	215 (57.2)	681 (88.0)	
Yes	224 (45.8)	161 (42.8)	93 (12.0)	
Antacids				<0.001
No	418 (85.1)	329 (87.5)	755 (97.4)	
Yes	73 (14.9)	47 (12.5)	20 (2.6)	
Aspirin				0.33
No	462 (94.1)	351 (93.4)	739 (95.4)	
Yes	29 (5.9)	25 (6.6)	36 (4.6)	

Table 1. *Cont.*

Variables	GE4GAC-Brazil (*n* = 1645)			*p*-Value [1]
	Cases (*n* = 492)	Control I (*n* = 377)	Control II (*n* = 776)	
	Median (P_{25}, P_{75}) or *n* (%)			
Other NSAIDs				<0.001
No	435 (88.6)	331 (88.0)	736 (95.0)	
Yes	56 (11.4)	45 (12.0)	39 (5.0)	
BMI (categories)				<0.001
Normal weight	208 (42.3)	148 (39.4)	322 (41.5)	
Underweight/Malnutrition	138 (28.0)	24 (6.4)	88 (11.4)	
Overweight	78 (15.9)	118 (31.4)	222 (28.6)	
Obesity	68 (13.8)	86 (22.9)	143 (18.5)	
Energy intake (kcal/day)	2193 (1664, 2824) [a]	2087 (1503, 2653) [a]	1792 (1352, 2391) [b]	<0.001
Sodium intake (g/day)	2.2 (1.7, 5.5) [a]	1.7 (1.5, 2.0) [c]	1.8 (1.5, 2.5) [b]	<0.001
Nutritional supplement				0.07
No	408 (83.1)	308 (81.7)	671 (86.5)	
Yes	83 (16.9)	69 (18.3)	105 (13.5)	
Anatomical location				-
Cardia	101 (22.3)	-	-	
Non-cardia	352 (77.7)	-	-	
Histological subtype				-
Diffuse	203 (50.1)	-	-	
Intestinal	174 (43.0)	-	-	
Mixed	28 (6.9)	-	-	
E-DII score	−0.45 (−1.46, 0.53) [b]	−0.73 (−2.00, 0.56) [a]	−0.83 (−2.03, 0.25) [a]	<0.001

Numbers may differ because of missing values. Control I individuals (endoscopy); Control II individuals (hospital). PPIs/H2RAs: proton pump inhibitors/H2-receptor antagonists; NSAIDs: non-steroidal anti-inflammatory drugs; BMI: body mass index; E-DII: energy-adjusted dietary inflammatory index. † ≤8 years = Illiterate to elementary school, 9 to 12 years = High school and ≥ 13 years = Higher education. § Low smoking: ≤ 10 packs/year and Intermediate/High smoking: >10 packs/year. ¥ Low: ≤12 g/day and Moderate/High: >12 g/day alcohol. * 195 cases and 54 control I individuals were not tested. [1] Pearson χ^2 test for categorical variables and Kruskal–Wallis test and Dunn–Bonferroni post hoc test for continuous variables. Different letters on the same line mean statistical difference between groups. Significance *p*-value < 0.05.

Cases in the highest quartile of the E-DII (Q4) were predominantly male (65.9%), younger (median age 56 years), declared themselves to be brown (49.6%), had diabetes (4.1%), and consumed aspirin (4.1%). These individuals had a higher sodium intake (median 6.2 g/day) when compared with lowest quartile (Q1) ($p < 0.001$). Control I participants in the Q4 were younger (median age 48 years), married (58.5%), had 9 to 12 years of schooling (44.7%), and a family history of cancer in first-degree relatives (58.5%). In addition, 40.4% had intermediate/high consumption of alcoholic beverages and 10.4% consumed nutritional supplements. These individuals had a higher energy (median 2328 kcal) and sodium (median of 1.8 g/day) intake when compared with Q1 ($p < 0.001$). Control II participants in Q4 were mostly male (58.8%), also younger (median 49 years), and 44.8% declared themselves to be brown. Moreover, 10.8% consumed PPIs/H2RAs, 3.1% antacids, 1.5% aspirin, and 8.8% nutritional supplements. Control II participants from Q4 also showed a higher sodium intake (median 4.8 g/day) when compared with Q1 ($p < 0.001$) (Table S1 from the Supplementary Material).

Compared with both control groups, cases had a higher consumption of protein, SFAs and TFAs, cholesterol, vitamins B12 and D, selenium, and zinc; however, these individuals consumed less iron, omega-6, vitamins A, B1, B6, E, β-carotene, folic acid, fiber, magnesium, caffeine, and onion. The highest scores observed in the control I and control II quartiles indicated a more pro-inflammatory diet, with a lower intake of carbohydrates, iron, omega-3, vitamins A, B1, B2, B6, C, D, E, β-carotene, folic acid, fiber, magnesium, selenium, onion, and pepper. Q4 participants from both control groups consumed more pro-inflammatory compounds than anti-inflammatory ones compared to Q1 (Table 2).

Table 2. Dietary intake of the participants, GE4GAC-Brazil (2016–2022).

Components	Cases (n = 492)	Control I (n = 377)	Control II (n = 776)	p-Value [1]	E-DII Quartiles §									
					Control I					Control II				
					Q1 n = 94 (−5.55, −2.01)	Q2 n = 94 (−2.00, −0.74)	Q3 n = 95 (−0.73, 0.56)	Q4 n = 94 (>0.56)	p-Value [1] ‡	Q1 n = 194 (−5.09, −2.04)	Q2 n = 194 (−2.03, −0.83)	Q3 n = 194 (−0.82, 0.25)	Q4 n = 194 (>0.25)	p-Value [1] ‡
	Median (P_{25}, P_{75})				Median (P_{25}, P_{75})					Median (P_{25}, P_{75})				
Pro-inflammatory														
Carbohydrates (g/day)	119.7 (104.8, 133.4)	122.1 (107.8, 136.5)	121.5 (106.5, 136.4)	0.23	131.8 (118.4, 147.3) [bc]	122.8, 113.6, 135.7) [e]	118.2 (105.8, 134.0)	112.7 (97.0, 126.1)	<0.001	130.4 (115.6, 147.2) [bc]	126.0 (112.7, 141.1) [de]	115.5 (101.7, 130.0)	111.7 (96.0, 125.4)	<0.001
Proteins (g/day)	43.7 (38.9, 49.5) [a]	41.5 (37.5, 47.1) [b]	43.0 (37.5, 48.7) [a]	<0.001	40.7 (36.3, 45.5)	42.0 (36.2, 46.8)	40.2 (36.7, 46.6)	43.0 (36.4, 49.5)	0.45	42.6 (36.7, 43.4) [bc]	41.7 (36.1, 46.9) [de]	44.0 (39.1, 51.1)	44.1 (38.1, 51.1)	<0.001
Total fats (g/day)	39.9 (35.1, 44.4)	40.4 (35.4, 44.8)	39.8 (34.7, 44.5)	0.54	36.9 (32.6, 43.5) [c]	39.4 (35.3, 43.2) [e]	41.4 (36.7, 45.0)	42.7 (39.3, 46.8)	<0.001	38.5 (33.4, 43.3) [c]	38.6 (33.6, 43.0) [e]	40.6 (35.3, 44.8)	41.5 (38.0, 46.3)	<0.001
SFAs (g/day)	12.7 (11.0, 14.2) [a]	12.2 (10.3, 14.3) [ab]	12.2 (10.5, 14.2) [bc]	0.03	10.8 (9.0, 12.6) [bc]	11.6 (9.9, 13.4) [e]	12.6 (10.8, 14.3) [f]	14.3 (12.5, 15.3)	<0.001	10.9 (9.7, 12.7) [bc]	11.7 (10.1, 13.5) [de]	12.7 (10.9, 14.4) [f]	13.8 (11.7, 15.3)	<0.001
TFAs (g/day)	0.9 (0.7, 1.1) [ab]	0.9 (0.7, 1.2) [ab]	0.8 (0.6, 1.1) [c]	0.001	0.6 (0.5, 0.9) [bc]	0.9 (0.6, 1.1) [e]	1.0 (0.8, 1.2) [f]	1.2 (0.9, 1.4)	<0.001	0.7 (0.5, 0.9) [bc]	0.8 (0.6, 0.9) [de]	0.9 (0.7, 1.1)	1.0 (0.8, 1.2)	<0.001
Cholesterol (mg/day)	153.2 (119.6, 196.8) [a]	131.1 (102.0, 166.0) [c]	144.5 (110.2, 187.0) [b]	<0.001	115.4 (96.0, 163.5) [c]	128.2 (96.4, 155.5)	135.6 (108.4, 161.0)	143.6 (118.0, 178.3)	0.01	128.6 (99.0, 175.0) [bc]	130.6 (102.2, 170.7) [de]	152.6 (115.6, 198.0)	159.2 (125.0, 199.7)	<0.001
Iron (mg/day)	6.2 (5.6, 7.0) [b]	6.5 (5.7, 7.4) [a]	6.4 (5.6, 7.2) [ab]	0.03	6.5 (5.8, 7.3)	6.7 (5.8, 7.5) [e]	6.9 (6.0, 7.6) [f]	6.1 (5.6, 6.7)	0.001	7.0 (5.9, 7.8) [abc]	6.4 (5.6, 7.3) [e]	6.3 (5.6, 6.9)	6.0 (5.3, 6.7)	<0.001
Vitamin B12 (mg/day)	1.9 (1.5, 2.3) [a]	1.7 (1.3, 2.0) [c]	1.8 (1.4, 2.3) [b]	<0.001	1.5 (1.2, 1.9) [c]	1.7 (1.2, 1.9) [e]	1.7 (1.4, 2.1)	1.8 (1.5, 2.4)	<0.001	1.6 (1.2, 2.0) [bc]	1.7 (1.3, 2.1) [de]	1.8 (1.5, 2.3)	2.0 (1.6, 2.5)	<0.001
Anti-inflammatory														
Omega-3 (g/day)	1.2 (1.1, 1.5)	1.2 (1.0, 1.5)	1.3 (1.1, 1.5)	0.14	1.4 (1.1, 1.6) [bc]	1.2 (1.1, 1.4)	1.2 (1.0, 1.4) [f]	1.1 (0.9, 1.3)	<0.001	1.3 (1.1, 1.6) [bc]	1.2 (1.1, 1.5)	1.2 (1.0, 1.4)	1.2 (1.0, 1.4)	0.001
Omega-6 (g/day)	7.8 (6.6, 9.1) [b]	8.1 (7.0, 9.5) [a]	8.0 (6.8, 9.5) [b]	0.01	8.2 (7.0, 9.5)	8.2 (7.0, 9.3)	8.1 (7.1, 9.4)	8.0 (6.4, 9.6)	0.76	8.4 (6.9, 9.9)	8.0 (6.8, 9.6)	8.0 (6.7, 9.3)	7.8 (6.5, 9.1)	0.076
MUFAs (g/day)	13.4 (11.6, 15.1)	13.7 (11.6, 15.8)	13.5 (11.4, 15.4)	0.21	12.7 (10.7, 16.2) [c]	13.3 (11.4, 15.0) [e]	13.7 (11.7, 15.4)	14.6 (13.1, 16.4)	0.003	13.4 (11.2, 15.3)	13.1 (11.0, 14.8) [e]	13.6 (11.5, 15.4)	14.3 (12.2, 15.8)	0.008
Vitamin A (RE/day)	258.1 (195.7, 348.5) [c]	322.4 (234.1, 432.1) [a]	280.1 (209.8, 387.0) [b]	<0.001	374.4 (272.3, 577.3) [c]	336.3 (231.1, 502.7) [e]	327.2 (258.3, 418.0) [f]	245.1 (190.6, 348.6)	<0.001	384.7 (294.9, 560.7) [abc]	284.0 (211.7, 373.1) [de]	246.0 (186.0, 340.2)	238.2 (180.1, 318.6)	<0.001

Table 2. *Cont.*

Components	Cases (n = 492)	Control I (n = 377)	Control II (n = 776)	p-Value [1]	E-DII Quartiles §									
					Control I					Control II				
					Q1 n = 94 (−5.55, −2.01)	Q2 n = 94 (−2.00, −0.74)	Q3 n = 95 (−0.73, 0.56)	Q4 n = 94 (>0.56)	p-Value [1] ‡	Q1 n = 194 (−5.09, −2.04)	Q2 n = 194 (−2.03, −0.83)	Q3 n = 194 (−0.82, 0.25)	Q4 n = 194 (>0.25)	p-Value [1] ‡
	Median (P_{25}, P_{75})				Median (P_{25}, P_{75})					Median (P_{25}, P_{75})				
β-carotene (µg/day)	982.7 (610.2, 1476.3) [b]	1257.6 (809.7, 1833.0) [a]	1144.3 (700.5, 1786.6) [a]	<0.001	2005.6 (1581, 2820.0) [abc]	1437.2 (1011.3, 1931.0) [de]	1082.5 (817.7, 1454.1) [f]	714.8 (489.0, 1038.6)	<0.001	2205.6 (1578.3, 3041.6) [abc]	1245.8 (862.7, 1646.5) [de]	922.0 (567.6, 1251.1)	745.4 (544.3, 1093.6)	<0.001
Vitamin B1 (mg/day)	0.7 (0.6, 0.8) [b]	0.8 (0.7, 0.9) [a]	0.7 (0.6, 0.8) [ab]	0.003	0.8 (0.7, 0.9) [bc]	0.8 (0.7, 0.9) [e]	0.8 (0.7, 0.8) [f]	0.7 (0.6, 0.8)	<0.001	0.8 (0.7, 0.9) [abc]	0.8 (0.7, 0.9) [de]	0.7 (0.6, 0.8)	0.7 (0.6, 0.8)	<0.001
Vitamin B2 (mg/day)	0.7 (0.6, 0.8)	0.7 (0.6, 0.8)	0.7 (0.6, 0.8)	0.38	0.8 (0.7, 0.9) [bc]	0.7 (0.6, 0.8)	0.7 (0.6, 0.8)	0.7 (0.6, 0.8)	<0.001	0.8 (0.7, 0.9) [abc]	0.7 (0.6, 0.8)	0.7 (0.6, 0.8)	0.7 (0.6, 0.8)	<0.001
Niacin (mg/day)	10.0 (8.6, 11.4)	9.8 (8.3, 11.2)	9.8 (8.4, 11.4)	0.13	9.6 (8.2, 11.2)	9.8 (8.3, 11.4)	9.3 (8.3, 11.1)	10.0 (8.6, 11.7)	0.39	9.5 (7.9, 10.6) [bc]	9.4 (7.9, 10.6) [de]	10.4 (9.1, 12.1)	10.3 (8.5, 11.9)	<0.001
Vitamin B6 (mg/day)	1.0 (0.9, 1.2) [a]	1.0 (0.8, 1.2) [b]	1.0 (0.9, 1.2) [a]	0.002	1.1 (1.0, 1.3) [abc]	1.0 (0.9, 1.1)	0.9 (0.8, 1.1)	0.9 (0.7, 1.0)	<0.001	1.1 (1.0, 1.2) [abc]	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)	1.0 (0.9, 1.1)	<0.001
PUFAs (g/day)	9.3 (8.2, 11.0)	9.8 (8.3, 11.4)	9.7 (8.2, 11.3)	0.06	9.8 (8.3, 11.5)	9.8 (8.4, 11.2)	9.8 (8.4, 11.1)	9.6 (7.9, 11.2)	0.67	10.2 (8.4, 11.9)	9.7 (8.3, 11.5)	9.6 (8.1, 11.0)	9.5 (8.1, 10.8)	0.090
Folic acid (µg/day)	214.5 (184.8, 256.3) [c]	235.7 (202.0, 274.5) [a]	227.0 (190.5, 266.2) [b]	<0.001	267.5 (224.8, 306.7) [bc]	247.5 (219.0, 285.7) [e]	236.7 (209.7, 267.3) [f]	196.0 (172.7, 223.8)	<0.001	256.2 (229.1, 302.5) [abc]	239.8 (208.6, 279.2) [de]	216.3 (186.1, 249.0) [f]	193.8 (169.8, 224.8)	<0.001
Vitamin C (mg/day)	57.3 (33.6, 83.5)	54.8 (34.0, 94.4)	59.0 (36.7, 93.1)	0.11	111.1 (87.8, 150.0) [abc]	69.0 (51.3, 95.7) [de]	45.6 (30.7. 58.5) [f]	32.1 (23.2, 42.2)	<0.001	106.5 (74.4, 145.3) [abc]	70.7 (49.6, 99.9) [de]	46.4 (31.5, 62.8)	38.2 (25.7, 53.4)	<0.001
Vitamin D (µg/day)	3.0 (2.0, 4.3) [a]	2.0 (1.4, 2.9) [c]	2.6 (1.7, 3.8) [b]	<0.001	2.6 (1.8, 3.3) [bc]	2.1 (1.4, 3.0)	1.8 (1.3, 2.7)	1.8 (1.4, 2.3)	<0.001	2.8 (1.8, 3.8)	2.4 (1.6, 3.4)	2.6 (1.5, 3.7)	2.6 (1.8, 4.2)	0.092
Vitamin E (mg/day)	3.2 (2.8, 3.7) [b]	3.6 (3.1, 4.3) [a]	3.5 (2.9, 4.2) [a]	<0.001	4.6 (4.0, 5.2) [abc]	3.6 (3.3, 4.3) [de]	3.3 (3.0, 3.7) [f]	3.0 (2.6, 3.5)	<0.001	4.3 (3.9, 5.0) [abc]	3.6 (3.1, 4.3) [de]	3.1 (2.8, 3.6)	3.0 (2.6, 3.4)	<0.001
Fibers (g/day)	10.5 (8.3, 13.3) [b]	11.8 (9.4, 14.8) [a]	11.4 (8.6, 14.5) [a]	<0.001	16.0 (14.2, 19.1) [abc]	13.1 (11.5, 15.2) [de]	10.8 (9.5, 12.7) [f]	8.3 (7.1, 9.7)	<0.001	16.1 (13.3, 20.3) [abc]	12.8 (10.9, 15.0) [de]	10.1 (8.2, 11.6) [f]	8.2 (7.0, 10.0)	<0.001
Magnesium (g/day)	133.7 (119.8, 156.6) c	139.5 (121.0, 163.3) abc	141.0 (122.4, 165.5) ab	0.01	175.8 (157.0, 200.2) [abc]	146.4 (133.2, 163.3) [de]	131.5 (122.8, 143.3) [f]	114.4 (102.7, 123.3)	<0.001	175.7 (152.9, 218.4) [abc]	152.8 (133.1, 167.2) [de]	129.8 (118.1, 141.8)	121.0 (109.6, 134.2)	<0.001
Selenium (g/day)	62.1 (54.2, 75.0) [a]	58.8 (51.4, 71.2) [c]	61.8 (52.8, 75.2) [ab]	0.003	59.0 (50.8, 75.4)	58.4 (51.5, 68.0)	58.3 (52.4, 72.4)	60.3 (51.3, 70.2)	0.79	66.2 (54.1, 78.9) [c]	59.8 (50.5, 73.0)	62.6 (53.7, 72.7)	61.1 (53.1, 71.1)	0.018
Zinc (mg/day)	6.5 (5.7, 7.4) [a]	6.3 (5.4, 7.2) [ab]	6.3 (5.5, 7.2) [b]	0.03	6.0 (5.3, 6.9)	6.5 (5.4, 7.3)	6.5 (5.8, 7.2)	6.4 (5.7, 7.5)	0.13	6.2 (5.3, 6.8) [bc]	6.1 (5.3, 7.3) [e]	6.5 (5.8, 7.4)	6.6 (5.7, 7.4)	0.001
Caffeine (mg/day)	0.6 (0.1, 2.7) [b]	2.0 (0.4, 23.0) [a]	0.6 (0.9, 3.3) [b]	<0.001	0.4 (0.0, 1.6) [abc]	1.5 (0.2, 22.8) [e]	7.8 (0.8, 28.0)	14.5 (1.4, 31.0)	<0.001	0.5 (0.5, 1.7)	0.7 (0.2, 2.9)	0.6 (0.1, 4.9)	0.8 (0.0, 5.3)	0.470

Table 2. *Cont.*

Components	Cases (n = 492)	Control I (n = 377)	Control II (n = 776)	p-Value [1]	E-DII Quartiles §									
					Control I					Control II				
					Q1 n = 94 (−5.55, −2.01)	Q2 n = 94 (−2.00, −0.74)	Q3 n = 95 (−0.73, 0.56)	Q4 n = 94 (>0.56)	p-Value [1] ‡	Q1 n = 194 (−5.09, −2.04)	Q2 n = 194 (−2.03, −0.83)	Q3 n = 194 (−0.82, 0.25)	Q4 n = 194 (>0.25)	p-Value [1] ‡
	Median (P_{25}, P_{75})				Median (P_{25}, P_{75})					Median (P_{25}, P_{75})				
Onion (g/day)	2.5 (0.0, 6.1) [c]	3.9 (1.6, 8.4) [a]	3.5 (0.6, 6.5) [b]	<0.001	5.7 (2.1, 12.0) [c]	4.5 (1.2, 9.3)	4.0 (1.8, 8.4)	2.9 (1.2, 5.1)	0.001	5.1 (2.1, 9.4) [bc]	4.0 (1.8, 6.4) [de]	2.7 (0.0, 5.6)	2.2 (0.0, 5.0)	<0.001
Pepper (g/day)	0.0 (0.0, 0.8)	0.0 (0.0, 0.4)	0.0 (0.0, 0.7)	0.21	0.0 (0.0, 0.0)	0.0 (0.0, 0.5)	0.0 (0.0, 0.8)	0.0 (0.0, 0.5)	0.15	0.0 (0.0, 0.6)	0.0 (0.0, 0.2) [d]	0.0 (0.0, 0.8)	0.0 (0.0, 0.9)	0.016

Control I individuals (endoscopy); Control II individuals (hospital). § Based on control I and control II scores. SFAs: saturated fatty acids; TFAs: trans fatty acids; MUFAs: monounsaturated fatty acids; PUFAs: polyunsaturated fatty acids. [1] Kruskal–Wallis test and Dunn–Bonferroni post hoc test. Significance p-value < 0.05. ‡ Difference between quartiles: [a] Quartiles 1 × 10^2; [b] Quartiles 1 × 10^3; [c] Quartiles 1 × 10^4; [d] Quartiles 2 × 10^3; [e] Quartiles 2 × 10^4; [f] Quartiles 3 × 10^4.

When comparing cases and control I individuals, we observed that a more pro-inflammatory diet was 2.6 times as likely to be present in this instance than in the first quartile (OR_{Q4vsQ1}: 2.60, 95% CI: 1.16–5.70, *p*-trend: 0.01). In Q3, there was a 2.1-fold increase in all GA when compared with Q1 (OR_{Q3vsQ1}: 2.10, 95% CI: 1.06–3.98). An increased GA risk was observed with increasing E-DII score per 1-point increment ($OR_{E\text{-}DII}$: 1.24, 95% CI: 1.05–1.46). Cases in the highest E-DII quartile were 3.93 times as likely to have GA in the non-cardia region (OR_{Q4vsQ1}: 3.93, 95% CI: 1.59–9.70, *p*-trend: 0.01). This association was consistent when the non-cardia region was evaluated using the continuous E-DII variable per 1-point increment ($OR_{E\text{-}DII}$: 1.28, 95% CI: 1.07–1.55). The pro-inflammatory diet was associated with increased GA of the diffuse subtype in Q3 and Q4 (OR_{Q3vsQ1}: 2.36, 95% CI: 1.06–5.23; OR_{Q4vsQ1}: 2.90, 95% CI: 1.06–7.82, *p*-trend: 0.01) and increasing E-DII score per 1-point increment ($OR_{E\text{-}DII}$: 1.30, 95% CI: 1.06–1.60) (Table 3).

Table 3. Odds ratios between energy-adjusted Dietary Inflammatory Index (E-DII) and gastric adenocarcinoma by anatomical location and histological subtype in cases versus control I individuals, GE4GAC-Brazil (2016–2022).

	E−DII Quartiles					
	Q1 (−5.55, −2.01)	**Q2 (−2.00, −0.74)**	**Q3 (−0.73, 0.56)**	**Q4 (>0.56)**	**Per 1-Point Increment in the E-DII Score**	***p*−Trend ‡**
	OR	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**		
All [1]						
Cases/Controls	68/94	134/94	169/95	121/94	492/377	
Crude	1.00	1.97 (1.31–2.96)	2.46 (1.65–3.67)	1.78 (1.18–2.68)	1.15 (1.05–1.26)	0.003
Model 1	1.00	1.62 (0.97–2.70)	1.94 (1.14–3.30)	1.70 (0.88–3.27)	1.17 (1.02–1.35)	0.02
Model 2 [a]	1.00	1.51 (0.81–2.81)	2.10 (1.06–3.98)	2.60 (1.16–5.70)	1.24 (1.05–1.46)	0.01
Anatomical location [2]						
Cardia						
Cases/Controls	13/94	32/94	30/95	26/94	101/377	
Crude	1.00	2.46 (1.22–4.98)	2.28 (1.12–4.65)	2.00 (0.96–4.13)	1.19 (1.03–1.38)	0.02
Model 1	1.00	1.90 (0.85–4.20)	2.02 (0.87–4.64)	1.81 (0.69–4.73)	1.26 (1.03–1.54)	0.03
Model 2	1.00	1.22 (0.50–2.97)	1.49 (0.58–3.83)	1.49 (0.49–4.53)	1.19 (0.95–1.50)	0.13
Non-cardia						
Cases/Controls	49/94	93/94	126/95	84/94	352/377	
Crude	1.00	1.90 (1.21–2.97)	2.54 (1.65–3.94)	1.71 (1.09–2.70)	1.13 (1.03–1.25)	0.01
Model 1	1.00	1.60 (0.89–2.88)	2.28 (1.24–4.19)	1.82 (0.86–3.88)	1.19 (1.02–1.40)	0.03
Model 2	1.00	1.75 (0.86–3.60)	2.54 (1.19–5.41)	3.93 (1.59–9.70)	1.28 (1.07–1.55)	0.01
Histological subtype [2]						
Diffuse						
Cases/Controls	29/94	55/94	76/95	43/94	203/377	
Crude	1.00	1.90 (1.11–3.23)	2.59 (1.55–4.34)	1.48 (0.86–2.57)	1.12 (0.99–1.25)	0.06
Model 1	1.00	1.68 (0.87–3.17)	2.43 (1.26–4.68)	2.30 (1.00–5.23)	1.23 (1.07–1.51)	0.01
Model 2	1.00	1.45 (0.67–3.13)	2.36 (1.06–5.23)	2.90 (1.06–7.82)	1.30 (1.06–1.60)	0.01
Intestinal						
Cases/Controls	25/94	48/94	62/95	39/94	174/377	
Crude	1.00	1.92 (1.10–3.37)	2.45 (1.42–4.23)	1.56 (0.87–2.78)	1.13 (0.99–1.23)	0.06
Model 1	1.00	1.93 (0.98–3.84)	2.34 (1.15–4.77)	1.53 (0.63–3.70)	1.20 (1.00–1.44)	0.05
Model 2	1.00	1.75 (0.75–4.10)	2.16 (0.88–5.30)	2.58 (0.89–7.44)	1.26 (1.00–1.57)	0.04

[1] Binary logistic regression. [2] Multinomial logistic regression. The mixed histological subtype was not considered because the number of cases was <30. Reference: Quartile 1 (maximum anti-inflammatory diet). OR: Odds ratio. 95% CI: 95% confidence interval. Model 1: adjusted for sex, age (years), marital status, schooling, self-reported ethnicity, family history of cancer in first-degree relatives, study region, PPIs/H2RAs, antacids, NSAIDs, aspirin, nutritional supplement, BMI (categories), tobacco smoking, alcohol beverage consumption, diabetes, sodium intake (g/day). Model 2: Model 1 + peptic ulcer, *H.pylori* status. [a] Hosmer–Lemeshow test = 13.35, $p = 0.10$ (E-DII quartiles) and 12.08, $p = 0.15$ (E-DII continuous). ‡ *p*-value for trend derived from models using the E-DII continuous variable.

The risk of having GA was 2.7 times as likely in participants eating the most pro-inflammatory diets compared to those consuming the most more anti-inflammatory diets

(OR_{Q4vsQ1}: 2.70, 95% CI: 1.60–4.54, *p*-trend: <0.001). In Q3, the risk of GA was 2.27-fold increase that of Q1 (OR_{Q3vsQ1}: 2.27, 95% CI: 1.44–3.58). An increased GA risk was observed with increasing E-DII score per 1-point increment ($OR_{E\text{-}DII}$: 1.27, 95% CI: 1.13–1.43). There was a >3-fold risk of GA in the cardia region associated with the most pro-inflammatory diet (OR_{Q4vsQ1}: 3.31, 95% CI: 1.32–8.24, *p*-trend: 0.007) and increasing E-DII score per 1-point increment ($OR_{E\text{-}DII}$: 1.31, 95% CI: 1.08–1.60). There also was an increase in GA in the non-cardia region in Q3 and Q4 compared with Q1 (OR_{Q3vsQ1}: 2.43, 95% CI: 1.44–4.09; OR_{Q4vsQ1}: 2.97, 95% CI: 1.64–5.39, *p*-trend: <0.001; $OR_{E\text{-}DII}$: 1.30, 95% CI: 1.14–1.50). Those individuals in the highest E-DII quartile had a higher risk of GA of the diffuse and intestinal subtypes (OR_{Q4vsQ1}: 2.48, 95% CI: 1.23–5.00, *p*-trend: 0.003 for diffuse; OR_{Q4vsQ1}: 2.82, 95% CI: 1.38–5.74, *p*-trend: 0.002 for intestinal). Although there was an increased risk for both subtypes in E-DII quartile 3, it was highest for the diffuse subtype (OR_{Q3vsQ1}: 2.80, 95% CI: 1.54–5.10). This association was consistent when diffuse and intestinal GA subtypes were evaluated using the continuous E-DII variable per 1-point increment ($OR_{E\text{-}DII}$: 1.26, 95% CI: 1.08–1.48, and $OR_{E\text{-}DII}$: 1.30, 95% CI: 1.10–1.51; respectively) (Table 4).

Table 4. Odds ratios between Energy-adjusted Dietary Inflammatory Index (E-DII) and gastric adenocarcinoma by anatomical location and histological subtype in cases versus controls II, GE4GAC-Brazil (2016–2022).

	E-DII Quartiles				**Per 1-Point Increment in theE-DII Score**	***p*-Trend ‡**
	Q1 (−5.09, −2.04)	**Q2 (−2.03, −0.83)**	**Q3 (−0.82, 0.25)**	**Q4 (>0.25)**		
	OR	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**		
All [1]						
Cases/Controls	65/194	119/194	156/194	152/195	492/777	
Crude	1.00	1.83 (1.28–2.65)	2.41 (1.69–3.44)	2.35 (1.65–3.36)	1.20 (1.11–1.29)	<0.001
Model 1 [a]	1.00	1.42 (0.91–2.22)	2.27 (1.44–3.58)	2.70 (1.60–4.54)	1.27 (1.13–1.43)	<0.001
Anatomical location [2]						
Cardia						
Cases/Controls	11/194	30/194	24/194	36/195	101/777	
Crude	1.00	2.72 (1.33–5.60)	2.18 (1.04–4.58)	3.27 (1.62–6.62)	1.24 (1.08–1.43)	0.002
Model 1	1.00	1.87 (0.84–4.15)	2.18 (0.95–5.04)	3.31 (1.32–8.24)	1.31 (1.08–1.60)	0.007
Non-cardia						
Cases/Controls	48/194	84/194	118/194	103/195	352/777	
Crude	1.00	1.75 (1.17–2.63)	2.46 (1.66–3.63)	2.15 (1.44–3.19)	1.18 (1.08–1.28)	<0.001
Model 1	1.00	1.44 (0.86–2.39)	2.43 (1.44–4.09)	2.97 (1.64–5.39)	1.30 (1.14–1.50)	<0.001
Histological subtype [2]						
Diffuse						
Cases/Controls	28/194	48/194	71/194	56/195	203/777	
Crude	1.00	1.71 (1.03–2.85)	2.53 (1.56–4.10)	2.00 (1.21–3.26)	1.16 (1.05–1.29)	0.005
Model 1	1.00	1.33 (0.73–2.43)	2.80 (1.54–5.10)	2.48 (1.23–5.00)	1.26 (1.08–1.48)	0.003
Intestinal						
Cases/Controls	23/194	46/194	54/194	51/195	174/777	
Crude	1.00	2.00 (1.17–3.43)	2.35 (1.38–3.98)	2.21 (1.30–3.75)	1.17 (1.05–1.31)	0.006
Model 1	1.00	1.66 (0.89–3.06)	2.52 (1.34–4.74)	2.82 (1.38–5.74)	1.30 (1.10–1.51)	0.002

[1] Binary logistic regression. [2] Multinomial logistic regression. The mixed histological subtype was not considered due to the number of cases < 30. Reference: Quartile 1 (maximum anti-inflammatory diet). OR: Odds ratio. 95% CI: 95% confidence interval. Model 1: adjusted for sex, age (years), marital status, schooling, self-reported ethnicity, family history of cancer in first-degree relatives, study region, PPIs/H2RAs, antacids, NSAIDs, aspirin, nutritional supplement, BMI (categories), tobacco smoking, alcohol consumption, diabetes, sodium intake (g/day). [a] Hosmer–Lemeshow test = 11.00, $p = 0.20$ (E-DII quartiles) and 11.92, $p = 0.16$ (E-DII continuous). ‡ *p*-value for trend derived from models using the E-DII continuous variable.

4. Discussion

There was a positive association between E-DII score and GA in the Brazilian population. A pro-inflammatory diet was associated with an increased risk of cardia and non-cardia GA of both intestinal and diffuse subtypes.

Our findings are consistent with those found in populations from Italy (OR: 2.35; 95% CI: 1.32–4.20) [34], South Korea (OR: 1.63; 95% CI: 1.15–2.29) [11], and Iran (OR: 3.39; 95% CI: 1.59–7.22) [35]. These results are also consistent with those from a prospective cohort conducted in Sweden, in which 163 cases of GC (92 cases in men and 71 in women) were diagnosed, and a low-DII diet was associated with a lower risk of GC just in men (HR: 0.73; 95% CI: 0.53–0.99) [36]. In yet another cohort conducted in the US, no association was observed between E-DII score and either cardia or non-cardia GA [37].

In the subgroup analyses based on histological subtype in cases versus control I individuals, we observed an increased risk of diffuse GA. A minority (10%) of diffuse GA is associated with genetic alterations and family history, while 80 to 90% of such cases are considered "sporadic" [5,38]. The association between *H. pylori* infection and the sporadic diffuse type (without association with atrophic gastritis and intestinal metaplasia) remains an enigma [39]. It has been recently shown that the diffuse subtype shares co-factors usually associated with the non-diffuse subtype, such as smoking, high salt intake, and low fruit and vegetable intake. Notably, some high-risk countries for GA in East Asia and Central America report that approximately 50% of GA belong to the diffuse subtype. In the US, the occurrence of this subtype was higher in young adults between 2000 and 2019 [5], which corroborates our own findings demonstrating a higher prevalence of the diffuse subtype in the Brazilian population. The risk of diffuse GA in this study was found to be associated with a more pro-inflammatory diet among adults < 50 years of age.

Countries with high incidence of GA, such as Japan and South Korea, have national prevention programs, such as endoscopic screening, for early detection of this type of cancer in the asymptomatic population, which has reduced mortality caused by GA [4,40]. Brazil lacks an organized GA detection program. Thus, although the incidence rates in Brazil are one quarter of those recorded in Japan and South Korea, mortality from GA is high, which demonstrates the need for preventive activities and early diagnosis in an organized manner.

Based on histological subtype, when comparing cases with the control II group we observed an increased risk of intestinal GA, for which the main risk factor is *H. pylori* infection, whose prevalence in Latin America and the Caribbean is one of the largest in the world—69.26% in adults [4,41]. Gastric carcinogenesis caused by *H. pylori* infection was described by Correa and Piazuelo [42]. It is now common knowledge that diet can influence the inflammatory process or inhibit the inflammatory cascade. Thus, a synergy between infection and environmental carcinogens (nitrosamines, heterocyclic amines, nitrites, dietary salt, alcohol) may occur, not to mention complex interactions with antioxidants, resulting in decreased protective effects and promotion of carcinogenesis. Daily consumption of fruits and vegetables, which are sources of antioxidant/anti-inflammatory nutrients (vitamin E, ascorbic acid, and β-carotene), as well as allium vegetables that contain flavonoids and organosulfur compounds, promote gastric cyto-protection, and can reverse premalignant lesions [6,43–45]. Additionally, regular use of nutritional supplementation was associated with reducing risk of CG and non-cardia CG, regardless of lifestyle [46–48]. However, use of high doses of anti-inflammatory nutrients, such as β-carotene, vitamin C, and vitamin E, for cancer prevention purposes in generally healthy populations has not shown beneficial effects on incidence and mortality, regardless of cancer type [49]. In this study, we observed a more pro-inflammatory dietary pattern in the Brazilian population, with lower consumption of the anti-inflammatory nutrients.

A case–control study carried out in Korea with 1164 adults (388 cases and 776 controls) was the only one so far to associate a pro-inflammatory diet—represented by the highest tertile of DII in relation to the lowest tertile of the histological GA subtypes—with a higher risk of the intestinal subtype in men (OR = 2.03, 95% CI: 1.09–3.77) and the intestinal and diffuse subtypes in women (OR = 4.87, 95% CI: 1.47–16.07 for intestinal, OR = 2.93, 95% CI: 1.47–5.84 for diffuse) [11]. Our study is a pioneering contribution to the literature on the risk of GA stratified by histological subtypes, presenting a comparison between cases and two controls groups. Our findings indicate that a pro-inflammatory diet is associated

with a higher risk of diffuse GA in the endoscopic control, which may be related to early detection of intestinal GA by endoscopy.

The central-western region of Brazil is internationally known for its agrobusiness sector, with the production of soy, corn, sugar cane, and cattle. This region is responsible for 41% of the Brazilian agricultural production, although fruit production is incipient [50,51]. However, organic agriculture in this region is still limited, and it is known that activities involving the application of pesticides can contribute to carcinogenesis [52]. In the 2017–2018 biennium, the inclusion of minimally processed foods in the Brazilian population's diet was higher in the northern region and lower in the southeastern and central-western regions. The consumption of ultra-processed foods was higher in the southeastern and central-western regions and lower in the northern region of Brazil. The diet of the Brazilian population is still predominantly composed of fresh, minimally processed foods and processed culinary ingredients. However, there has been an increase in the consumption of ultra-processed foods [53], mainly in adults [54]. The consumption of processed and ultra-processed foods was associated with GA in individuals from Belém and São Paulo [30]. In addition, early onset GC of diffuse subtype was identified in younger adults [4]. Our results corroborate these findings, as we observed a higher consumption of a pro-inflammatory diet and a decrease in the consumption of an anti-inflammatory diet, especially among adults. However, a lower E-DII score was observed in individuals aged over 50 years, which may be related to the presence of comorbidities that motivate changes in diet. Moreover, the association of ultra-processed foods with low-grade inflammation is only partially explained by the high pro-inflammatory potential of these foods [55].

In this study, approximately 50% of hospital controls were overweight (overweight and obese), which contributes to the increased risk of cardia GA. Metabolically active visceral adipose tissues produce inflammatory mediators and cytokines (e.g., TNF-α and leptin), inhibit adiponectin secretion, and facilitate the development of insulin resistance and subsequent hyperinsulinemia, promoting carcinogenesis partly by stimulating an increase in insulin-like growth factor 1 (IGF-1) expression [43]. It has been reported that the level of adiponectin is lower in patients with cardia GA than in control individuals [56]. With the consumption of a predominantly pro-inflammatory diet, the release of inflammatory mediators can be potentiated and contribute to carcinogenesis.

Sodium intake by cases and hospital controls who consumed a more pro-inflammatory diet was more than twice the maximum recommended by the WHO (2 g/day). In 2021, the Pan American Health Organization launched new targets to reduce average salt/sodium consumption by 30% in the population of the Americas by 2025 [57,58]. In addition to the risk factors cited here and despite the efforts to reduce sodium consumption, the Brazilian population in this study displayed high sodium intake, which may contribute to gastric carcinogenesis.

The strengths of this study are (1) its relatively large sample size in which both diet and GA were analyzed; (2) it is the first Brazilian multicenter case–control study that uses the E-DII tool; and (3) it is the first multicenter study that includes individuals from three capitals located in three different regions of Brazil. Despite its strengths, this study has limitations, such as (1) recall and selection biases that are frequent in case–control studies; (2) the reverse causation bias (in case–control study), as a diet may be affected by the diagnosis of GA; and (3) another limitation to be considered is the use of the NDSR® software for dietary nutritional analysis of the participants. As it is a US food database, it may not reliably reflect the nutritional composition of Brazilian foods; however, it is considered a robust and complete nutrient database, widely used in epidemiological studies both in Brazil and in other countries. Because there is no Brazilian nutritional composition table with these characteristics, its use was adopted with the inclusion of typically national foods.

5. Conclusions

In conclusion, a pro-inflammatory diet, estimated by higher E-DII scores, was associated with an increased risk of GA in both the cardia and non-cardia anatomic regions

and both intestinal and diffuse histological subtypes in this Brazilian population. However, E-DII needs improvement for GA with the inclusion of nutrients, such as sodium, given the importance of the nutrient in carcinogenesis. Additional studies on inflammatory diet and GA in this population are needed to better understand the relationship between anti-inflammatory components of the Brazilian diet and GA.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/nu15132867/s1, Table S1: Sociodemographic, clinical, and nutritional characteristics of cases and controls by Energy-adjusted Dietary Inflammatory Index (E-DII) score quartiles.

Author Contributions: A.R.C.S., V.R.G. and M.P.C. were involved in the conception and design of this study and designed the data analysis. M.S.B. and P.P.d.A. supervised data collection at participating centers. L.Z. computed the DII and E-DII scores, and M.D.W. and J.R.H. consulted on this aspect. A.R.C.S. and G.A.F. did the statistical analyses and drafted the version of the manuscript. A.R.C.S., V.R.G., T.S.S.P., L.Z., M.D.W., J.R.H., G.A.F. and M.P.C. interpreted results from the data analyses. M.P.C. obtained the funding and supervised the work. V.R.G., T.S.S.P., L.Z., M.D.W., J.R.H., G.A.F., and M.P.C. critically revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki after obtaining the approval of the Committee on Ethics in Human Research of Antônio Prudente Foundation—A.C. Camargo Cancer Center, as well as the local ethics committees of the study centers, under registration on the Brazil platform linked to the National Health Council of Brazil.

Informed Consent Statement: Informed consent was obtained from all participants involved in the study.

Data Availability Statement: The datasets generated and/or analyzed during this study are available from the corresponding author upon request.

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Conflicts of Interest: James R. Hébert owns controlling interest in Connecting Health Innovations LLC (CHI), a company that has licensed the right to his invention of the dietary inflammatory index (DII®) from the University of South Carolina in order to develop computer and smart phone applications for patient counseling and dietary intervention in clinical settings. CHI owns exclusive right to the E-DIITM. Dr. Michael Wirth has an interest in CHI. The subject matter of this paper will not have any direct bearing on that work, nor has that activity exerted any influence on this project. The other authors declare no conflict of interest.

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APÊNDICE B

BMC Medicine

RESEARCH

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Exploring the link between dietary patterns and gastric adenocarcinoma in Brazil: a mediation analysis

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Abstract

Background The causal pathway between different dietary patterns (DPs) and gastric adenocarcinoma (GA) remains largely unexplored. The study aimed to identify DPs and evaluate how selected nutrients mediate the relationship between DPs and GA.

Methods This multicenter case–control study in Brazil involved 1751 participants (600 cases, 377 endoscopic controls, and 774 hospital controls). DPs were identified through exploratory factor analysis. A counterfactual-based mediation analysis was performed to decompose the total effect of DPs on GA into direct and indirect effects mediated by saturated fatty acids, added sugars, total fiber, and sodium intakes. Effects were expressed as ORs and 95% CIs.

Results Two DPs were identified—"unhealthy dietary pattern" (UDP) and "healthy dietary pattern" (HDP), which were associated with an increased and decreased risk of GA, respectively. Added sugars partly mediated the association between UDP and GA (percentage mediated between 7.3 and 21.7%), while sodium intake mediated most of the association between HDP and GA (percentage mediated between 52.4 and 100%). No significant mediating effects were detected for saturated fatty acids and total fiber.

Conclusions This study contributes innovative insights into the DPs-GA relationships, highlighting the significant mediating roles of sodium and added sugars, offering valuable information for preventive strategies and public health interventions targeting GA.

Keywords Gastric cancer, Cancer prevention, Nutrients, Added sugars, Sodium, Mediation analysis, Risk factors, Dietary patterns, Case–control study

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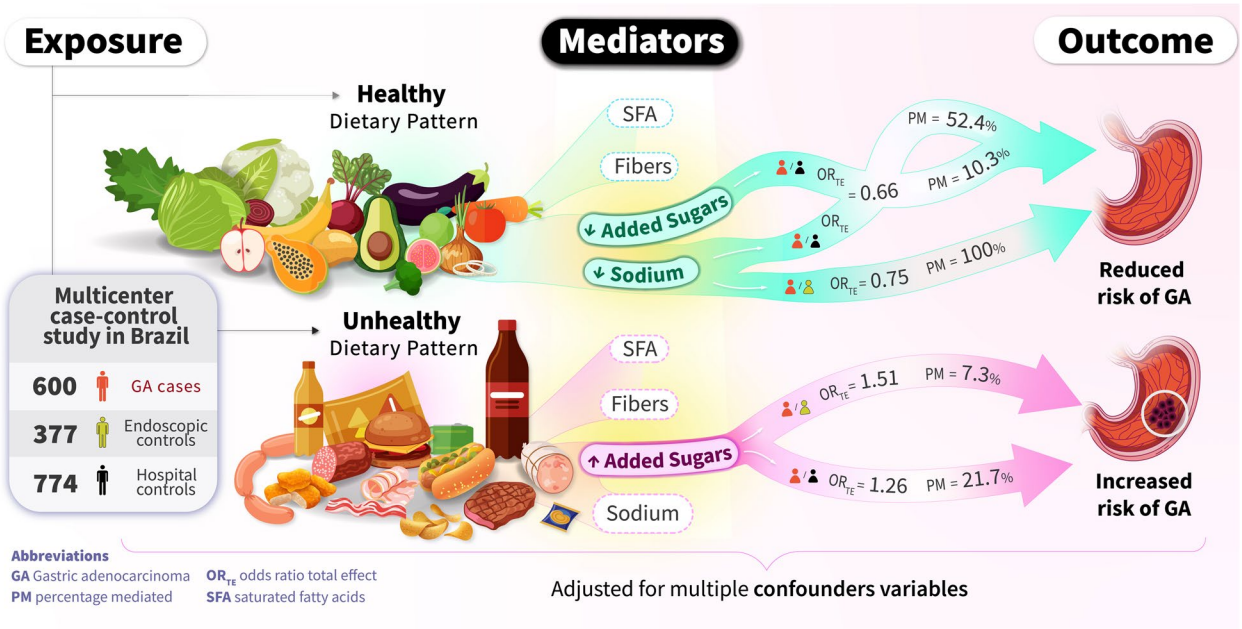
Graphical Abstract



Background

The incidence and mortality of gastric cancer (GC) have decreased in recent decades, but it is still the fifth most incident and the fifth in cancer mortality worldwide [1, 2]. Notably, in the Americas, there is a rising trend in GC incidence attributed to aging and growing of high-risk populations [3]. In Brazil, an estimated 21,480 new cases are expected from 2023 to 2025, positioning GC as the fifth most frequently diagnosed cancer in the country [4].

Gastric adenocarcinoma (GA) is the predominant histological type, accounting for 90% of all GC cases. The primary risk factor for non-cardia GA is *Helicobacter pylori* (*H. pylori*) infection, implicated in 90% of cases [5, 6]. GA is also associated with modifiable risk factors, notably the diet. Diet factors include alcohol consumption, excessive salt, nitrites, nitrates, red and processed meats, preserved foods, high-fat diets rich in saturated fatty acids (SFA), sucrose, cholesterol, and animal proteins. Conversely, protective factors for GA are related to consumption of diets rich in polyunsaturated fatty acids, vegetable fats (from olive oils, nuts), fruits, vegetables, fibers, and whole grains [7–9].

The conventional approach to studying the relationship between diet and cancer has typically focused on individual foods or nutrients, disregarding the broader perspective of dietary patterns. The complexity arises from the interrelationship of various dietary factors [10, 11]. The United States 2020–2025, Dietary Guidelines, advocate shifting emphasis towards understanding overall dietary patterns, instead of looking exclusively at a single dietary component [12]. Dietary pattern analysis is preferred to the single food/nutrient approach because it considers how people typically combine different foods and drinks in their diet. This allows to capture the complex interplay between various dietary components, providing a more complete picture than focusing on individual foods or nutrients [10, 11]. A more recent review on dietary patterns and GC identified that "Western/Unhealthy" diets, rich in starchy, meat, fats, and alcohol, associated with an increased GA risk, while "Prudent/Healthy" diets, abundant in fruits and vegetables, were associated with reduced risk [13, 14]. Others subsequent original research have been conducted [10, 15–18]. The only study on dietary patterns and GA in Brazil, conducted in a single center in Goiânia (Goiás state), identified three dietary patterns but they did not analyze the association between these patterns and GA risk [19]. Moreover, little is known regarding the role of varying levels of nutrient intakes, which characterize the identified dietary patterns, on the evaluate potential mechanisms of action these patterns to GA risk.

Therefore, our study aims to identify dietary patterns within the Brazilian population and explore the

causal pathway linking the identified patterns to the associated risk of GA.

Methods

Study population and design

GE4GAC-Brazil is a large, hospital-based, multicenter case–control study carried out in five capitals of different Brazilian regions [20]. Briefly, all cases were diagnosed with GA, confirmed by histology, and coded according to the International Classification of Diseases in Oncology (C16). Two control groups were used. The control I included participants with gastric complaints who underwent endoscopy, with a negative diagnosis for GC or a premalignant lesion. Control II was composed of hospital individuals, without gastric disorders or gastric cancer, recruited from ophthalmology, traumatology, physiotherapy, and nutrition clinics and from cancer prevention programs organized by hospitals. The exclusion criteria for participants were previous malignancy, except for non-melanoma skin cancer; participants with impaired mobility due to illness or mental and cognitive conditions that prevented them from understanding the questions asked by the interviewers; and cases that had been diagnosed with GA more than 2 years prior to the interview or those with advanced cancer (i.e., terminal stage with no feasible chance of survival). The study was approved by the Committee on Ethics in Human Research of Antônio Prudente Foundation—A.C.Camargo Cancer Center, as well as the local ethics committees of the study centers, under registration on the Brazil platform linked to the National Health Council of Brazil (grant no. 4708881–February 2016, registration CAAE: 53,166,915.9.1001.5432). All participants provided written informed consent for data collection and storage.

This study used a database from four Brazilian capitals with complete data collection, São Paulo (São Paulo state; southeastern region/metropolitan), Belém (Pará state; northern region/Amazon Rainforest), Goiânia (Goiás state; central-western region/agrobusiness), and Fortaleza (Ceará state; northeast region/coastal). Recruitment was conducted from April 2016 to November 2023. In the central-western and northeast regions, pairing was not performed. All participants provided written informed consent for data collection and storage.

Participants with no dietary data information and implausible energy intake (< 500 or > 5000 kcal per day) [21] were excluded. A total of 1751 participants: 600 cases, 377 control I, and 774 control II, were included in the study (Fig. 1).

Data collection

Face-to-face interviews were conducted at baseline by trained personnel using an online structured epidemiological questionnaire on the REDCap® platform. Anonymized data were recorded on the platform at participating centers. We collected data on sex (female or male), age (years), education (≤ 8 years = illiterate to elementary school, 9 to 12 years = high school, and ≥ 13 years = higher education), and lifestyle habits (i.e., alcohol consumption and tobacco smoking). To calculate alcohol consumption (g/day), we used a previously reported method [22] and we classify as no consumption, low consumption (≤ 12 g/day), or moderate/higher (> 12 g/day alcohol) consumptions [23], while tobacco smoking was calculated in packs/year [24] and we classify as no consumption, low consumption (≤ 10 packs/year), or intermediate/higher (> 10 packs/year) consumptions [23].

Information was collected on the presence peptic ulcer (yes or no) and clinical data/family history of cancer in first-degree relatives (yes or no). Additionally, in accordance with the guidelines of the World Health Organization (WHO), we measured weight (kg) and height (m) for the calculation of body mass index (BMI, kg/m^2) and BMI category (< 18.5, 18.5–24.9, 25–29.9, ≥ 30 kg/m^2) [25]. For cases, clinical information on anatomical location (cardia or non-cardia), tumor histological subtype (diffuse, intestinal, or mixed) [26], and status of *H. pylori* infection (positive or negative) were collected from medical records, the latter also having been collected for control I individuals based on gastric endoscopy reports.

Assessment of dietary patterns

To assess food and nutrient intakes of study participants, we used a validated food frequency questionnaire (FFQ) containing 130 food items [27]. The FFQ asked about their usual food consumption over the past year. Each item was collected based on the frequency and portion size: (1) frequency of food consumption—ranging from 1 to 10 times daily, weekly, monthly, or yearly and (2) size of the portion ingested—small, medium, or large (each food had its portion in grams and its equivalent in slices, spoons, and/or cups/glasses). Consumption of each item was calculated in grams per day.

Nutrient intake was determined using the Nutrition Data System for Research software—NDSR® version 2021 (Minneapolis, MN, USA). Nutrients were energy adjusted using the density method per 1000 kcal [28].

The 130 food items listed in the FFQ were grouped into 31 food groups based on similarities of nutrient profiles and culinary usage (Table S1).

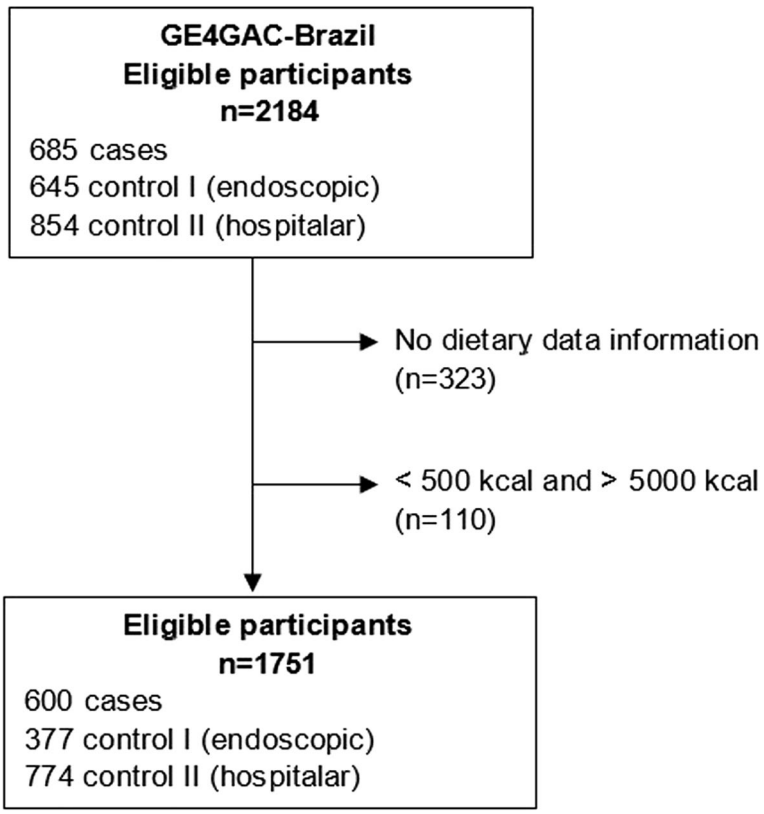


Fig. 1 Flow chart of study population selection

We conducted an exploratory factor analysis to extract dietary patterns potentially linked to GC from the 31 food groups. Initially, these food consumption data were recorded in grams per day, but they exhibited a right-skewed distribution and zero-inflation. To address this, we categorized the data into ordinal variables with four categories based on tertiles computed among consumers: (1) no consumption, (2) < 1 tertile, (3) ≥ 1 and < 2 tertile, and (4) ≥ 2 tertile. We then conducted an exploratory factor analysis using a polychoric correlation matrix calculated from the 31 food groups. We opted for the polychoric correlation matrix over the Pearson correlation matrix because the latter assumes continuous variables following a multivariate normal distribution. We assessed the adequacy of the polychoric correlation matrix using Bartlett's test of sphericity, where a significant result indicates that the matrix is suitable for factor analysis. Additionally, we considered the overall Kaiser–Meyer–Olkin (KMO) measure of sampling adequacy, with a value greater than 0.80 indicating suitability for factor analysis. The principal factor solution was used as factoring method. To determine the number of factors to retain, we considered the scree plot, the eigenvalue > 1 criterion, and the interpretability of the retained factors. Factor loadings were obtained through varimax rotation, and food groups were assigned to factors based on their highest contribution. The names of the rotated factors were derived from the variables with the strongest correlations. The factor analysis was performed using the "*fa*" function of the R package "*psych*."

Association between dietary patterns and gastric cancer risk

To assess the association between the dietary patterns and the risk of GA, participants were categorized into four groups based on quartiles of factor scores within the control population. We then estimated the odds ratios (OR) and their corresponding 95% confidence intervals (95% CI) for each group using multivariable logistic regression models. The group with the lowest factor score served as the reference category. The models were adjusted for the following covariates: sex, age (continuous), education, family history of cancer, BMI category, tobacco smoking, alcohol consumption, study region, and energy intake (continuous). Additionally, for control I, we adjust for peptic ulcer and *H. pylori* status. We also conducted tests for linear trend by regressing the OR on the midpoint of the limits defining the factor score groups.

All tests were two-sided, and the significance level (α) was 5%. Analyses were performed using the software STATA© 17.0 (College Station, TX, USA).

Mediation analysis

To further explore the role of specific nutrients within the dietary pattern, we conducted a mediation analysis to decompose the total effect of the dietary pattern into direct and indirect effect mediated by a priori defined set of nutrients. This set included SFA (% of kcal), added sugars (% of kcal), total fiber (g/1000 kcal), and sodium (g/1000 kcal) intakes. These nutrients are relevant sources of concern in the diet of many Brazilians who tend to have a high intake of SFA, added sugars, and sodium and low intake of fiber [29–31]. The exposure variables in this analysis were the factor scores (in continuous) related to the two dietary patterns identified in the factor analysis.

The mediation analysis employed the technique described by Yu and Li [32], implemented in the R package "*mma*." This technique allows for the simultaneous consideration of multiple mediators of different types, enabling the separation of individual mediators' indirect effects from the total effect.

The *mma* package includes a function to identify mediators, i.e., variables significantly associated to both the predictor and the outcome. Variables that did not meet both conditions were considered as covariates. To identify mediators, we set the alpha values for association at 0.1. The directed acyclic graph (DAG) which depicts the hypothesized causal model is shown in Fig. 2. General linear models were used to fit the variable relationships and to estimate the mediation effects, which were presented as OR (95% CI). The OR for the indirect effects indicates the effect of the dietary patterns on GA risk conveyed by the mediator.

The percentage mediated (PM) was calculated as the ratio of the indirect effect to the total effect, both on the log scale, and then multiplied by 100. Inferences on the mediation effects were made using the bootstrap method with 500 resamples.

We conducted separate mediation analyses using control group I or II. For control I, we employed regression models with a complete set of covariates, including also adjustments for peptic ulcer and *H. pylori* infection.

Results

The cases were predominantly males (59.0%), with a median age of 58 years, and education levels ≤ 8 years (52.7%). Approximately 62.8% of the cases had a family history of cancer in first-degree relatives, 41.1% exhibited intermediate/high tobacco smoking, and 47.5% reported intermediate/high alcohol consumption. Additionally, 11.0% had peptic ulcer disease, and 41.6% were obese, with a median energy intake of 2265 kcal, which was higher than that observed in the control groups ($p < 0.001$). Most cases (78.3%) had GA located in the non-cardia region, and 48.7% were classified as diffuse type (Table 1).

The Bartlett test of sphericity ($p < 0.001$) and the KMO (0.85) indicated the adequacy of the correlation matrix for factor extraction. Consequently, we proceeded with

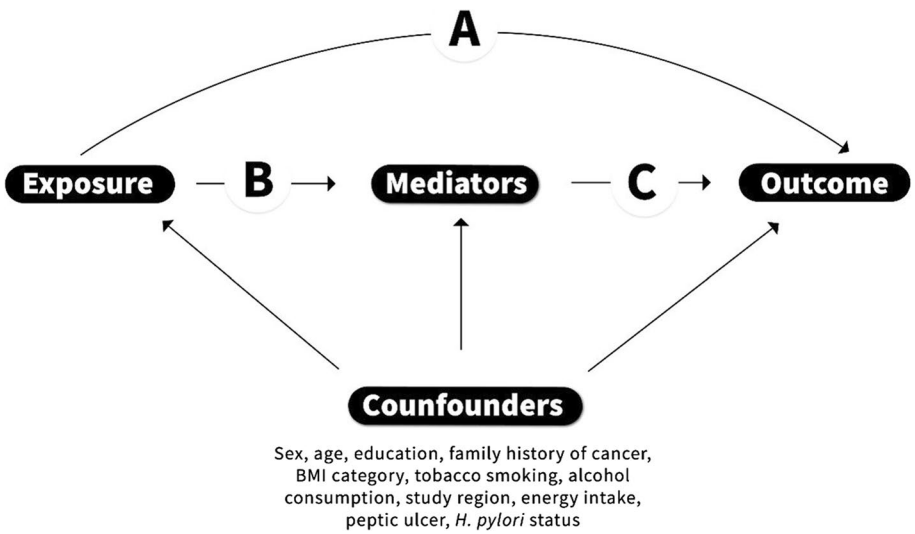


Fig. 2 Directed acyclic graph dietary patterns' relation to gastric adenocarcinoma risk and effect decomposition. Arrow A displays the direct effect (DE) of dietary patterns on gastric adenocarcinoma risk, while path B + C displays the indirect effect (IE) mediated by the sodium, added sugars, fibers, and saturated fatty acids. The sum of DE and IE gives the total effect

Table 1 Characteristics of the cases and controls enrolled in the study, GE4GAC-Brazil (2016–2023)

Variables	GE4GAC-Brazil $n = 1751$			p -value[1]
	Cases $n = 600$	Control I $n = 377$	Control II $n = 774$	
	Median (P_{25}, P_{75}) or n (%)			
Sex				0.001
Female	246 (41.0)	195 (51.7)	378 (48.8)	
Male	354 (59.0)	182 (48.3)	396 (51.2)	
Age (years)	58 (49, 66)[a]	57 (44, 64)[b]	55 (44, 64)[b]	< 0.001
Education (years) †				< 0.001
≤ 8	316 (52.7)	96 (25.5)	172 (22.2)	
9 – 12	55 (9.2)	46 (12.2)	89 (11.5)	
≥ 13	229 (38.1)	235 (62.3)	513 (66.3)	
Family history of cancer in first-degree relatives				< 0.001
No	374 (62.8)	217 (57.7)	382 (49.5)	
Yes	222 (37.2)	159 (42.3)	390 (50.5)	
Tobacco smoking §				< 0.001
No	100 (16.8)	66 (17.6)	107 (13.9)	
Low	250 (42.1)	82 (21.9)	171 (22.2)	
Intermediate/High	244 (41.1)	277 (60.5)	492 (63.9)	
Alcohol consumption ¥				< 0.001
No	102 (17.4)	90 (24.2)	106 (13.9)	
Low	206 (35.1)	102 (27.4)	148 (19.5)	
Moderate/High	279 (47.5)	180 (48.4)	507 (66.6)	
Peptic ulcer				0.001
No	504 (89.0)	358 (95.0)		
Yes	62 (11.0)	19 (5.0)		
H. pylori* status				0.262
Negative	148 (74.0)	232 (69.5)		
Positive	52 (26.0)	102 (30.5)		
BMI (kg/m^2)				< 0.001
< 18.5	173 (29.8)	24 (6.4)	82 (10.7)	
18.5 – 24.9	91 (15.7)	118 (31.5)	222 (29.0)	
25.0 – 29.9	75 (12.9)	86 (22.9)	140 (18.3)	
≥ 30	241 (41.6)	147 (39.2)	321 (42.0)	
Energy intake (kcal/day)	2265 (1686, 2885)[a]	2080 (1518, 2675)[b]	1780 (1337, 2375)[c]	< 0.001
Anatomical location				
Cardia	108 (21.7)			
Non-cardia	390 (78.3)			
Histological subtype				
Diffuse	213 (48.7)			
Intestinal	198 (45.3)			
Mixed	26 (6.0)			

Numbers may differ because of missing values. Control I individuals (endoscopic controls); Control II individuals (hospital controls). † ≤ 8 years = Illiterate to elementary school, 9 to 12 years = High school and ≥ 13 years = Higher education. § Low smoking: ≤ 10 packs/year and Intermediate/High smoking: > 10 packs/year. ¥ Low: ≤ 12 g/day and Moderate/High: > 12 g/day alcohol. * 400 cases and 43 control I individuals were not tested. [1] Pearson χ^2 test for categorical variables. Kruskal–Wallis test with a Dunn–Bonferroni post hoc test for continuous variables. Different letters on the same line mean statistical difference between groups. Significance p-value < 0.05

a factor analysis involving two latent factors. Figure 3 shows the factor loading matrix for the two latent factors. Collectively, these two factors explained 25.8% of the variance. Factor 1 explained 13.1% of the total variance and was characterized by high factor loadings (≥ 0.6) for the food groups "preserved, processed and

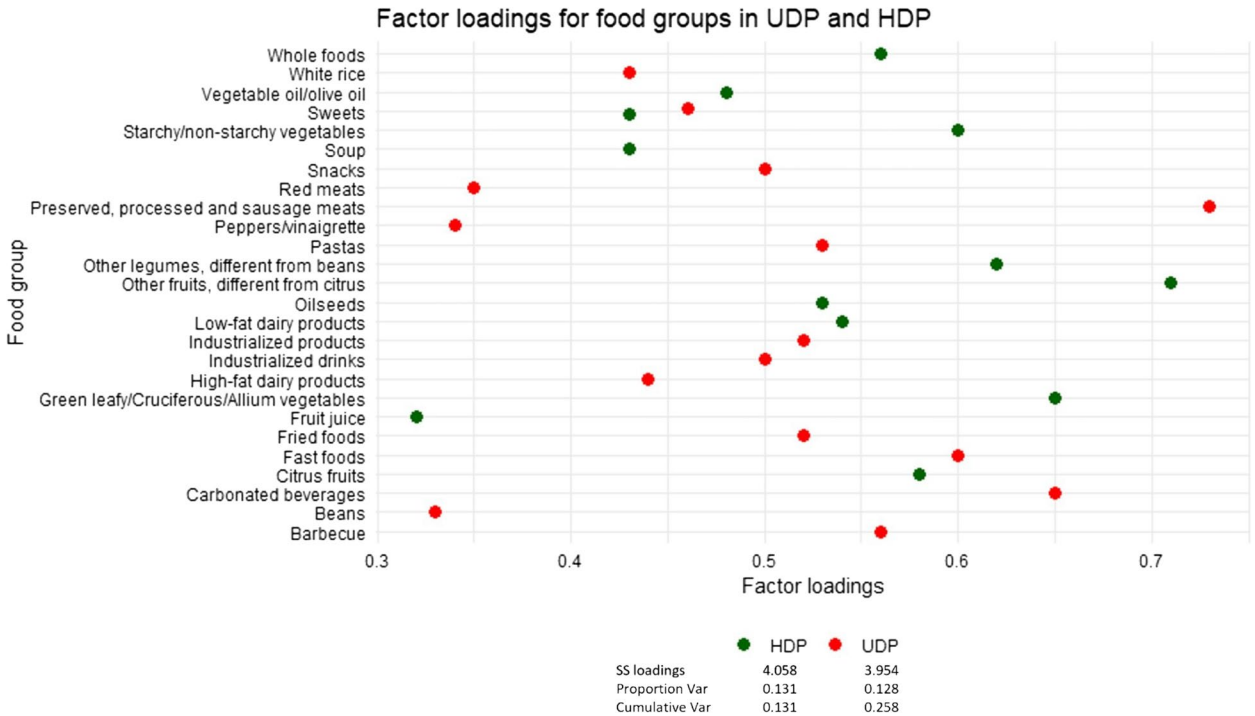


Fig. 3 Factor loading matrix for food groups in two dietary patterns from factor analysis extraction. Abbreviations: HDP, healthy dietary pattern; UDP, unhealthy dietary pattern. Only factor loadings with absolute value > 0.30 are shown

sausage meats," "carbonated beverages," and "fast food." We named factor 1 "unhealthy dietary pattern" (UDP). Factor 2 explained 12.7% of the total variance and exhibited high factor loadings (> 0.6) for the food groups "other fruits, different from citrus," "green leafy/cruciferous/allium vegetables," "starchy/non-starchy vegetables," and "other legumes, different from beans." We named factor 2 "healthy dietary pattern" (HDP).

Figure 4 shows the OR and the corresponding 95% CI for the association between the dietary patterns and GC. The estimates were obtained using different types of controls and adjustments. In the analysis using control I, we found a significant increased risk associated with the UDP, and no significant association with the HDP. The OR for participants with the highest factor score (G4) for UDP compared to those with the lowest score (G1) was 1.70 (95% CI: 1.01–2.05) in the partially adjusted model and 3.96 (95% CI: 1.75–8.96) in the fully adjusted model. In the analysis using control II, we found a positive association with the UDP (OR_{G1vsG4}: 2.17, 95% CI: 1.39–3.39) and a negative association with the HDP (OR_{G1vsG4}: 0.50, 95% CI: 0.32–0.78). The test for trend indicated a significant linear trend in the associations mentioned above.

Individuals with elevated scores in the UDP showed higher consumption of animal protein, added sugars, total fat, SFA, monounsaturated fatty acids (MUFA), and sodium and lower intake of total fiber and total carbohydrates. On the other hand, those with higher scores in the HDP had increased consumption of vegetable protein, total carbohydrates, added sugars, MUFA, and total fiber, while reducing their intake of total protein, animal protein, and sodium (Table S2).

Table 2 presents the mediation analysis results. The estimates of the effects of each dietary pattern are presented as OR for GC associated with 1-point increase in the dietary factor score. Added sugars was a significant mediator in the association between UDP and GA, as indicated in both analyses involving control I (PM: 7.3%, $p = 0.04$) and control II (PM: 21.7%, $p < 0.01$).

Regarding HDP, the total effect of HDP was an OR of 0.75. Given that the OR for the indirect effect of sodium was 0.64 (an effect greater than the total effect), it indicates that sodium intake fully mediated the association with GA in control I (100%, $p < 0.01$). In the control II analysis, sodium intake partially mediated the association between HDP and GA (PM: 52.4%, $p < 0.01$). Added sugars mediated 10.3% of the association between HDP and GA ($p < 0.01$) in the control II analysis. Neither fiber nor SFA intakes showed significant mediation effects in the association between dietary patterns and GA (Table 2).

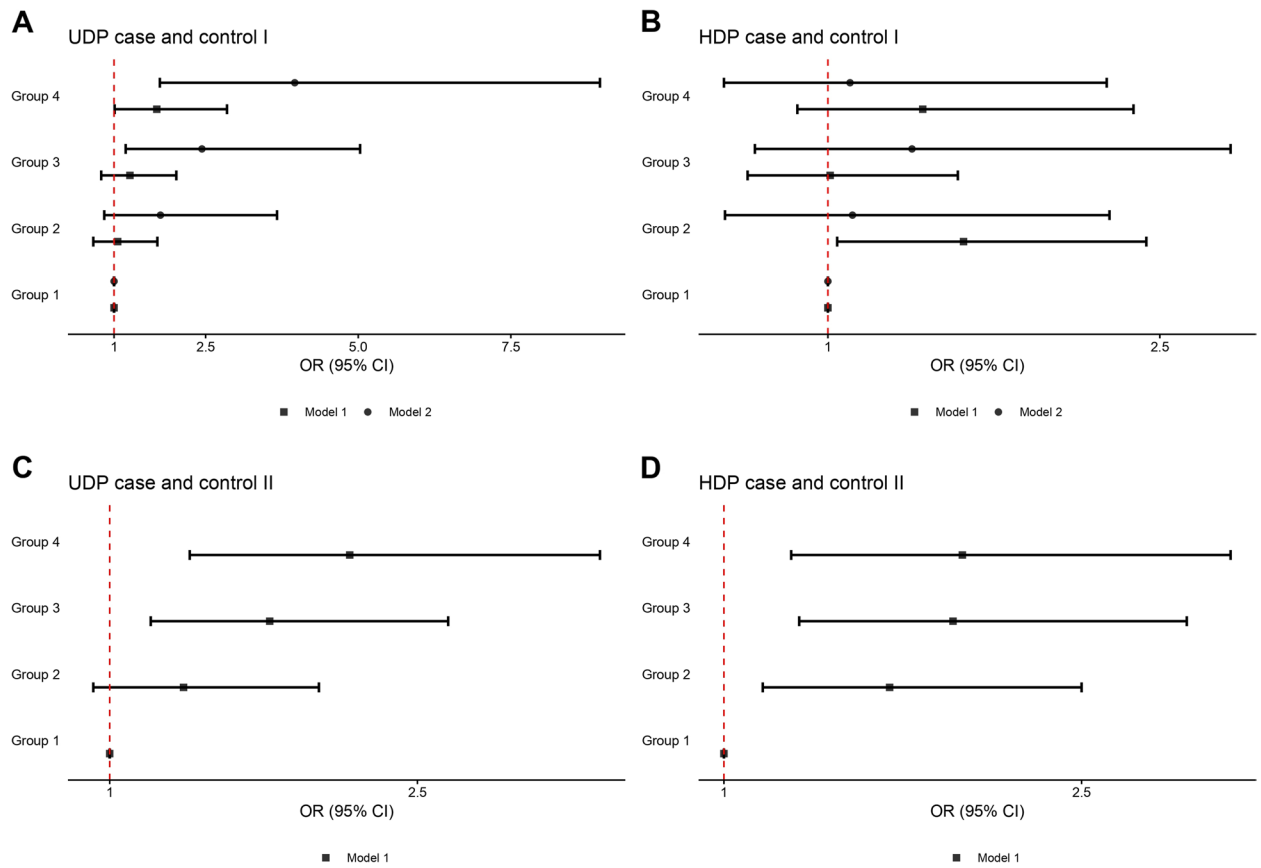


Fig. 4 Odds ratios for gastric adenocarcinoma based on dietary patterns, controls, and adjustments. Abbreviations: HDP, healthy dietary pattern; UDP, unhealthy dietary pattern. Control I individuals (endoscopic controls); control II individuals (hospital controls). Model 1: adjusted for sex, age, education, family history of cancer in first-degree relatives, study region, total energy intake, BMI categories, tobacco smoking, and alcohol consumption. Model 2: further adjusted for peptic ulcer and *H. pylori* status

Discussion

We evaluated the relationship between different dietary patterns and GA risk in a large population of GA cases and controls in Brazil, integrating a counterfactual-based mediation analysis to identify the main nutrients implicated in these associations. This novel approach provides unique insights into how selected nutrients mediate the relationship between dietary patterns and GA.

Several studies have examined the association between dietary patterns and the risk of GA in populations from China, Iran, Jordan, Korea, Mexico, Uruguay, and Canada. They generally concluded that patterns labeled as Healthy/Prudent/Mediterranean reduce the risk of GA, while Unhealthy/Western patterns increase the risk of GA [10, 15–17, 33–36].

While these studies focused only on food or nutrient groups as risk factors for GA, our study not only assessed food patterns as exposure factors but also estimated the mediated effect of multiple nutrients related to healthy or unhealthy dietary patterns, and potentially implicated in the risk of GA. Previous studies employing mediation analysis to explore the relationship between diet and cancer risk have mainly focused on individual nutrients rather than dietary patterns, thus limiting direct comparisons with our findings due to the absence of similar methodologies in previous literature [37–43].

Our study highlights sodium as a strong mediator in the association between a HDP and GA risk. Sodium demonstrates a complete mediated effect in cases versus control I analysis and a partially mediated effect in cases versus control II. A recent national dietary survey estimated that approximately 60% of the Brazilian adult population exceed the recommended limits for sodium intake, primarily through white bread, toast, beans, white rice, beef, and poultry meat [31]. However, products labeled as "whole grain" such as breakfast cereals, bread, and cookies, for instance, may contain high sodium content [44]. Therefore, strategies involving the reading of food labels, for example, may have the potential to decrease sodium intake through these products. In 2022, Brazil implemented new food labeling legislation to enhance the comprehension of nutritional information

Table 2 Mediation effects of the nutrients on the relationship between dietary patterns and gastric adenocarcinoma

Dietary pattern, type of control	Effects[a]	OR (95% CI)[b]	*p*-value	PM (%)[c]
UDP, I	Total	1.51 (1.07–2.59)	0.04	–
	Direct	1.39 (1.04–2.46)	0.04	–
	Indirect—total	1.03 (1.00–1.07)	0.04	7.3
	Indirect—added sugars	1.03 (1.00–1.07)	0.04	7.3
HDP, I	Total	0.75 (0.49–1.07)	0.12	–
	Direct	1.15 (0.88–1.67)	0.32	–
	Indirect—total	0.64 (0.47–0.87)	< 0.01	100
	Indirect—SFA	1.02 (1.00–1.04)	0.12	–
	Indirect—sodium	0.64 (0.47–0.85)	< 0.01	100
UDP, II	Total	1.26 (1.07–1.52)	< 0.01	–
	Direct	1.20 (1.01–1.45)	0.04	–
	Indirect—total	1.05 (1.02–1.08)	< 0.01	21.7
	Indirect—added sugars	1.05 (1.02–1.08)	< 0.01	21.7
HDP, II	Total	0.66 (0.54–0.76)	< 0.01	–
	Direct	0.75 (0.61–0.89)	< 0.01	–
	Indirect—total	0.88 (0.74–0.99)	0.02	31.0
	Indirect—sodium	0.80 (0.70–0.86)	< 0.01	52.4
	Indirect—added sugars	1.03 (1.01–1.06)	< 0.01	10.3
	Indirect—total fiber	1.06 (0.97–1.17)	0.22	–

Control I individuals (endoscopic controls); control II individuals (hospital controls)

Abbreviations: *HDP* healthy dietary pattern, *UDP* unhealthy dietary pattern, *SFA* saturated fatty acids, *PM* percentage mediated

[a] The following variables were tested as potential mediators: saturated fatty acid (% of kcal), added sugars (% of kcal), total fiber (g/1000 kcal), and sodium (g/1000 kcal) intakes. For a variable to be considered as a mediator, it had to be significantly associated to both the predictor and the outcome. Variables that did not meet both conditions were considered as covariates, and no indirect effect was estimated

[b] The ORs were estimated for 1-unit increase in the dietary factor score

[c] When the estimate of the indirect effect exceeds the total effect, it indicates that the variable fully mediates the association between the dietary pattern and GA

on product labels. The goal is to aid consumers in making informed and conscientious food choices, with an emphasis on highlighting elevated nutrient levels on packaging [45].

Sodium is a well-established and significant risk factor that directly influences gastric carcinogenesis. Excessive sodium intake has detrimental effects on the gastric mucosal membrane, resulting in inflammation and synergistic interactions with *H. pylori* colonization. The disruption of the mucosal barrier can further enhance the penetration of recognized carcinogens, such as N-methyl-N-nitro-nitrosoguanidine from the diet. Moreover, increased sodium intake can independently induce atrophic gastritis and metaplasia, stemming from the chronic irritation of the gastric mucosa, thereby accelerating the progression of intestinal metaplasia leading to GA [7, 46, 47].

The association between the UDP and GA is partly mediated by added sugars, with higher scores in this dietary pattern linked to an increased GA risk. Existing studies on the link between added sugars and GA are limited. Li et al. [48] found no direct association between sugars intake and the incidence and mortality related to GA. Nevertheless, excessive sugar consumption is a recognized factor for adiposity, obesity, diabetes, and cardiometabolic disturbances—established risk factors for various cancer sites, including cardia GA [8, 9, 49]. It has also been suggested that sugars are associated with other mechanisms for cancer, including oxidative stress, inflammation, or activation of the insulin pathway leading to insulin resistance, even in the absence of weight gain [49]. To our knowledge, there are no established mechanisms directly linking excessive consumption of added sugars to gastric carcinogenesis.

Added sugars are introduced during food processing and can be found in sweeteners such as table sugar, syrups, honey, industrialized fruit or vegetable juices, soft drinks, and energy beverages. Importantly, natural sugars of milk, fruits, and vegetables are not considered added sugars [50]. In Brazil, 9.2% of adults regularly consume soft drinks, with higher prevalence among men and the younger population. Recent estimates show a 14% frequency of soft drink consumption on five or more days per week, with a higher prevalence among men compared to women in Brazilian capitals [51]. Overall, our findings suggest that the

implementation of additional initiatives and strategies for healthier food options, with a focus on reducing sodium and added sugars intake, is crucial to decreasing the risk of GA.

The strengths of this study include (1) it represents the first robust multicenter case–control study employing exploratory factor analysis to determine dietary patterns and assess GA risk in the Brazilian population; (2) its relatively large sample size with individuals from four capitals located in four different regions of Brazil; (3) the innovative approach used to identify the mediators involved in the link between dietary patterns and GC risk. To our knowledge, it is also the first in the literature to use nutrients related to gastric carcinogenesis as mediators; and (4) the completeness and accuracy of dietary intake data collected thorough a comprehensive and validated FFQ.

Despite its strengths, this study has some limitations: (1) the derivation of dietary patterns from the exploratory factor analysis method involved subjective decisions when selecting and grouping the food items, when extracting the number of factors, and even when labeling the patterns. Additionally, dietary patterns are closely related to country-specific properties (e.g., food availability and cultural habits). Therefore, patterns may lack robustness and reproducibility, especially when assessed in different populations or with different numbers of diet components; (2) two dietary patterns derived from the analysis accounted for approximately 25% of the total variation in food intake, which is a small proportion of the variation in diet. Although it is a common trend in other studies that have conducted dietary pattern analyses, the identified patterns may not thoroughly capture the interindividual variation in dietary habits [52]; (3) the recall and selection biases that are frequent in case–control studies; (4) the reverse causation bias (in case–control study), as a diet may be affected by the diagnosis of GA; and (5) the use of the NDSR® software for dietary nutritional analysis of the participants. As it is a US food database, it may not reliably reflect the nutritional composition of Brazilian foods; however, it is considered a robust and complete nutrient database, widely used in epidemiological studies both in Brazil and in other countries. Because there is no Brazilian nutritional composition table with these characteristics, its use was adopted with the inclusion of typically national foods. Finally, we only tested the mediation effect of a limited set of nutrients using a theoretical model that cannot capture the complexity of the additive or synergistic effects of various nutrients and phytochemicals introduced through the diet.

Conclusions

This study provides new insights into the link between diet and GC, highlighting the mediating role of added sugars and sodium in the association between dietary patterns and GC risk. Our results show a protective association between a HDP characterized by high vegetable and fruit consumption and GA risk. Conversely, an UDP marked by high consumption of preserved and processed meats, carbonated beverages, and fast food was associated with an increased GA risk. Sodium emerged a pivotal mediator in both the HDP-GA risk association. The research contributes to elucidating the mechanisms involved in gastric carcinogenesis from an epidemiological perspective, with implications for public health.

Abbreviations

BMI	Body mass index
CG	Gastric cancer
CI	Confidence interval
DAG	Directed acyclic graph
DP	Dietary pattern
FFQ	Food frequency questionnaire
GA	Gastric adenocarcinoma
HDP	Healthy dietary pattern
H. pylori	Helicobacter pylori
KMO	Kaiser–Meyer–Olkin test
MUFA	Monounsaturated fatty acids
NDSR	Nutrition Data System for Research
OR	Odds ratio
PM	Percentage mediated
SFA	Saturated fatty acids
UDP	Unhealthy dietary pattern
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03785-2.

Additional file 1: Tables S1-S2. Tables S1- Food groups. Tables S2- Nutrients distribution across dietary patterns categories.

Acknowledgements

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Authors' contributions

Conceptualization: ARCS, MPC; Methodology: ARCS, MPC, GA, VRG, PPFG; Data collection: PPA, MSB, ROS, FJFC; Formal analysis and investigation: ARCS, MPC, GA, PPFG; Writing—original draft preparation: ARCS, MPC, GA, VRG; Writing—review and editing: All authors; Funding acquisition: MPC; Resources: MPC; Supervision: MPC. All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki after obtaining the approval of the Committee on Ethics in Human Research of Antônio Prudente Foundation—A.C.Camargo Cancer Center under registration on the Brazil platform linked to the National Health Council of Brazil (grant no. 4708881–February 2016, registration CAAE: 53166915.9.1001.5432), as well as the local ethics committees of the study centers. All participants provided written informed consent for data collection and storage.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Publisher's Note

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CORRECTION

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Correction: Exploring the link between dietary patterns and gastric adenocarcinoma in Brazil: a mediation analysis

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The original article contains an error in Fig. 4D whereby the horizontal lines representing the odds ratios should instead appear to the left of the red line – the authors wish to clarify this error by presenting the corrected version of the image which can be viewed ahead in this Correction article.

The article also presents an error in the following sentence: "Approximately 62.8% of the cases had a family history of cancer in first-degree relatives."

'62.8%' should instead state'37.2%'.

The original article can be found online at https://doi.org/10.1186/s12916-024-03785-2.

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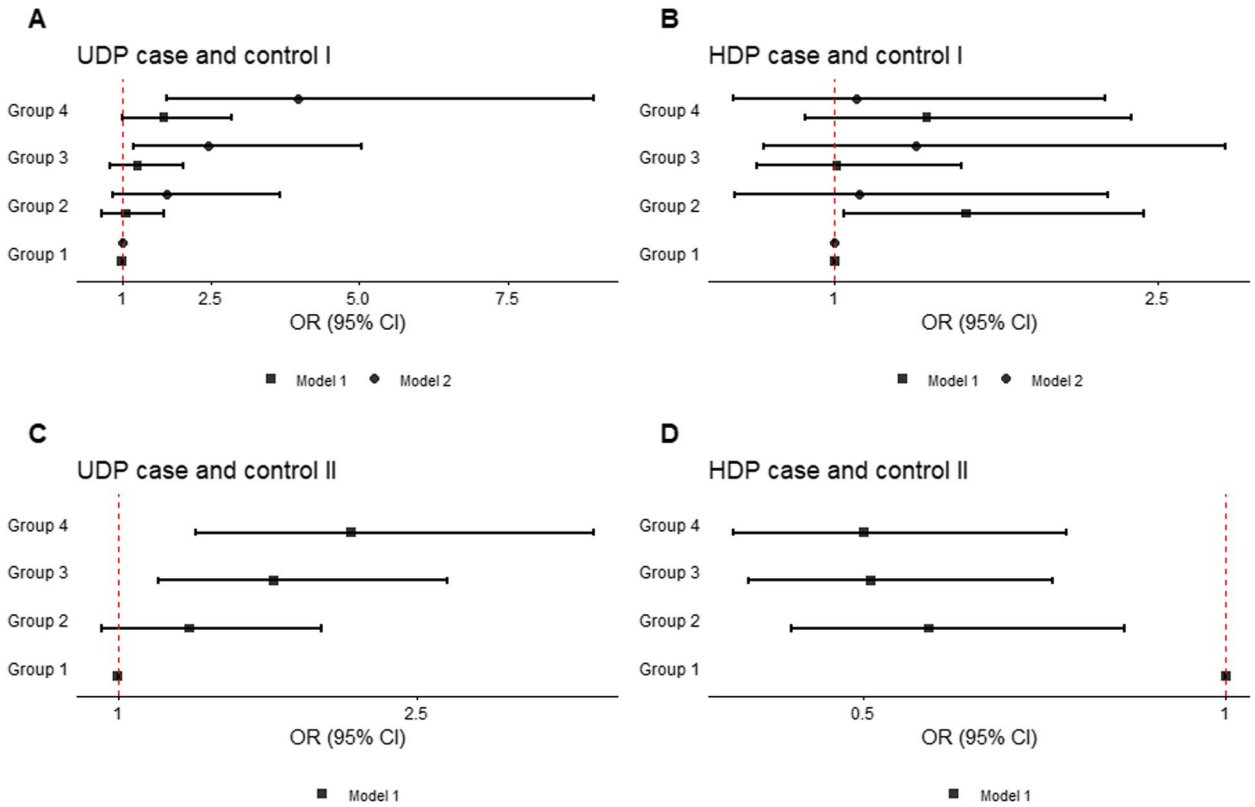

Fig. 4 Odds ratios for gastric adenocarcinoma based on dietary patterns, controls, and adjustments. Abbreviations: HDP, healthy dietary pattern; UDP, unhealthy dietary pattern. Control I individuals (endoscopic controls); control II individuals (hospital controls). Model 1: adjusted for sex, age, education, family history of cancer in first-degree relatives, study region, total energy intake, BMI categories, tobacco smoking, and alcohol consumption. Model 2: further adjusted for peptic ulcer and *H. pylori* status

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Calcium intake and gastric cancer risk: A systematic review and dose–response meta-analysis of observational studies

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ABSTRACT

Calcium has been proposed as a protective factor against certain types of cancer, but findings related to gastric cancer (GC) are inconsistent. This meta-analysis aimed to assess the association between calcium intake and the risk of GC. A comprehensive search was conducted in PubMed, Scopus, EMBASE, LILACS, and Web of Science for cohort and case-control studies published up to August 19, 2024. The quality of the studies was assessed using the Newcastle–Ottawa Scale. Publication bias was tested using Egger's and Begg's tests. Relative risks (RRs) and 95 % confidence intervals (CIs) were pooled through a random-effects model. Given the substantial heterogeneity and potential variation in intake levels across populations, a dose-response analysis was conducted to explore potential trends across the full range of calcium consumption. Thirteen studies involving 1,610,992 participants met the inclusion criteria. A non-significant inverse association was observed between total calcium intake and GC risk when comparing the highest vs lowest intake categories (RR: 0.85; 95 % CI: 0.70–1.05). While this categorical comparison was not statistically significant, the dose-response analysis revealed a significant linear protective effect, with a 10 % reduction in risk per 300 mg/day increase in dietary calcium intake (RR: 0.90; 95 % CI: 0.82–0.99). To account for potential variations across intake levels, a non-linear model was also applied, indicating a clearer risk reduction above 400 mg/day (p for non-linearity < 0.001). Overall, this dose-response meta-analysis suggests that higher dietary calcium intake may have a protective effect against GC, reinforcing the importance of considering calcium in dietary strategies for GC prevention, although more studies are needed to confirm these findings.

1. Introduction

Gastric cancer (GC) continues to be a leading cause of cancer-related deaths worldwide, despite a decline in its incidence over recent decades [1]. In 2022, GC was the fifth most diagnosed cancer globally, after lung, breast, colorectal, and prostate cancers, with estimates predicting a 62 % increase in cases by 2040, reaching 1.77 million cases [2,3]. Its incidence varies across regions, being more prevalent in low- and middle-income countries, particularly in Eastern Asia, Central and Eastern Europe, and South America [3].

Gastric adenocarcinoma accounts for approximately 90 % of GC cases, with two main subsites: cardia and non-cardia, which have distinct pathogenesis and risk factors [4]. Infection with *Helicobacter pylori* (*H. pylori*), a Group 1 carcinogen, is a major risk factor for non-cardia GC [5], in addition to modifiable factors such as diet, smoking, and alcohol consumption [3].

Calcium, an essential micronutrient, acquired solely through dietary intake or supplementation and plays a vital role in bone metabolism, neuromuscular function, blood coagulation, and intracellular signaling [6]. At the cellular level, calcium acts as a key second messenger involved in processes such as cell proliferation, differentiation, and apoptosis—biological events that are tightly linked to tumorigenesis [7,

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