UNIVERSIDADE FEDERAL DE UBERLÂNDIA
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE

ASSOCIAÇÃO DO ÁCIDO ÚRICO SÉRICO COM O CONSUMO ALIMENTAR E METABÓLITOS DA CAFEÍNA NA URINA NA POPULAÇÃO DOS ESTADOS UNIDOS. NHANES 2011-2012

LARISSA SILVA LIMIRIO

UBERLÂNDIA
2023

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Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Faculdade de Medicina da Universidade Federal de Uberlândia, como requisito para a obtenção do título de Doutora em Ciências da Saúde.

Área de concentração: Ciências da Saúde.

Orientador: Prof. Dr. Erick Prado de Oliveira.

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ATA DE DEFESA - PÓS-GRADUAÇÃO

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FOLHA DE APROVAÇÃO

Larissa Silva Limirio.

Associação do ácido úrico sérico com o consumo alimentar e metabólitos da cafeína na urina na população dos Estados Unidos. NHANES 2011-2012

Presidente da banca: Prof. Dr. Erick Prado de Oliveira

Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Faculdade de Medicina da Universidade Federal de Uberlândia, como requisito para a obtenção do título de Doutora em Ciências da Saúde.

Área de concentração: Ciências da Saúde.

Orientador: Prof. Dr. Erick Prado de Oliveira.

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Instituição: Universidade Federal de Uberlândia/MG

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Titular: Profª. Dr. Marcos Ferreira Minicucci
Instituição: Universidade Estadual Paulista Botucatu/SP

DEDICATÓRIA

Dedico a Deus por me permitir a oportunidadede crescimento moral e intelectual;
À minha mãe por toda a dedicação à minha criação e formação profissional;
Aos meus irmãos, Matheus e Gabriella por serem a luz da minha vida;
Ao meu amor, Brendow, por tudo e por tanto.

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"*Progresso é a soma dos problemas solucionados.*

Evolução é barreira vencida.

Dificuldade é medida de resistência.

Tribulação é o cadinho da fé."

Chico Xavier

RESUMO

Introdução: A hiperuricemia, condição caracterizada pela presença de níveis elevados de ácido úrico (AU) no organismo, tem sido amplamente estudada para compreender suas associações com fatores dietéticos e metabólitos da cafeína. No entanto, é importante ressaltar que os resultados desses estudos são controversos, tornando a compreensão da relação entre dieta e AU um campo ainda em desenvolvimento. Além da avaliação do consumo alimentar, é fundamental considerar a associação do AU com marcadores bioquímicos que predizem de forma mais precisa o consumo, tais como os metabólitos da cafeína presentes no organismo. **Objetivo:** avaliar a associação da ingestão dietética e dos metabólitos de cafeína com os níveis séricos de AU. **Metodologia:** Foi realizado um estudo transversal utilizando dados da Pesquisa Nacional de Exame de Saúde e Nutrição (NHANES) 2011-2012. A amostra consistiu em 3956 adultos com idade acima de 20 anos e uma subamostra de 1252 indivíduos com informações sobre cafeína e seus metabólitos na urina. A ingestão dietética foi avaliada por meio de dois recordatórios alimentares de 24 horas. A presença de cafeína e 15 de seus metabólitos na urina foi avaliada por LC-tandem MS com ionização por electrospray. O AU sérico foi medido pelo método colorimétrico. Foram realizadas regressões lineares e logísticas para as associações. **Resultados:** Nas análises de regressão linear, a ingestão de carboidratos (β=-0,001; p=0,043), gordura saturada (β=-0,020; p=0,015), fibras (β=-0,018; p=0,012), cálcio (β=-0,004; p=0,006), magnésio (β=-0,008; p=0,050) e cereais (β=-0,009; p=0,029) estavam inversamente associados ao AU sérico, enquanto a ingestão de álcool (β=0,010; p<0,001) estava positivamente associada aos níveis séricos de AU. Nas análises de regressão logística, a ingestão de álcool (OR=1,02, IC 95%= 1,007 - 1,037) estava associada a uma maior chance de hiperuricemia, enquanto a ingestão de vegetais (OR=0,99, IC 0,989 – 0,998) estava associada a uma menor chance de hiperuricemia. Os fatores dietéticos explicaram os níveis séricos de AU de 0,1% a 1,0%. Os metabólitos de cafeína, paraxantina (β= -0,004, p= 0,006), teobromina (β= -0,004, p= <0,001), ácido 7-metilúrico (β= -0,003, p= 0,0033), ácido 3,7-dimetilúrico (β= -0,029, p= 0,024), 3-metilxantina (β= -0,001, p= 0,038) e 7-metilxantina (β= -0,001, p= 0,001) estavam inversamente associados ao AU sérico, enquanto o ácido 1,3-dimetilúrico (β= 0,001, p= 0,012) estava positivamente associado ao AU sérico. Nas análises de regressão logística, a teobromina, o ácido 3-metilúrico, o ácido 7-metilúrico e a 3-metilxantina estavam associados a uma menor chance de hiperuricemia. **Conclusão:** Este estudo evidencia que a ingestão de carboidratos, gordura saturada, fibras, cálcio, magnésio e cereais está inversamente associada aos níveis séricos de AU, enquanto a ingestão de álcool apresenta uma associação positiva. Além disso, a presença de teobromina e seus metabólitos, juntamente com a paraxantina, mostraram uma associação inversa com os níveis séricos de AU, enquanto o ácido 1,3-dimetilúrico apresentou uma associação positiva. Estes resultados destacam a importância da dieta e dos metabólitos e

sua associação com AU sérico.
Palavras-chave: Ácido úrico; hiperuricemia; ingestão alimentar; cafeína; metabólitos de cafeína.

ABSTRACT

Introduction: Hyperuricemia, a condition characterized by elevated levels of uric acid (UA) in the body, has been extensively studied to understand its associations with dietary factors and caffeine metabolites. However, it is important to note that the results of these studies are controversial, making the understanding of the relationship between diet and UA a field still under development. In addition to evaluating dietary intake, it is essential to consider the association of UA with biochemical markers that more accurately predict consumption, such as caffeine metabolites present in the body. **Objective:** To evaluate the association of dietary intake and caffeine metabolites with serum UA levels. Methods: A cross-sectional study was conducted using data from the National Health and Nutrition Examination Survey (NHANES) 2011-2012. The sample consisted of 3956 adults aged over 20 years, and a subsample of 1252 individuals with information on caffeine and its metabolites in urine. Dietary intake was assessed through two 24-hour dietary recalls. The presence of caffeine and 15 of its metabolites in urine was evaluated by LC-tandem MS with electrospray ionization. Serum UA was measured by the colorimetric method. Linear and logistic regressions were performed for the associations. **Results:** In linear regression analyses, carbohydrate intake (β=-0.001; p=0.043), saturated fat intake (β=-0.020; p=0.015), fiber intake (β=-0.018; p=0.012), calcium intake (β=-0.004; p=0.006), magnesium intake (β=-0.008; p=0.050), and cereal intake (β=-0.009; p=0.029) were inversely associated with serum UA levels, whereas alcohol intake (β=0.010; p<0.001) was positively associated with serum UA levels. In logistic regression analyses, alcohol intake (OR=1.02, 95% CI= 1.007 - 1.037) was associated with a higher chance of hyperuricemia, while vegetable intake (OR=0.99, 95% CI= 0.989 – 0.998) was associated with a lower chance of hyperuricemia. Dietary factors explained serum UA levels from 0.1% to 1.0%. Caffeine metabolites, including paraxanthine (β= -0.004, p= 0.006), theobromine (β= -0.004, p= <0.001), 7-methyluric acid (β= -0.003, p= 0.0033), 3,7-dimethyluric acid (β= -0.029, p= 0.024), 3-methylxanthine (β= -0.001, p= 0.038), and 7-methylxanthine (β= -0.001, p= 0.001), were inversely associated with serum UA levels, while 1,3-dimethyluric acid (β= 0.001, p= 0.012) was positively associated with serum UA levels. In logistic regression analyses, theobromine, 3-methyluric acid, 7-methyluric acid, and 3-methylxanthine were associated with a lower chance of hyperuricemia. **Conclusion:** This study highlights that carbohydrate intake, saturated fat intake, fiber intake, calcium intake, magnesium intake, and cereal intake are inversely associated with serum UA levels, while alcohol intake shows a positive association. Furthermore, the presence of theobromine and its metabolites, along with paraxanthine, exhibited an inverse association with serum UA levels, while 1,3-dimethyluric acid showed a positive association. These studies emphasize the importance of dietary factors and metabolites and their association with serum UA.

Keywords: Uric acid; hyperuricemia; dietary intake; caffeine; caffeine metabolites.

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Artigo 1: Association between dietary intake and serum uric acid: NHANES 2011-2012

Artigo 2: Association of caffeine and caffeine metabolites in the urine with serum uric acid levels and hyperuricemia. NHANES 2011-2012

LISTAS DE ABREVIATURAS

AU	Ácido Úrico
ATP	Trifosfato de Adenosina
CKD-EPI	Equação *Chronic Kidney Disease Epidemiology Collaboration*
HDL	Lipoproteína de Alta Densidade
IMC	Índice de Massa Corporal
IMMA	Índice de Massa Muscular Apendicular
LDL	Lipoproteína de Baixa Densidade
Mg/dL	Miligramas por Decilitro
NADPH	Dinucleotídeo de Adenina e Nicotinamida
OR	Odds Ratio
TFG-e	Taxa de Filtração Glomerular estimada
R^2	Coeficiente de Determinação
UI	Unidades Internacionais
VLDL	Lipoproteína de Muito Baixa Densidade
XO	Xantina Oxidase
ǂ	Média e Desvio Padrão
¥	Mediana, mínimo e máximo
*	Significância estatística
β	Coeficiente de Regressão

Sumário

1. INTRODUÇÃO

A hiperuricemia é caracterizada por níveis elevados de ácido úrico (AU), sendo amplamente definida pelo ponto de corte > 7,0 mg/dL e > 6,0 mg/dL para homens e mulheres, respectivamente (BOBULESCU; MOE, 2012; DE OLIVEIRA, E. P.; BURINI, R. C., 2012a; FANG; LI; LUO; WANG *et al.*, 2013). Níveis séricos elevados de AU podem ser causados pelo aumento da produção hepática e/ou redução da excreção intestinal e/ou renal desse metabólito (DE OLIVEIRA, E. P.; BURINI, R. C., 2012a). A produção exacerbada pode ocorrer pelo aumento da disponibilidade de nucleoproteínas (endógenas) e purinas dietéticas (exógenas), que são substratos para a via de síntese de AU (FATHALLAH-SHAYKH; CRAMER, 2014). A excreção reduzida pode ser predominantemente devido à função renal prejudicada, que representa 65-75% da excreção (FATHALLAH-SHAYKH; CRAMER, 2014).

A ingestão dietética tem sido amplamente estudada devido à sua capacidade de afetar os níveis de AU, e vários fatores dietéticos têm sido associados à hiperuricemia (CHAUDHARY; BRIDGES; SAAG; RAHN *et al.*, 2020; HUANG; LI; HUANG; WANG *et al.*, 2012; KAKUTANI-HATAYAMA; KADOYA; OKAZAKI; KURAJOH *et al.*, 2015; TAKAHASHI; DE OLIVEIRA; DE CARVALHO; DE SOUZA DANTAS *et al.*, 2011). A ingestão de carne, frutos do mar e álcool foi associada ao aumento da produção de AU (KANEKO; AOYAGI; FUKUUCHI; INAZAWA *et al.*, 2014), enquanto a ingestão de laticínios, cereais, hortaliças, frutas, legumes, vitamina C e café foi associada à redução da produção e, principalmente, aumento da renal excreção de AU (KAKUTANI-HATAYAMA; KADOYA; OKAZAKI; KURAJOH *et al.*, 2015; MAJOR; TOPLESS; DALBETH; MERRIMAN, 2018).

A cafeína é um composto encontrado em muitas bebidas e alimentos, como café, chá, refrigerantes e chocolate, e seu consumo está associado a uma variedade de efeitos fisiológicos, incluindo o aumento do estimulo do sistema nervoso central e aumento da excreção urinária de água e sódio (RYBAK, M. E.; STERNBERG, M. R.; PAO, C.-I.; AHLUWALIA, N. *et al.*, 2015). Os metabólitos da cafeína na urina, como a teofilina e a paraxantina, são frequentemente utilizados como indicadores do consumo de café e outros produtos que contêm cafeína (GRANT; TANG; KALOW, 1983).

No entanto, não existe um consenso na literatura que demonstre quais fatores dietéticos estão associados com AU na população geral (Macfarlane e Kim, 2014), uma vez que os mesmos fatores alimentares podem apresentar resultados conflitantes quanto

a sua associação com o ácido úrico sérico. Além disso, ainda não está claro se os metabólitos da cafeína estão associados com os níveis séricos de AU (KAKUTANI-HATAYAMA; KADOYA; OKAZAKI; KURAJOH *et al.*, 2015; ZGAGA; THEODORATOU; KYLE; FARRINGTON *et al.*, 2012).

A associação entre o AU sérico e o consumo alimentar juntamente com os metabólitos da cafeína é um tema relevante de pesquisa, pois o aumento do AU está associado a uma variedade de doenças crônicas, incluindo doenças cardiovasculares, diabetes mellitus tipo 2, hipertensão arterial e doenças renais (TAKAHASHI; DE OLIVEIRA; DE CARVALHO; DE SOUZA DANTAS *et al.*, 2011; ZOU; ZHAO; WANG, 2021). Além disso, a dieta pode ser um dos determinantes dos níveis séricos de AU, uma vez que a dieta têm sido associada como um dos fatores determinantes dos níveis séricos de AU (CHOI; ATKINSON; KARLSON; WILLETT *et al.*, 2004a; CHOI; LIU; CURHAN, 2005; EKPENYONG; DANIEL, 2015).

Apesar da importância da relação entre AU, consumo alimentar e metabólitos da cafeína na urina, ainda existem lacunas no conhecimento sobre essa associação em uma amostra representativa de americanos não institucionalizados. Estudos anteriores foram realizados em amostras específicas, como pacientes com diabetes ou doença renal crônica (JOHNSON; BAKRIS; BORGHI; CHONCHOL *et al.*, 2018), em pesquisas anteriores do NHANES (CHOI; LIU; CURHAN, 2005; RYBAK, M. E.; STERNBERG, M. R.; PAO, C.-I.; AHLUWALIA, N. *et al.*, 2015) e populações de outros países, com diferentes padrões alimentares e culturais. Em adição, ainda não está claro se os metabólitos da cafeína estão associados com os níveis séricos de AU (RYBAK, M. E.; STERNBERG, M. R.; PAO, C.-I.; AHLUWALIA, N. *et al.*, 2015).

2. FUNDAMENTAÇÃO TEÓRICA

2.1. Metabolismo do ácido úrico

2.1.1. Síntese do ácido úrico

O AU (2,6,8-trihidroxipurina C5H4N4O3) é um composto orgânico produzido pelo fígado como produto final do metabolismo das purinas (hipoxantina, adenina e guanina) pela ação da xantina oxidase (XO), que pode ser inibida farmacologicamente por medicamentos hipouricêmicos, como Allopurinol® e Febuxostat® (BOBULESCU; MOE, 2012). As purinas exógenas podem variar de acordo com a dieta, através da ingestão de fontes de proteínas. As purinas endógenas são derivadas de nucleoproteínas, que podem se originar da depleção celular ou dos nucleotídeos gerados durante a

decomposição do trifosfato de adenosina (ATP) (DE OLIVEIRA, E. P.; BURINI, R. C., 2012a; EKPENYONG; DANIEL, 2015; JOHNSON; LANASPA; GAUCHER, 2011). Além disso, os nucleotídeos podem ser reciclados por vias de recuperação ou por síntese *de novo*, o que requer o uso de dinucleotídeo de nicotinamida e adenina fosfato (NADP) (DE OLIVEIRA, ERICK PRADO; BURINI, ROBERTO CARLOS 2012). Através dos processos de desaminação, hidrólise e fosforilação, os nucleotídeos monofosfato de adenosina (AMP), monofosfato de guanosina (GMP) e monofosfato de inosina (IMP) são metabolizados em hipoxantina, guanina e xantina (BOBULESCU; MOE, 2012). Em seguida, a hipoxantina é metabolizada em xantina pela ação da XO, enquanto a guanina sofre biotransformação em xantina através do processo de desaminação (BOBULESCU; MOE, 2012; JOHNSON; LANASPA; GAUCHER, 2011). A xantina resultante é novamente oxidada pela XO e sofre biotransformação em AU como metabólito final (MAIUOLO, J.; OPPEDISANO, F.; GRATTERI, S.; MUSCOLI, C. *et al.*, 2016).

2.1.2. Excreção do ácido úrico

Na maioria dos mamíferos, as concentrações séricas de AU são baixas (1-3 mg) devido à ação da enzima uricase, que degrada o AU em 5-hidroxiisourato e alantoína (SAUTIN; JOHNSON, 2008). No entanto, durante a evolução da espécie humana, houve uma mutação inativadora da enzima uricase, resultando em maiores concentrações circulantes de AU (JOHNSON; BAKRIS; BORGHI; CHONCHOL *et al.*, 2018). O AU é um ácido diprótico fraco e a maior parte dele está presente no fluido extracelular (DE OLIVEIRA, ERICK PRADO; BURINI, ROBERTO CARLOS 2012). Em pH fisiológico (pH 7.4), o AU existe principalmente como urato (o sal do AU), que tem baixa solubilidade no plasma, uma vez que os níveis sanguíneos de AU em humanos estão próximos do limite de solubilidade (6,8 mg/dL) (BOBULESCU; MOE, 2012; DE OLIVEIRA, ERICK PRADO; BURINI, ROBERTO CARLOS 2012). No entanto, o AU apresenta uma solubilidade plasmática 70% maior quando está ligado à albumina (o principal transportador no fluxo sanguíneo) (DE OLIVEIRA, ERICK PRADO; BURINI, ROBERTO CARLOS 2012).

O AU precisa ser continuamente excretado para manter a homeostase (HUANG; LI; HUANG; WANG *et al.*, 2012). Aproximadamente 25% a 35% é excretado pelo intestino e metabolizado por bactérias intestinais no processo de uricolise intestinal, mas o mecanismo de transporte desse AU é incerto (BOBULESCU; MOE, 2012; JOHNSON; BAKRIS; BORGHI; CHONCHOL *et al.*, 2018). Aproximadamente 65% a 75% do AU é

eliminado pelos rins (FATHALLAH-SHAYKH; CRAMER, 2014; HUANG; LI; HUANG; WANG *et al.*, 2012). Em indivíduos saudáveis, a maior parte do AU circulante é livremente filtrada nos glomérulos renais e aproximadamente 90% é reabsorvida no segmento S1 do túbulo proximal (reabsorção pré-secretória). No segmento S2 do túbulo proximal, a maior parte do AU é secretada e uma quantidade menor é reabsorvida. A reabsorção pós-secretória ocorre em uma região distal do túbulo proximal (BOBULESCU; MOE, 2012; MAIUOLO, J.; OPPEDISANO, F.; GRATTERI, S.; MUSCOLI, C. *et al.*, 2016; MAIUOLO, JESSICA; OPPEDISANO, FRANCESCA; GRATTERI, SANTO; MUSCOLI, CAROLINA *et al.*, 2016). Os principais transportadores que promovem a reabsorção do AU são os transportadores de urato humano 1 (URAT1) e os transportadores de glicose 9 (GLUT9), que ocorrem na membrana apical (membrana luminal) dos néfrons e na membrana basolateral dos rins humanos, respetivamente (BOBULESCU; MOE, 2012; EKPENYONG; DANIEL, 2015).

Vários fatores podem afetar o equilíbrio do AU, como aumento da concentração plasmática, volume sanguíneo, moduladores do fluxo plasmático renal e diminuição da taxa de filtração glomerular (TFG), o que pode influenciar a reabsorção e excreção renal do AU (DE OLIVEIRA, ERICK PRADO; BURINI, ROBERTO CARLOS 2012). Assim, doenças renais podem promover perdas na excreção, aumentando as concentrações séricas de AU (DE OLIVEIRA, ERICK PRADO; BURINI, ROBERTO CARLOS 2012; MOUNT; KWON; ZANDI-NEJAD, 2006).

2.2. Hiperuricemia

2.2.1. Hiperuricemia e gota

A hiperuricemia é caracterizada por concentrações séricas de AU que excedem o valor médio de normalidade, comumente definido como > 7.0 mg/dL (> 420 μmol/L) para homens adultos e > 6.0 mg/dL (> 360 μmol/L) para mulheres adultas (BOBULESCU; MOE, 2012; FANG; LI; LUO; WANG *et al.*, 2013), embora não haja consenso na literatura em relação a esses valores de corte (COHEN; PILLINGER; TOPROVER, 2020). As concentrações séricas de AU geralmente são mais baixas em mulheres antes da menopausa devido aos efeitos uricosúricos dos estrogênio (JOHNSON; BAKRIS; BORGHI; CHONCHOL *et al.*, 2018). Após a menopausa, ocorre um aumento do AU, atingindo concentrações semelhantes às observadas em homens (JOHNSON; BAKRIS; BORGHI; CHONCHOL *et al.*, 2018). Considerando que a solubilidade do

plasma humano é de aproximadamente 6,8 mg/dL, concentrações de AU de 7.0 mg/dL podem ser consideradas elevadas (BOBULESCU; MOE, 2012; DE OLIVEIRA, ERICK PRADO; BURINI, ROBERTO CARLOS 2012). No entanto, o aumento na solubilidade do AU ligado à albumina pode resultar em concentrações acima de 10.0 mg/dL sem produção de cristais de AU (JOHNSON; BAKRIS; BORGHI; CHONCHOL *et al.*, 2018).

A hiperuricemia crônica é um fator de risco para o desenvolvimento da gota, que é caracterizada pela deposição crônica e/ou episódica de cristais de monourato de sódio nas articulações (ZHANG, 2021). No entanto, embora a hiperuricemia possa ser um fator predisponente para a gota, apenas 10% dos pacientes com hiperuricemia desenvolvem a doença (ZHANG, 2021). Isso pode ser parcialmente explicado por fatores ambientais, processos inflamatórios decorrentes da doença subjacente do indivíduo e hereditariedade (RICHETTE; BARDIN, 2010; ZHANG, 2021).

2.2.2. Fatores relacionados à hiperuricemia

As comorbidades associadas à AU são amplamente descritas na literatura (CHAUDHARY; BRIDGES; SAAG; RAHN *et al.*, 2020; HUANG; LI; HUANG; WANG *et al.*, 2012; TAKAHASHI; DE OLIVEIRA; DE CARVALHO; DE SOUZA DANTAS *et al.*, 2011). Dados epidemiológicos prospectivos mostram AU como um fator de risco para a síndrome metabólica, seus componentes e obesidade devido a processos inflamatórios, disfunção das células endoteliais e estresse oxidativo que geralmente aumentam em pacientes juntamente com o aumento dos níveis séricos de AU (SUI; CHURCH; MERIWETHER; LOBELO *et al.*, 2008; WANG; ZHANG; SUN; GUO, 2018). No entanto, a relação entre AU e essas comorbidades é complexa e pode ser bidirecional, pois a fisiopatologia dessas comorbidades pode aumentar os níveis séricos de AU, uma vez que há diminuição da excreção renal de AU devido à resistência vascular e/ou resistência à insulina aumentada (DE OLIVEIRA, E. P.; BURINI, R. C., 2012a; FATHALLAH-SHAYKH; CRAMER, 2014). Além disso, a hiperlipidemia presente nesses pacientes, especialmente a hipertrigliceridemia, pode aumentar as concentrações séricas de AU, uma vez que a síntese de ácidos graxos no fígado está associada à síntese de purina *de novo*, acelerando a produção de AU (DE OLIVEIRA, E. P.; BURINI, R. C., 2012a). O raciocínio bidirecional também pode ser observado na doença renal crônica, uma vez que há diminuição da taxa de filtração glomerular (TFG), devido à diminuição da secreção tubular ou aumento da reabsorção tubular, resultando

em diminuição da filtração e aumento das concentrações de AU (FATHALLAH-SHAYKH; CRAMER, 2014). Por outro lado, maiores níveis de AU sérico têm sido associados com desfechos favoráveis como maior força e massa muscular (NAHAS; DE BRANCO; AZEREDO; RINALDI *et al.*, 2022; NAHAS; ROSSATO; DE BRANCO; AZEREDO *et al.*, 2021).

A ingestão alimentar tem sido amplamente associada aos níveis de AU, sendo propostas como estratégias não farmacológicas para controlar os níveis de AU (BEYL; HUGHES; MORGAN, 2016; EKPENYONG; DANIEL, 2015; KAKUTANI-HATAYAMA; KADOYA; OKAZAKI; KURAJOH *et al.*, 2015; LI; ZHANG; ZENG, 2020; MACFARLANE; KIM, 2014; RODDY; CHOI, 2014). Alguns mecanismos explicam a relação entre os fatores dietéticos e o aumento da produção, diminuição da produção e/ou aumento da excreção renal de AU (BEYL; HUGHES; MORGAN, 2016; CHOI, 2010).

2.3. Dieta e ácido úrico

2.3.1. Carnes e frutos do mar

Não há consenso na literatura sobre quais tipos de carnes e frutos do mar estão associados ao aumento dos níveis de AU (CHOI; ATKINSON; KARLSON; WILLETT *et al.*, 2004b; VILLEGAS; XIANG; ELASY; XU *et al.*, 2012). No entanto, um dos mecanismos propostos sugere que fontes de proteína animal podem estar envolvidas na via de síntese de AU devido ao seu alto teor de purinas, que são substratos para a produção de AU (DE OLIVEIRA, E. P.; BURINI, R. C., 2012b). Além disso, as carnes possuem maiores quantidades de hipoxantina, que pode ser oxidada em quantidades maiores do que outras purinas, como a adenina e a guanina (KANEKO; AOYAGI; FUKUUCHI; INAZAWA *et al.*, 2014). Além disso, os produtos de degradação de nucleotídeos e nucleoproteínas presentes na carne podem causar efeitos hiperuricêmicos mais elevados (KANEKO; AOYAGI; FUKUUCHI; INAZAWA *et al.*, 2014; MAIUOLO, JESSICA; OPPEDISANO, FRANCESCA; GRATTERI, SANTO; MUSCOLI, CAROLINA *et al.*, 2016).

2.3.2. Álcool

O consumo de bebidas alcoólicas tem sido reconhecido como um fator de risco para o aumento dos níveis de AU (CHOI; ATKINSON; KARLSON; WILLETT *et al.*, 2004a; SILVA; DINIZ; COELHO; VIDIGAL *et al.*, 2019; TOWIWAT, P.; LI, Z., 2015).

O consumo de álcool está fortemente associado a um maior risco de gota, e esse risco varia substancialmente de acordo com o tipo de bebida alcoólica, sendo a cerveja aparentemente a de maior risco em comparação com outros tipos de bebida (CHOI; ATKINSON; KARLSON; WILLETT *et al.*, 2004a; SILVA; DINIZ; COELHO; VIDIGAL *et al.*, 2019).

Os mecanismos incluem o metabolismo do acetato, que aumenta a produção de nucleotídeos de adenosina, resultando em um substrato para a via de produção de AU (CHOI; CURHAN, 2005). O consumo de cerveja contribui para um aumento de AU, mesmo com um teor alcoólico moderado, devido ao alto teor de purinas, predominantemente guanosina, que é facilmente absorvida e causa efeitos hiperuricêmicos (KANEKO; AOYAGI; FUKUUCHI; INAZAWA *et al.*, 2014). Além disso, o consumo crônico de álcool pode desencadear um aumento nos níveis séricos de lactato, o que reduz a excreção renal de AU pelos túbulos renais (EKPENYONG; DANIEL, 2015).

2.3.3. Cereais, frutas, legumes, vegetais e oleaginosas

O consumo de cereais, frutas, legumes, vegetais e oleaginosas têm sido associados aos menores níveis de AU sérico (CHOI; ATKINSON; KARLSON; WILLETT *et al.*, 2004b; VILLEGAS; XIANG; ELASY; XU *et al.*, 2012). Esse alimentos contêm polifenóis (flavonoides, isoflavonas e ácidos fenólicos) em sua composição (EKPENYONG; DANIEL, 2015). Esses compostos competem pela ligação com a enzima XO e podem atuar na via de inibição da produção de AU. Além disso, os polifenóis possuem ação antioxidante, o que pode reduzir o estresse oxidativo, aumentando a excreção renal de AU e exercendo um efeito anti-hiperuricêmico (EKPENYONG; DANIEL, 2015; MEHMOOD; ZHAO; WANG; NADEEM *et al.*, 2019). A fibra alimentar presente em vegetais, frutas e grãos também pode contribuir para a redução do AU sérico, inibindo a digestão e absorção de nucleotídeos e nucleoproteínas presentes na dieta (EKPENYONG; DANIEL, 2015; NAKAGAWA; TUTTLE; SHORT; JOHNSON, 2005).

2.3.4. Laticínios

Os produtos lácteos (como leite, queijo e iogurte) podem desempenhar um papel protetor para as altas concentrações de AU (CHOI; ATKINSON; KARLSON; WILLETT *et al.*, 2004b; CHOI; LIU; CURHAN, 2005; EKPENYONG; DANIEL, 2015; SILVA;

DINIZ; COELHO; VIDIGAL *et al.*, 2019). Essa proteção pode ser explicadas pela composição desses alimentos (EKPENYONG; DANIEL, 2015). Proteínas presentes no leite, como caseína e lactoalbumina, podem exercer efeitos uricosúricos (EKPENYONG; DANIEL, 2015). Além disso, o ácido orótico e o cálcio, presentes no leite, podem reduzir a concentração sérica de AU, promovendo a diminuição da reabsorção e o aumento da excreção renal de AU. No entanto, são necessários mais estudos para confirmar esses mecanismos (DE OLIVEIRA, ERICK PRADO; BURINI, ROBERTO CARLOS 2012; EKPENYONG; DANIEL, 2015; KAKUTANI-HATAYAMA; KADOYA; OKAZAKI; KURAJOH *et al.*, 2015; KANEKO; AOYAGI; FUKUUCHI; INAZAWA *et al.*, 2014).

2.3.5. Vitamina C

A ingestão de vitamina C e as menores concentrações séricas de AU (efeito uricosúrico) têm sido demonstradas em vários estudos (HUANG; APPEL; CHOI; GELBER *et al.*, 2005; JURASCHEK; MILLER; GELBER, 2011; STAMP; O'DONNELL; FRAMPTON; DRAKE *et al.*, 2013). O mecanismo potencial pelo qual a vitamina C pode reduzir as concentrações séricas de AU inclui o efeito de aumentar a TFG e, consequentemente, promover o aumento da excreção urinária de AU. Esse efeito pode ser devido à competição da vitamina C com a AU pelos transportadores aniônicos dependentes de sódio e com o URAT1 na reabsorção renal (BEYL; HUGHES; MORGAN, 2016; EKPENYONG; DANIEL, 2015; MACFARLANE; KIM, 2014). Além disso, a vitamina C é um potente antioxidante que pode aumentar a excreção de AU pelos rins, reduzindo a isquemia microvascular nos glomérulos, o que leva ao aumento do fluxo sanguíneo no local, dilatação das arteríolas aferentes e competição pela reabsorção com íons como sódio e potássio, que exercem efeitos osmóticos (TOWIWAT, P.; LI, Z.-G., 2015).

2.3.6. Cafeína

O consumo de cafeína e suas fontes (café e chás) está associado a concentrações mais baixas de AU no soro (CHOI; CURHAN, 2007; 2010; CHOI; WILLETT; CURHAN, 2007; PARK; KIM; AHN; KIM *et al.*, 2016). Possíveis explicações para essas associações incluem o fato de que a cafeína é uma metilxantina que possui afinidade com a enzima XO, levando a uma diminuição na produção de AU ao reduzir a disponibilidade de XO para a via de síntese de AU (EKPENYONG; DANIEL, 2015; RODDY; DOHERTY, 2010). Além disso, outros compostos presentes no café e nos

chás, como o ácido clorogênico e as catequinas, que são polifenóis, podem inibir competitivamente a ação da enzima XO, além de atuarem como antioxidantes, reduzindo o estresse oxidativo e a resistência à insulina, resultando em um efeito uricosúrico (conforme demonstrado em experimentos com ratos) (BEYL; HUGHES; MORGAN, 2016; MACFARLANE; KIM, 2014; MEHMOOD; ZHAO; WANG; NADEEM *et al.*, 2019; PARK; KIM; AHN; KIM *et al.*, 2016).

2.4. Cafeína e metabolitos da cafeína

2.4.1. Metabolismo da cafeína

O metabolismo da cafeína é descrito como um processo de eliminação de primeira ordem em humanos saudáveis, com uma eliminação não significativa de primeira passagem. A cafeína é metabolizada principalmente no fígado por enzimas do citocromo P450, com a CYP1A2 sendo responsável por mais de 90% da sua eliminação (NEHLIG, 2018). A metabolização da cafeína pode ser saturável em doses mais baixas, especialmente na demetilação em paraxantina, que é seletivamente catalisada pela CYP1A2 (TEMPLE; BERNARD; LIPSHULTZ; CZACHOR *et al.*, 2017). A cinética da cafeína também pode ser influenciada pela presença de alimentos no estômago e pelo esvaziamento gástrico (LELO; BIRKETT; ROBSON; MINERS, 1986). A variação interindividual na atividade da CYP1A2 pode influenciar a disposição da cafeína e pode ser influenciada por fatores como gênero, raça, polimorfismos genéticos e exposição a indutores (DE KESEL; LAMBERT; STOVE, 2015).

2.4.2. Metabólitos da cafeína

Os principais metabólitos da cafeína incluem a paraxantina (1,7-dimetilxantina), teobromina (3,7-dimetilxantina) e teofilina (1,3-dimetilxantina) (GRZEGORZEWSKI; BARTSCH; KÖLLER; KÖNIG, 2021). Além disso, foram identificados vários outros metabólitos, incluindo uracil derivados produzidos a partir de cafeína, 1,3,7-dimetilurato (1,3,7DAU), 1,3,8-trimetilalanina, 1,3-dimetilurato (1,3DMU), 3-metilxantina (3MX), 1-metilurato (1MU), 1,7-dimetilurato (1,7DMU), 1,3,7-trimetilurato (1,3,7TMU), 7-metilurato (7MU), 3-metiluracil (3MU) e 6-amino-5-(N-formilmetilamino)-1-metiluracil (3,7DAU). As vias metabólicas variam entre as espécies animais e humanos, com diferentes enzimas envolvidas na metabolização da cafeína (ARNAUD, M. J., 2011; GRZEGORZEWSKI; BARTSCH; KÖLLER; KÖNIG, 2021).

2.4.3. Excreção da cafeína na urina e seus metabolitos

A excreção da cafeína e seus metabólitos na urina é um processo importante na eliminação da substância do organismo. Aproximadamente 70% da dose oral de cafeína é excretada na urina em humanos, com menos de 2% sendo excretado inalterado na forma de cafeína. A excreção urinária de cafeína e seus metabólitos é altamente dependente do fluxo urinário, variando com a quantidade de urina produzida. A cafeína e seus metabólitos primários, como a paraxantina, a teobromina e a teofilina, são extensivamente reabsorvidas no túbulo renal, com cerca de 98% de reabsorção tubular renal. (ARNAUD, M. J., 2011; NEHLIG, 2018). A excreção urinária de cafeína e seus metabólitos pode ser influenciada por fatores como a dose de cafeína consumida, a atividade das enzimas hepáticas envolvidas em sua metabolização, a presença de alimentos no estômago e o esvaziamento gástrico. A proporção de cada metabólito excretado na urina pode variar dependendo desses fatores. Em humanos, os metabólitos da cafeína mais comuns excretados na urina são a 1,7-dimetilurato, o ácido 1-metilurato, o ácido 1,3-dimetilurato, o ácido 1,3,7-trimetilurato e a própria cafeína (ARNAUD, MAURICE J., 2011; CARRILLO; BENITEZ, 2000; GLADE, 2010).

2.4.4. Metabolitos da cafeína na urina

A cafeína é metabolizada no fígado em três metabólitos principais primários: paraxantina, teobromina e teofilina. A paraxantina é o principal metabólito da cafeína na urina, representando cerca de 84% da dose excretada (CARRILLO; BENITEZ, 2000). A teobromina e a teofilina são excretadas em quantidades menores, representando cerca de 12% e 4% da dose excretada, respectivamente (NEHLIG, 2018). Outros metabólitos menores também podem ser encontrados na urina, como a 1,3-dimetilxantina e a 1-metilxantina. A proporção de cada metabólito excretado na urina pode variar dependendo de fatores como a dose de cafeína consumida e a atividade das enzimas hepáticas envolvidas em sua metabolização (ARNAUD, M. J., 2011).

2.4.5. Paraxantina

A paraxantina é a principal via para o metabolismo da cafeína em humanos (72%) e raramente é encontrada como um composto dietético (RYBAK, M. E.; STERNBERG, M. R.; PAO, C. I.; AHLUWALIA, N. *et al.*, 2015). Em humanos, a paraxantina é um dos principais metabólitos da cafeína e é metabolizada principalmente pelo citocromo P450 1A2 (CYP1A2)(GUNES; DAHL, 2008). Além disso, a paraxantina é convertida em seu

metabólito conjugado, paraxantina glucuronídeo, que é excretado na urina (GUILLEMETTE; LÉVESQUE; ROULEAU, 2014). Em ratos, a paraxantina é metabolizada em vários metabólitos, incluindo 1-metilxantina, 3-metilxantina, 7-metilxantina, 1,7-dimetilxantina e 3,7-dimetilxantina, enquanto que em humanos a paraxatia é matabolizada em 1-metilxantina, 7-metilxantina e 1,7-dimetilúrico (CASCORBI, 2003) (Figura 1).

2.4.6. Teofilina

A teofilina é uma metilxantina encontrada naturalmente em algumas plantas, como o chá verde, o café e o cacau (FARZAEI; BAHRAMSOLTANI; ABBASABADI; BRAIDY *et al.*, 2019). No entanto, a teofilina também é produzida sinteticamente e é usada como medicamento para tratar doenças respiratórias, como a asma e a doença pulmonar obstrutiva crônica (DPOC) (HANSEL; TENNANT; TAN; HIGGINS *et al.*, 2004).

O metabolismo da teofilina é complexo e envolve várias enzimas do citocromo P450 (CYP). A principal via metabólica é a N-demetilação, que é catalisada principalmente pela enzima CYP1A2 (BALL; MCGUIRE, 2013). Outras vias metabólicas incluem a O-demetilação, a hidroxilação e a formação de uracil derivados. A taxa de metabolismo da teofilina é não linear e pode ser afetada por fatores como a idade, a dieta e o uso de medicamentos que afetam as enzimas do CYP. A teofilina é excretada principalmente na urina, com uma pequena quantidade sendo excretada na bile (ARNAUD, MAURICE J., 2011; HALEY, 1983).

Os principais metabólitos da teofilina são 1,3-dimetilurico (1,3-DMU), e a 1-metilxantina (1-MX). A 1,3-DMU é o principal metabólito e é formada principalmente pela enzima CYP1A2. A 1-MX e a 3-MX são formadas pela N-demetilação da teofilina e são catalisadas principalmente pela enzima CYP1A2 em humanos. Outros metabólitos incluem a 7-acetilxantina, a 1,7-dimetilxantina e a 3,7-dimetilxantina (ARNAUD, MAURICE J., 2011; HALEY, 1983). A proporção de cada metabólito varia dependendo da dose e da via de administração da teofilina, bem como da idade e do estado de saúde do indivíduo (BARNES, 2010) (Figura 1).

2.4.7. Teobromina

A teobromina é encontrada naturalmente em algumas plantas, como o cacau, o chá mate e o chá verde. O cacau é a principal fonte de teobromina na dieta humana, sendo

encontrada em produtos de chocolate, como barras de chocolate, chocolate em pó e bebidas de chocolate. A teobromina também é usada como ingrediente em alguns alimentos e bebidas, como refrigerantes e suplementos energéticos. Além disso, a teobromina é produzida sinteticamente e é usada como medicamento para tratar a tosse e outras condições respiratórias (ARNAUD, MAURICE J., 2011; ZOUMAS; KREISER; MARTIN, 1980).

O metabolismo da teobromina é semelhante ao da teofilina, pois ambas são metilxantinas. A principal via metabólica da teobromina é a N-demetilação, que é catalisada principalmente pela enzima CYP1A2. Outras vias metabólicas incluem a O-demetilação, a hidroxilação e a formação de uracil derivados. Os principais metabólitos da teobromina são a 3-metilxantina (3-MX), a 7-metilxantina (7-MX) e a 3,7-dimetilurico (3,7-DMU) (TARKA JR; ARNAUD; DVORCHIK; VESELL, 1983). A proporção de cada metabólito varia dependendo da dose e da via de administração da teobromina, bem como da idade e do estado de saúde do indivíduo (ZHOU; XUE; YU; LI *et al.*, 2007). A teobromina é excretada principalmente na urina, com uma pequena quantidade sendo excretada na bile (ARNAUD, MAURICE J., 2011) (Figura 1).

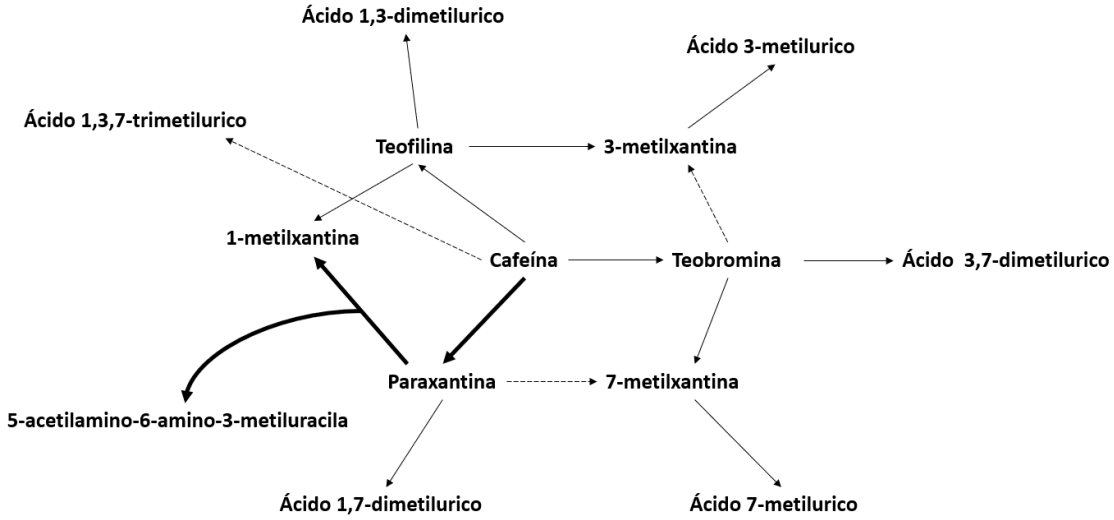

Figura 1. Resumo das vias metabólicas da cafeína e dos seus metabólitos.
Imagem adaptada (RYBAK, M. E.; STERNBERG, M. R.; PAO, C. I.; AHLUWALIA, N. et al., 2015)

2.5. Cafeína e ácido úrico

Alguns estudos investigaram a associação entre o consumo de café e de seus

componentes, como a cafeína, sobre os níveis de AU e a ocorrência de hiperuricemia. Choi e Curhan observaram que a ingestão de 4 a 5 e ≥ 6 xícaras/dia de café estava inversamente associada aos níveis séricos de AU. A ingestão de cafeína de 93-159 mg/dia foi inversamente associada aos níveis séricos de AU. Houve uma associação inversa modesta entre a ingestão de café descafeinado e os níveis séricos de AU (CHOI; CURHAN, 2007). Kiyohara, et al. investigaram a associação entre a ingestão de café e chá verde com os níveis séricos de AU em 2240 trabalhadores de meia-idade que eram ex-militares. Os autores descobriram que a ingestão de café de > 5 xícaras/dia estava associada a menores níveis séricos de AU, enquanto a ingestão de chá verde não estava associada aos níveis séricos de AU (KIYOHARA; KONO; HONJO; TODOROKI *et al.*, 1999). Em contraste, Bae, et al. não encontraram uma associação entre a ingestão de café e cafeína e hiperuricemia em mulheres, apenas uma associação positiva para a ingestão de chá verde e AU sérico em homens (BAE; PARK; CHUN; CHOI *et al.*, 2015).

Embora esses estudos sugiram uma possível associação entre cafeína e AU sérico, os resultados dos estudos são inconsistentes e ainda não há consenso na literatura científica. Além disso, no melhor do nosso conhecimento, não foram realizados estudos avaliando a associação entre os metabolitos da cafeina isolados (paraxantina, teobromina, teofilina, entre outros) e o AU sérico.

2.6. National Health and Nutrition Examination Survey

O National Health and Nutrition Examination Survey (NHANES) é um programa contínuo realizado pelo National Center for Health Statistics (NCHS), que faz parte do Centers for Disease Control and Prevention (CDC). O objetivo do NHANES é avaliar a saúde e o estado nutricional dos indivíduos nos Estados Unidos (EUA) (CDC, 2019). Iniciado na década de 60 e tornando-se um programa contínuo a partir de 1999, o NHANES é realizado bienalmente e abrange uma ampla gama de variáveis demográficas, socioeconômicas, dietéticas e relacionadas à saúde para atender às necessidades emergentes. A amostra do NHANES é representativa da população dos EUA em todas as faixas etárias, incluindo idosos. Com o crescimento significativo do número de idosos nos EUA nas últimas décadas, o NHANES desempenha um papel fundamental no aumento do conhecimento sobre a saúde dessa população (CDC, 2023).

O NHANES foi projetado para facilitar a condução de pesquisas e incentivar a participação da população. As entrevistas de saúde são realizadas nas residências dos participantes, enquanto as avaliações físicas são feitas em unidades móveis que percorrem

todo o país. Um sistema avançado de computadores é utilizado para coletar e processar todos os dados do NHANES, reduzindo a necessidade de formulários em papel e operações de codificação manual. As informações obtidas no NHANES são disponibilizadas por meio de publicações no site do programa e em artigos científicos, e os dados são publicamente acessíveis online em todo o mundo (CDC, 2023).

Os resultados das avaliações realizadas no NHANES são amplamente utilizados em pesquisas epidemiológicas na área da saúde. Eles são essenciais para determinar a prevalência de doenças, fatores de risco e fatores de proteção, além de contribuírem para o desenvolvimento de políticas públicas de saúde, orientando a promoção da saúde e a prevenção de doenças (CDC, 2023).

3. OBJETIVOS

3.1. Objetivo geral

Avaliar a associação entre consumo alimentar, metabólitos da cafeína na urina e níveis de AU em adultos.

3.2. Objetivos específicos

- Associar o consumo alimentar com os níveis séricos de AU.
- Associar a cafeína na urina e os metabólitos da cafeína na urina com os níveis séricos de AU.

4. ARTIGOS

Artigo 1: Association between dietary intake and serum uric acid: NHANES 2011-2012

Original Article

Association between dietary intake and serum uric acid: NHANES 2011-2012

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Abstract

Objective: To evaluate the association of dietary intake with serum uric acid (UA) levels. **Methods:** A Cross-sectional study was performed evaluating 3956 adults aged over 20 years from National Health and Nutrition Examination Survey (NHANES) 2011-2012. The dietary intake was assessed using two 24-hour food recalls. We evaluated the usual intake of energy, carbohydrate, total protein, animal and vegetable protein, total fat, cholesterol, saturated fat, monounsaturated and polyunsaturated fatty acids, omega-3, omega-6, fiber, sugar, alcohol, caffeine, theobromine, vitamin C, calcium, zinc, magnesium, and food groups. UA was measured by the colorimetric method. Linear and logistic regression were performed for the associations. **Results:** In linear regression analyses, carbohydrate (β=-0.001; p=0.043), saturated fat (β=-0.020; p=0.015), fiber (β=-0.018; p=0.012), calcium (β=-0.004; p=0.006), magnesium (β=-0.008; p=0.050), and cereals (β=-0.009; p=0.029) intakes were inversely associated with serum UA, whereas alcohol intake (β=0.010; p<0.001) was positively associated with serum UA levels. In logistic regression analyses, alcohol intake (OR=1.02, CI 95%= 1.007 - 1.037) was associated with a higher chance of hyperuricemia, while vegetables intake (OR=0.99, CI 0.989 – 0.998) was associated with a lower chance of hyperuricemia. Dietary factors explained serum UA levels from 0.1% to 1.0%. **Conclusion:** Carbohydrate, saturated fat, fiber, calcium, magnesium, and cereals intakes were inversely associated with serum UA levels, while vegetable intake was associated with a lower chance of hyperuricemia. Alcohol intake was positively associated with serum UA levels and with a higher chance of hyperuricemia. Several nutrients showed significant associations, however, the biological significance is questionable since UA variations is small.

Keywords: Uric acid; hyperuricemia; dietary intake

Introduction

Hyperuricemia is characterized by elevated uric acid (UA) levels, being widely defined by the cutoffs > 7.0 mg/dL, and > 6.0 mg/dL for men and women, respectively [1-3]. Elevated serum UA levels may be caused by increased production (hepatic) and/or reduced excretion (intestinal and/or renal) of this metabolite [1]. Exacerbated production can occur through the increased availability of nucleoproteins (endogenous) and dietary purines (exogenous), which are substrates for the UA synthesis pathway [4]. The reduced excretion may be predominantly due to impaired renal function, which represents 65-75% of excretion [4]. Elevated UA levels may be an important risk factor for cardiovascular disease [5], is related to the progression of chronic kidney disease [6], and one of the factors associated with metabolic syndrome [7].

Some foods and nutrients have been widely studied due to their capacity to affect UA levels and may increase synthesis and/or decrease the excretion of UA levels and, therefore, may be associated with hyperuricemia [7-10]. The intake of meat, seafood, and alcohol was associated with increased production of UA [11], while the intake of dairy products, cereals, vegetables, fruits, legumes, vitamin C, and coffee was associated with reduced production and, mainly, increased renal UA excretion [10, 12]. Previous studies have evaluated the association of dietary factors with serum UA, however, there is still a lack of conclusive evidence [13, 14], since there are conflicting results regarding foods and nutrients associated with serum UA[15, 16]. Additionally, the studies did not include important confounding variables such as medication use, serum triglyceride levels, and glomerular filtration rate that may confound the associations found due to possible modulatory effects on serum UA levels [1, 17-19]. Although several studies have already evaluated the association between diet and UA levels [12, 20, 21], few studies have evaluated the biological significance of the associations between UA and dietary factors [22].

Moreover, despite current evidence evaluated the general population [16, 20], the findings regarding the associations between nutrients and foods and serum levels of UA have not been fully elucidated. Therefore, the present study aimed to evaluate the association of dietary factors intake with UA levels.

Methods

Study Design and Subjects' Characteristics

This was a cross-sectional study based on data from the National Health and

Nutrition Examination Survey (NHANES) survey conducted by The National Center for Health Statistics of the Centers for Disease Control and Prevention, based on a multistage, probability, and stratified sampling design to assess the nutritional status and health of a nationally representative sample of the noninstitutionalized U.S. population.

Participants completed in-home interviews, physical examinations, biochemical tests, dietary interviews, and other examinations [23]. A total of 9756 individuals were evaluated in NHANES 2011-2012. The present study evaluated adults aged over 20 years from NHANES 2011-2012. Individuals with available demographic, health conditions (diabetes, hypertension, chronic kidney disease (CKD), arthritis, menopause, gout, allopurinol use) and behavior (physical activity and smoking status), anthropometric, biochemical parameters, and dietary data were included in the analyzes. However, in the present study, individuals who did not have dietary data assessment of two days, missing information on serum UA, glomerular filtration rate (eGFR), and anthropometry; women who were pregnant, and women who were breastfeeding were excluded. Thus, the present study evaluated 3956 individuals (3,234 individuals with normal UA levels and 722 individuals with elevated UA levels) (Figure 1). NHANES is a public data set and all participants provided written informed consent, consistent with approval from the National Center for Health Statistics Research Ethics Review Board (NCHS ERB) (Protocol #2011-17 for NHANES cycle 2011-2012).

Demographic data, health conditions, and behavior

The demographic characteristics evaluated were age (years), sex (men or women), race/ethnicity (non-Hispanic white or other), marital status single/divorced/widowed/never married or married/living as married), annual family income (0 to $19,999, from $20,000 to 54,999, $55,000 to 74,999, over $75,000) and educational level (under/ high school graduate and some college or over). Health conditions and behavior included in the present study were self-report of diabetes (no, yes, or pre-diabetes), hypertension (no or yes), CKD (no or yes), gout (no or yes), arthritis (no or yes), menopause (only for women; no or yes), physical activity (no or yes), smoking status (no or yes). Medicines included were allopurinol use (no or yes), aspirin (no or yes), and prednisone (no or yes). Annual family income a missing variable was created.

Anthropometric measurements

Body weight and height were evaluated according to Lohman's protocol [24] and body mass index (BMI) was calculated [25]. A retractable steel measuring tape was used to take circumferences. Waist circumference was measured from the point marked above the upper lateral border of the right ilium, crossing vertically with the midaxillary line, the tape was extending around the participant's waist [26].

Uric acid and biochemical analysis

UA and triglyceride levels were measured by the colorimetric method [27]. Elevated UA levels were defined as > 7.0 and > 6.0 mg/dl for men and women, respectively [28]. Urea was measured by the enzymatic conductivity rate method. Creatinine was measured by the Jaffe rate method. Serum creatinine was measured using the Roche/Hitachi Modular P Chemistry Analyzer [27]. eGFR was estimated by the CKD epidemiology collaboration (CKD-EPI) equation [29]. Glucose was measured by the oxygen rate method employing a Beckman Oxygen electrode (glucose oxidase method). Cholesterol and HDL-cholesterol were measured by the timed-endpoint method (through a reaction specific for HDL-cholesterol) [27]. LDL-cholesterol was obtained according to the Friedewald calculation: [LDL-cholesterol] = [total cholesterol] – [HDL-cholesterol] – [triglycerides/5] [27, 30].

Dietary intake

Dietary intake was assessed using two 24-hour food recalls for each volunteer. The first 24-hour food recall interview was collected in person and the second was collected by call 3 to 10 days later. Only individuals with two days of 24-hour food recall were considered to estimate the usual dietary intake [31]. The 24-hour dietary recalls were applied according to the 5-step multiple pass method [32], which conducts an interview in 5 steps (quick list, forgotten foods, time and occasion, detail cycle, and final probe). To process dietary intake, United States Department of Agriculture (USDA) Food and Nutrient Database for Dietary Studies (FNDDS) 2011-2012 was used for processing the 2011-2012 intakes (http://www.ars.usda.gov/ba/bhnrc/fsrg). The National Cancer Institute (NCI) method was used to estimate the usual intake of all nutrients, foods, and beverages [33] using SAS software.

The usual intake was evaluated for energy (kcal), carbohydrate (g), protein (g), protein (g/kg/day), animal protein (g) (from the protein of the combination of meat, poultry, and fish with additions), vegetable protein (g) (from the protein of the

combination of vegetable), total fat (g), cholesterol (mg), saturated fatty acids (g), monounsaturated fatty acids (g), polyunsaturated fatty acids (g), omega-3 (g) (sum of ALA (18:3n-3), DHA (22:6n-3), EPA (20:5n-3), and docosapentaenoic acid (DPA, 22:5n-3)), omega-6 (g) (linoleic acid (18:2n-6)), fiber (g), sugar (g), alcohol (g), caffeine (mg), theobromine (mg), vitamin C (mg), calcium (mg), zinc (mg), and magnesium (mg). The usual intake also was evaluated for foods and beverages as part of a combination, such as meat, poultry, and fish with additions (gravy, sauce, and condiments), cereals with additions (cereals ready-to-eat with milk, sugar, fruit, butter; bread, rolls, pancakes with butter, jam, syrup, fruit; cakes, pies with ice cream, toppings; crackers with cheese, dip, peanut butter; tacos and tortilla), fruits (g) with additions (toppings, milk, honey), vegetables (g), dried beans or tuber (g) with additions (beans with sauce, butter; and French fries, potatoes with catsup, gravy, butter, toppings), and coffee and teas (ml) with additions (with milk, cream, sugar).

Statistical analysis

Sociodemographic data, health conditions and behavior, medicines and supplements, anthropometric data, biochemical parameters, and dietary intake characteristics of individuals were described according to normal and elevated serum UA levels. The comparison between normal and elevated serum UA levels was performed through regression analysis. The continuous variables were described as mean and standard deviation and the categorical variables were described as percentage and confidence interval.

Linear regression analysis was performed to evaluate whether serum UA levels were associated with dietary intake. Each dietary component (independent variable) was inserted in the model with the confounder's variables to evaluate the prediction of the UA variances (dependent variable). The R^2 value of each statistical model was generated and then a second analysis (whether the dietary variable was significantly associated with UA) was performed removing the dietary variable from the model. The difference between the R^2 values of the 2 models was used to estimate the prediction of UA variances by the dietary component in an isolated form. Logistic regression analysis was performed to evaluate whether the presence of hyperuricemia was associated with dietary intake. All regression analyses were performed without adjustment (model 1) and adjusted for age, sex, race/ethnicity, education level, marital status, annual family income, diabetes, hypertension, smoking status, physical activity, allopurinol use, body mass index (kg/m^2),

eGFR (ml/min/1.73 m^2), serum triglyceride (mg/dL), and energy intake (kcal) (energy intake (kcal) was removed from the energy intake analyzes) (model 2). All analyses were performed using the "svy" command to incorporate information on the 'dietary two-day' sample weight, primary sampling units, and strata for correct variance estimation. The significance of the associations was considered when p-value <0.05. The analyses were performed using Stata software version 14.0 (StataCorp, College Station, TX, USA).

RESULTS

The characteristics of individuals according to normal and elevated serum UA levels are shown in Table 1. Participants with elevated serum UA levels had a higher prevalence of men, hypertension, and most women were in menopause, while higher prevalence of CKD and gout when comparing individuals with normal and elevated UA levels. Additionally, they had higher weight, body fat mass (kg), waist circumference, levels of creatinine, urea, triglycerides, and glucose, and had lower glomerular filtration rate and HDL cholesterol.

Dietary characteristics according to normal and elevated serum UA levels are shown in Table 2. Individuals with the highest levels of serum UA levels had lower consumption of protein g/kg, vegetable protein, fiber, vitamin C, calcium, and cereals.

Linear regression analyses of serum UA levels with dietary intake are shown in Table 3. In the unadjusted analyses, serum UA levels were positively associated with energy (kcal/day), carbohydrate (g/day), protein, (g/day), total fat (g/day), cholesterol (mg/day), saturated fat (g/day), monounsaturated fat (g/day), polyunsaturated fat (g/day), omega 3 (g/day), omega 6 (g/day), alcohol (g/day), caffeine (mg/day), and zinc (mg/day), while protein (g/kg/day), vitamin C (mg/day), and vegetable (g) were inversely associated with serum UA levels. However, after the adjustments for confounders, serum UA levels were inversely associated with carbohydrate (g/day), saturated fat (g/day), fiber (g/day), calcium (mg/day), magnesium (mg/day), cereals (g), and serum UA was positively associated with alcohol (g/day). These associations explained the variations of serum UA levels from 0.1% to 1%. (Table 3, Figure 2).

Logistic regression analyses of the presence of hyperuricemia with dietary intake are shown in Table 4. In the unadjusted analyses, the intake of protein (g/kg/day), fiber (g/day), vitamin C (mg/day), calcium (mg/day), cereals (g), vegetables (g) were associated with a lower chance of hyperuricemia. However, after the adjustments for confounders, the intake of alcohol (g/day) was associated with a higher chance of

hyperuricemia, while the intake of vegetables (g) was associated with a lower chance of hyperuricemia (Table 3, Figure 2).

Logistic regression analysis of presence of hyperuricemia and alcohol intake according to the servings are showing in Table 5. In the model without adjustment for confounding variables, an intake of ≥ 2 servings and < 3 servings were associated with a higher chance of hyperuricemia. After adjusting for confounding variables, intakes of ≥ 2 servings and < 3 servings, as well as ≥ 3 servings, were associated with a higher chance of hyperuricemia. The chance of hyperuricemia increased with the increase in the number of servings alcohol.

DISCUSSION

The main findings of the present study were that carbohydrate, saturated fat, fiber, calcium, magnesium, and cereals intakes were inversely associated with serum UA, whereas alcohol intake was positively associated with serum UA levels. Alcohol intake was associated with a higher chance of hyperuricemia, while vegetables with additions intake were associated with a lower chance of hyperuricemia. Furthermore, intakes of ≥ 2 servings and < 3 servings, as well as ≥ 3 servings, were associated with a higher chance of hyperuricemia. However, it is important to mention that the intake of these dietary factors explained 0.1% to 1% of variations in serum UA levels and the chance of hyperuricemia.

Carbohydrate, fiber, and cereals intakes were inversely associated with serum UA levels, while vegetable intake was associated with a lower chance of hyperuricemia. In the present study, carbohydrates were not differentiated between simple and complex, and all types of cereals, including whole grains, were included, limiting the ability for isolated interpretation. However, fiber intake was also associated, which allows us to speculate that these associations can be partially explained by the sources of these foods. Several studies demonstrate that cereals, vegetables, and fruit intake, sources of fiber and carbohydrates, are associated with lower serum UA concentrations and hyperuricemia in the general population [15, 21, 34, 35], and in decreased renal function patients [22]. The mechanisms that can explain these associations are based on polyphenols (flavonoids, isoflavones, and phenolic acids), compounds that have an antioxidant property that carries out their anti-hyperuricemic effect through their antioxidant/radical-scavenging activities and interactions with enzymes involved in UA synthesis [36, 37]. Polyphenols also seem to compete with the xanthine oxidase (the main enzyme of the UA synthesis pathway)

and, consequently, may decrease UA production [37]. Dietary fiber present in vegetables, fruits, and grains can also contribute to decreasing serum UA by inhibiting the digestion and absorption of nucleotides and nucleoproteins (main precursors of synthesis) present in the diet [37, 38].

Saturated fat, calcium, and magnesium intakes were inversely associated with serum UA levels. Saturated fat intake was moderately correlated with calcium, and magnesium intake ($r= 0.65$, $p<0.0001$; $r= 0.49$, $p<0.0001$, respectively, data not shown), while the total fat intake was moderately correlated with calcium, and magnesium intake ($r= 0.59$, $p<0.0001$; $r= 0.61$, $p<0.0001$, respectively, data not shown). These nutrients are present in dairy products (i.e., milk, cheese, and yogurt), which were not foods evaluated and included in the NHANES database in the biennium analyzed in the present study (2011-12), and are largely associated with lower serum UA concentrations in the general population [16, 37]. Even though dairy products were not evaluated in isolation, we can speculate that these inverse associations can be explained by the composition of these foods. Proteins contained in dairy products, such as casein and lactalbumin, can exert uricosuric effects [37]. In addition, orotic acid and calcium (present in dairy products) can reduce the serum concentration of UA by promoting decreased reabsorption and increased renal excretion of UA [10, 11, 37]. Magnesium, as a laxative, plays a potential role to increase the excretion of UA, via the gastrointestinal tract [39]; however, more studies are needed to confirm these mechanisms.

On the other hand, in the present study, alcohol intake was positively associated with serum UA levels and with a higher chance of hyperuricemia, and the chance of hyperuricemia increased with the increase in the number of servings of alcohol. Alcohol intake has been associated with higher chance serum of elevated serum UA concentrations, which has been widely demonstrated in the literature [40, 41] because of its ability to stimulate the production of acetate, which in turn increases the production of adenosine nucleotides, substrates for serum UA production [42]. In the study by Silva et. al.[40] with 14320 active and retired civil servants aged 35-74 years, the high alcohol consumption (>3 times per day) was positively associated with UA serum level in men ($\beta=0.47$; $p<0.001$) and in women ($\beta=0.16$; $p<0.001$). Furthermore, in the study by Choi et. al. [41], using data from 14,809 participants aged>20 years in The Third National Health and Nutrition Examination Survey (NHANES III - 1988 –1994), higher frequency of alcohol intake (>1.00 servings per day) had a higher coefficient of association with higher UA levels when compared with lower frequency (0.10 - 0.49 servings per day)

(β=0.33 and β=0.10; p= 0.001, respectively).

However, in the present study, it is important to emphasize that all dietary factors that were associated with UA levels explained 0.1% to 1% of the variations of serum UA (Table 3, Figure 2). The limited biological relevance of these dietary components in explaining variations in serum UA levels can be attributed to several factors. Firstly, the metabolism of uric acid (UA) is a complex process influenced by various genetic and physiological factors, including purine metabolism, renal function, and excretion rates. While dietary factors can contribute to the overall production and elimination of UA, they may have a relatively small impact compared to endogenous factors. Additionally, the observed associations between dietary factors and serum UA levels may be influenced by other lifestyle and health-related factors [4-6]. Isolating the specific effects of each dietary component becomes challenging when considering the broader context of an individual's overall diet and lifestyle[43]. Furthermore, the relatively low percentage of variance explained by these dietary components (0.1% to 1%, and 1.37% when the dietary components were analyzed together - data not shown) highlights the multifactorial nature of serum UA regulation. Other genetic, metabolic, and lifestyle factors not considered in this study likely play significant roles in determining UA levels. The associations found between alcohol intake and higher levels of serum UA raise questions about its biological relevance. Although alcohol consumption is associated with small variations in UA levels (only 0.8%), it is important to note that the alcohol-induced changes in UA levels may vary depending on the quantity and frequency of alcohol consumption, which can become more significant in individuals who consume alcohol regularly and in large quantities. Therefore, it is crucial to consider the individual's alcohol consumption patterns and overall health status when assessing the potential impact of alcohol on UA levels.

The present study has limitations. First, fruit intake may not have been associated with serum UA and hyperuricemia due to the few individuals who consumed this component in the sample, and therefore, a non-differential error could have been introduced in the analyses. However, we analyzed the food intake by a validated method that estimates the usual dietary intake [33], which allows a more reliable assessment of the individual's consumption. Second, the food components evaluated from the NHANES database contained additions from other foods (such as sauces, toppings, creams, etc.), which did not allow for isolating only the food individually. Third, due to the cross-sectional design, causality cannot be established. Fourth, in an observational study, we cannot rule out that part of the association found could be explained by residual

confounding. However, the analyses were adjusted for important potential confounders, which reduces this possibility. As a strength, the data of the present study can be generalized for the population of the USA, since the data were obtained from a representative sample from the USA.

CONCLUSION

Carbohydrate, saturated fat, fiber, calcium, magnesium, and cereals intakes were inversely associated with serum UA, whereas alcohol intake was positively associated with serum UA levels. Alcohol intake was associated with a higher chance of hyperuricemia, while vegetables with additions intake were associated with a lower chance of hyperuricemia. Although there are significant associations among nutrients and food intake with serum uric acid levels, there is a low clinical relevance. Future randomized clinical trials should be carried out to show whether the intake of these nutrients has important effects on UA levels.

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Conflict of interest

None.

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Figures and tables

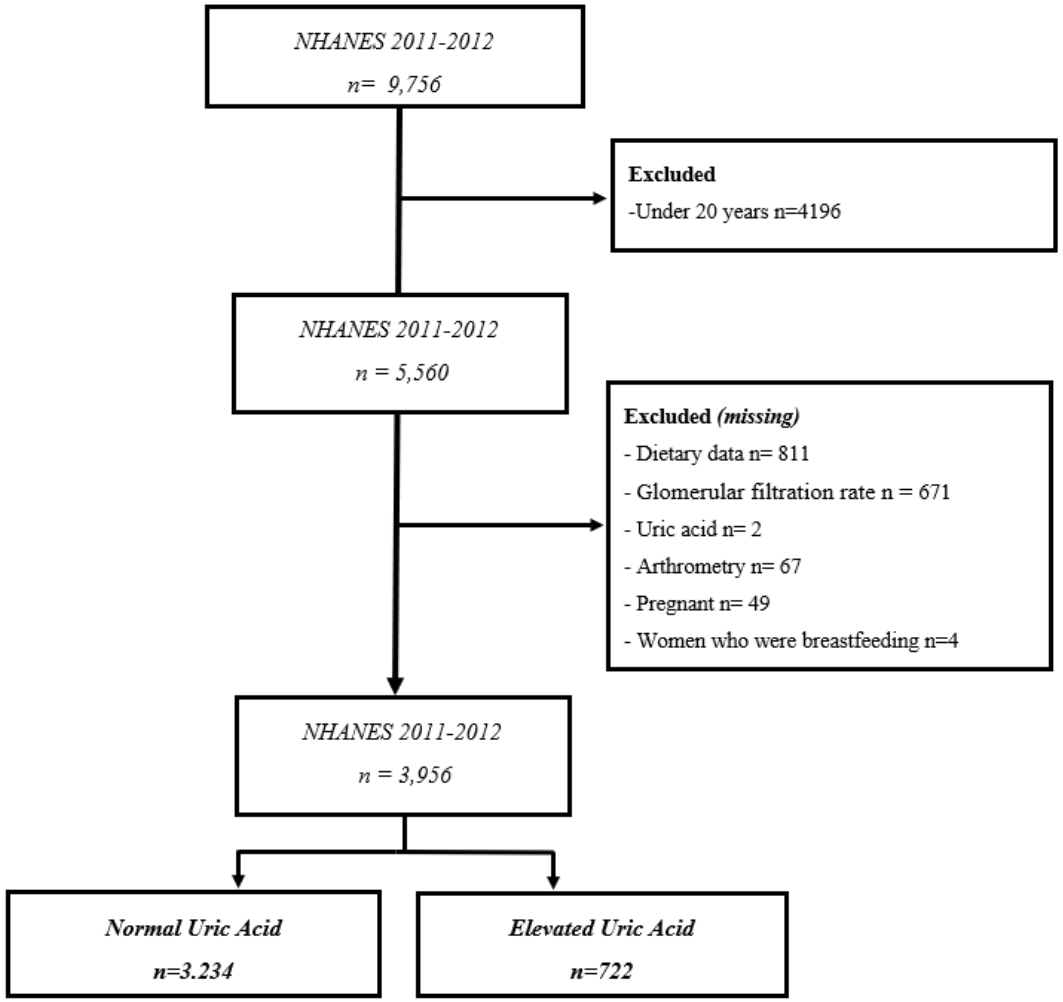

Figure 1. Flowchart of the sample selection according to normal and elevated serum UA levels from NHANES 2011-2012.

Table 1. Sociodemographic, health conditions and behavior, anthropometric, and biochemical parameters by total sample and according to normal and elevated uric acid. NHANES, 2011-2012.

	Total Sample	Normal Uric Acid	Elevated Uric Acid	*p-Value*
Uric acid, mg/dL	5.4 ± 1.4	5.0 ± 1.0	7.5 ± 1.0	**<0.001**
Sociodemographic data				
Age, y	47.3 ± 16.7	47.0 ± 16.4	49.0 ± 18.3	0.093
Sex, %				**0.032**
Men	49 (47.2; 50.9)	47.3 (44.7; 49.8)	57.8 (49.9; 65.3)	
Women	51.0 (49.1; 52.8)	52.7 (50.2; 55.3)	42.2 (34.7; 50.1)	
Race/ethnicity, %				0.136
Non-Hispanic white	67.6 (59.1; 75.1)	67.1 (58.4; 74.8)	70.0 (61.6; 77.1)	
Others	32.4 (24.9; 40.9)	32.9 (25.2; 41.6)	30.0 (22.9; 38.4)	
Marital status, %				0.180
Married/Living with partner	62.5 (57.5; 67.3)	63.4 (58.2; 68.4)	58.0 (49.4; 66.2)	
Single/Divorced/Widowed/Never Married	37.5 (32.7; 42.5)	36.6 (31.6; 41.8)	42.0 (33.8; 50.6)	
Annual Family Income, %				0.726
$0-19,999	19.7 (16.0; 24)	19.5 (16.2; 23.3)	20.4 (13.9; 29)	
$20,000-54,999	35.1 (31.3; 39.0)	34.6 (30.7; 38.7)	37.3 (32.5; 42.5)	
$55,000-74,999	12.2 (9.9; 15.1)	12.2 (9.9; 15.1)	12.1 (8.0; 18.0)	
Over $75,000	30.6 (25.0; 36.8)	31.3 (25.8; 37.4)	26.8 (19.2; 36.1)	
Missing	2.5 (1.8; 3.5)	2.3 (1.6; 3.4)	3.3 (1.7; 6.1)	
Educational level, %				0.479
Under high school graduate	35.6 (29.3; 42.5)	0.4 (0.3; 0.4)	0.4 (0.3; 0.5)	
Some college or over	64.4 (57.5; 70.7)	64.9 (57.0; 72.1)	61.8 (55.0; 68.1)	
Health Conditions and Behavior				
Diabetes, %				0.121
No	89.5 (87.9; 90.9)	90.1 (87.9; 91.9)	86.7 (83.1; 89.6)	
Yes	8.9 (7.8; 10.1)	8.2 (7.0; 9.6)	12.0 (9.5; 15.1)	
Pre-diabetes	1.6 (1.0; 2.7)	1.7 (0.9; 3.1)	1.3 (0.7; 2.7)	

Hypertension, %				**<0.001**
No	68.7 (65.2; 71.9)	71.8 (68.2; 75.1)	28.2 (24.9; 31.8)	
Yes	31.3 (28.1; 34.8)	53.6 (46.3; 60.7)	46.4 (39.3; 53.7)	
Chronic kidney disease, %				**<0.001**
No	97.4 (96.1; 98.3)	98.4 (97.7; 98.9)	92.5 (87.6; 95.6)	
Yes	2.6 (1.7; 3.9)	1.6 (1.1; 2.3)	7.5 (4.4; 12.4)	
Gout, %				**<0.001**
No	96 (94.4; 97.2)	97.3 (96.0; 98.3)	89.6 (84.3; 93.3)	
Yes	4.0 (2.8; 5.6)	2.7 (1.7; 4)	10.4 (6.7; 15.7)	
Arthritis, %				0.085
No	76.6 (72.3; 80.5)	77.6 (73.8; 80.9)	72.1 (62.5; 80)	
Yes	23.2 (19.4; 27.6)	22.3 (19.0; 26.1)	27.5 (19.6; 37.1)	
Menopause, %				**0.006**
No	50.1 (44; 56.1)	53.3 (46.2; 60.2)	31.3 (21.1; 43.7)	
Yes	49.9 (43.9; 56)	46.7 (39.8; 53.8)	68.7 (56.3; 78.9)	
Physical activity, %				0.269
Yes	40.9 (38.2; 43.7)	40.5 (37.7; 43.3)	43.2 (38.1; 48.4)	
No	59.1 (56.3; 61.8)	59.5 (56.7; 62.3)	56.8 (51.6; 61.9)	
Smoking status, %				0.593
No	80.2 (77.0; 83.0)	80.4 (77.2; 83.3)	79.0 (72.7; 84.2)	
Yes	19.8 (17.0; 22.9)	19.6 (16.7; 22.8)	21.0 (15.8; 27.2)	
Medicines				
Allopurinol, n (%)				0.411
No	98.8 (98.2; 99.2)	98.9 (98.1; 99.4)	98.3 (96.2; 99.3)	
Yes	1.2 (0.8; 1.8)	1.1 (0.6; 1.9)	1.7 (0.7; 3.8)	
Aspirin, n (%)				0.690
No	99.2 (98.8; 99.5)	99.3 (98.7; 99.6)	99.1 (98.3; 99.5)	
Yes	0.8 (0.5; 1.2)	0.7 (0.4; 1.3)	0.9 (0.5; 1.7)	
Prednisone, n (%)				0.790
No	98.9 (98.3; 99.3)	98.9 (98.2; 99.3)	98.9 (98; 99.5)	

Yes	1.1 (0.7; 1.7)	1.1 (0.7; 1.8)	1.1 (0.5; 2)	
Anthropometric data				
Weight, kg	82.2 ± 21.1	80.3 ± 20.1	91.3 ± 23.7	**<0.001**
Height, m	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	0.204
Body mass index, kg/m^2	28.8 ± 6.7	28.2 ± 6.4	31.6 ± 7.8	**<0.001**
Waist Circumference, cm	98.6 ± 16.1	97.1 ± 15.6	106.0 ± 16.3	**<0.001**
Biochemical parameters				
Creatinine, mg/dL	0.9 ± 0.3	0.9 ± 0.3	1.0 ± 0.4	**<0.001**
Urea, mg/dl	13.0 ± 5.2	12.5 ± 4.5	15.3 ± 7.5	**<0.001**
Glomerular filtration rate, ml/min/1.73^3	95.3 ± 22.6	97.7 ± 20.9	83.7 ± 26.8	**<0.001**
Triglycerides, mg/dL	151.8 ± 124.4	143.8 ± 121.9	190.5 ± 129.1	**<0.001**
Glucose, mg/dL	98.5 ± 32.1	97.9 ± 31.1	101.6 ± 36.6	**0.007**
Cholesterol, mg/dL	194.1 ± 40.4	193.2 ± 39.6	198.4 ± 44.1	0.054
HDL cholesterol, mg/dL	52.9 ± 15.3	53.9 ± 15.3	48 ± 14.3	**<0.001**
LDL cholesterol, mg/dL	115.5 ± 34.6	114.9 ± 33.4	118.4 ± 39.9	0.098

Data are described as mean ± standard deviation or percentage (confidence interval). Bold means that the p-value is statistically significant. Menopause was only analyzed for women.

Table 2. Dietary characteristics by total sample and according to normal and elevated uric acid. NHANES, 2011-2012.

	Total Sample	Normal Uric Acid	Elevated Uric Acid	*p-Value*
Energy, kcal/day	2127.5 ± 523.5	2132.1 ± 508.5	2104.9 ± 595.4	0.525
Carbohydrate, g/day	260.5 ± 66.5	261.9 ± 64.4	253.6 ± 76.5	0.153
Protein, g/day	82.4 ± 20.2	82.5 ± 20	82.3 ± 21.6	0.931
Protein, g/kg/day	1.1 ± 0.3	1.1 ± 0.3	0.9 ± 0.3	**<0.001**
Animal protein, g/day	4.5 ± 1.2	4.5 ± 1.2	4.6 ± 1.4	0.096
Vegetable protein, g/day	10.6 ± 3.9	10.7 ± 3.8	9.9 ± 4.1	**0.033**
Total fat, g/day	79.7 ± 21.6	80.0 ± 21.3	78.2 ± 23.2	0.264
Cholesterol, mg/day	282.2 ± 87	282.8 ± 87.8	279.1 ± 81.9	0.492
Saturated fat, g/day	25.5 ± 7.4	25.6 ± 7.3	25.0 ± 8	0.320
Monounsaturated fat, g/day	28.6 ± 8.1	28.7 ± 8	28.0 ± 8.5	0.247
Polyunsaturated fat, g/day	19.1 ± 4.8	19.2 ± 4.7	18.9 ± 5.4	0.356
Omega-3, g/day	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1	0.945
Omega-6, g/day	16.9 ± 4.4	16.9 ± 4.3	16.6 ± 4.9	0.392
Fiber, g/day	18.1 ± 5.9	18.4 ± 5.8	17.1 ± 6.2	**0.014**
Alcohol, g/day	9.4 ± 12.6	9.0 ± 11.9	11.4 ± 15.2	0.104
Sugar, g/day	113.6 ± 40	114.4 ± 38.8	109.4 ± 45.5	0.146
Caffeine, mg/day	157.4 ± 118	158.3 ± 116.4	153.1 ± 125.1	0.706
Theobromine, mg/day	35.9 ± 19.9	35.9 ± 19.4	35.6 ± 22.1	0.850
Vitamin C, mg/day	87.1 ± 40.5	88.5 ± 40.7	80.2 ± 38.8	**0.008**
Zinc, mg/day	11.4 ± 3.1	11.4 ± 3.1	11.1 ± 3.1	0.234
Calcium, mg/day	967.6 ± 279.9	977.1 ± 274	921.6 ± 303.7	**0.006**
Iron, mg/day	15.5 ± 4.0	15.6 ± 4.1	15 ± 3.9	0.064
Magnesium, mg/day	310.2 ± 88.8	312.3 ± 88.5	299.6 ± 89.2	0.077

Food groups				
Meat, Poultry and Fish, g	25.7 ± 6.9	25.6 ± 6.7	26.5 ± 7.9	0.112
Cereals, g	134.3 ± 61.5	136.3 ± 61.3	124.3 ± 61.5	**0.032**
Fruits, g	4.7 ± 7.2	4.7 ± 7.4	4.9 ± 6.3	0.589
Vegetables, g	36.4 ± 10.3	36.4 ± 10.2	36.3 ± 10.7	0.889
Dried beans or tuber, g	317.4 ± 266.8	317.0 ± 260.0	319.2 ± 299.5	0.923

Data are described as mean ± standard deviation or percentage (confidence interval). Bold means that the p-value is statistically significant.

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Table 3. Linear regression analysis of serum uric acid with dietary intake. NHANES, 2011-2012.

	Unadjusted		Adjusted			
	β	***p-Value***	**β**	**R^2 (%)***	**R^2 (%)†**	***p-Value***
Energy, kcal/day	0.003	**<0.001**	-0.001	39.9	-	0.721
Carbohydrate, g/day	0.005	**0.005**	**-0.001**	**40.1**	**0.1**	**0.043**
Protein, g/day	0.010	**<0.001**	-0.008	39.9	-	0.703
Protein, g/kg/day	-0.943	**<0.001**	-0.135	40.0	-	0.350
Animal protein, g/day	0.053	0.163	0.027	40.0	-	0.243
Vegetable protein, g/day	-0.025	0.136	-0.015	40.1	-	0.081
Total fat, g/day	0.062	**0.003**	-0.006	40.2	-	0.065
Cholesterol, mg/day	0.002	**0.001**	-0.002	39.9	-	0.529
Saturated fat, g/day	0.016	**0.008**	**-0.020**	**40.3**	**0.3**	**0.015**
Monounsaturated fat, g/day	0.017	**0.002**	-0.011	40.1	-	0.101
Polyunsaturated fat, g/day	0.019	**0.024**	-0.009	40.0	-	0.415
Omega-3, g/day	0.145	**0.028**	-0.105	40.0	-	0.190
Omega-6, g/day	0.020	**0.030**	-0.010	40.0	-	0.413
Fiber, g/day	-0.001	0.422	**-0.018**	**40.3**	**0.4**	**0.012**
Sugar, g/day	0.001	0.088	-0.009	40.0	-	0.288
Alcohol, g/day	0.010	**0.002**	**0.010**	**40.7**	**0.8**	**<0.001**
Caffeine, mg/day	0.006	**0.039**	-0.001	39.5	-	0.614
Theobromine, mg/day	-0.001	0.532	-0.002	40.1	-	0.087
Vitamin C, mg/day	-0.001	**0.011**	-0.001	40.1	-	0.072
Calcium, mg/day	0.001	0.348	**-0.004**	**40.3**	**0.4**	**0.006**
Zinc, mg/day	0.045	**0.004**	-0.011	39.9	-	0.385
Magnesium, mg/day	0.005	0.155	-0.008	40.1	0.1	**0.050**
Meat, Poultry and Fish, g	0.009	0.172	0.004	40.0	-	0.258
Cereals, g	-0.009	0.176	**-0.009**	**40.1**	**0.2**	**0.029**
Fruits, g	-0.024	0.695	0.005	40.1	-	0.332
Vegetables, g	-0.028	**0.004**	-0.001	40.0	-	0.179

Dried beans or tuber, g	-0.021	0.574	-0.001	39.9	-	0.536
Coffee and tea, ml	6.920	0.918	-0.001	39.9	-	0.458

Each variable adjusted for age, sex, race/ethnicity, education level, marital status, annual family income, diabetes, hypertension, smoking status, physical activity, allopurinol use, body mass index (kg/m²), estimated glomerular filtration rate (ml/min/173m^2), serum triglyceride (mg/dL), and energy intake (kcal). When energy intake (kcal) was analyzed, energy (kcal) was removed from the analyzes.

***R^2 value:** uric acid as a dependent variable. Independent variables were each dietary component (isolated) plus adjustments (age, sex, race/ethnicity, education level, marital status, annual family income, diabetes, hypertension, smoking status, physical activity, allopurinol use, body mass index (kg/m²), estimated glomerular filtration rate (ml/min/173m^2), serum triglyceride (mg/dL), and energy intake (kcal)). When energy intake (kcal) was analyzed, energy (kcal) was removed from the analyzes.

†R^2: the difference between R^2 (dietary component plus adjustments) and R^2 (adjustments without dietary component).

Table 4. Logistic regression analysis of presence of hyperuricemia with dietary intake. NHANES, 2011-2012.

	Unadjusted		Adjusted	
	OR	***CI (95%)***	**OR**	***CI (95%)***
Energy, kcal/day	1.00	(0.999 – 1.000)	1.00	(0.999 - 1.000)
Carbohydrate, g/day	1.00	(0.995 - 1.000)	1.00	(0.991 - 1.000)
Protein, g/day	1.00	(0.991 - 1.007)	1.00	(0.986 - 1.016)
Protein, g/kg/day	**0.24**	**(0.138 - 0.420)**	10.11	(0.325 - 10.812)
Animal protein, g/day	10.12	(0.990 - 10.259)	10.11	(0.987 - 10.256)
Vegetable protein, g/day	0.94	(0.887 - 1.001)	0.96	(0.895 - 1.026)
Total fat, g/day	1.00	(0.988 - 1.003)	0.98	(0.966 - 1.002)
Cholesterol, mg/day	1.00	(0.997 - 1.001)	1.00	0.996 - 1.000)
Saturated fat, g/day	0.99	(0.967 - 1.012)	0.97	(0.911 - 1.024)
Monounsaturated fat, g/day	0.99	(0.970 - 1.008)	0.97	(0.937 - 10.198)
Polyunsaturated fat, g/day	0.99	(0.951 - 1.019)	0.97	(0.920 - 1.025)
Omega-3, g/day	0.80	(0.626 - 1.016)	0.69	(0.468 - 1.019)
Omega-6, g/day	0.98	(0.947 - 1.023)	0.97	(0.915 - 1.030)
Fiber, g/day	**0.96**	**(0.929 - 0.992)**	0.97	(0.928 - 1.011)
Sugar, g/day	1.00	(0.991 - 1.001)	1.00	(0.989 - 1.001)
Alcohol, g/day	1.01	(0.998 - 1.027)	**1.02**	(**1.007 - 1.037**)
Caffeine, mg/day	1.00	(0.997 - 1.001)	1.00	(0.996 - 1.001)
Theobromine, mg/day	1.00	(0.991 - 1.007)	1.00	(0.988 - 1.009)
Vitamin C, mg/day	**0.99**	**(0.990 - 0.998)**	1.00	(0.990 - 1.001)
Calcium, mg/day	**0.99**	**(0.998 - 0.999)**	1.00	(0.998 - 1.000)
Zinc, mg/day	0.97	(0.916 - 1.024)	0.98	(0.913 - 1.045)
Magnesium, mg/day	1.00	(0.996 - 1.000)	1.00	(0.996 - 1.002)
Meat, Poultry and Fish, g	1.02	(0.997 - 1.039)	1.01	(0.996 - 1.040)
Cereals, g	**0.99**	**(0.993 - 0.999)**	0.99	(0.993 - 0.999)
Fruits, g	0.99	(0.987 - 1.022)	1.01	(0.993 - 1.035)
Vegetables, g	**0.99**	(**0.990 - 0.998**)	**0.99**	(**0.989 - 0.998**)

Dried beans or tuber, g	1.00	(0.987 - 1.010)	1.00	(0.992 - 1.014)
Coffee and tea, ml	1.00	(0.999 - 1.000)	0.99	(0.999 - 1.000)

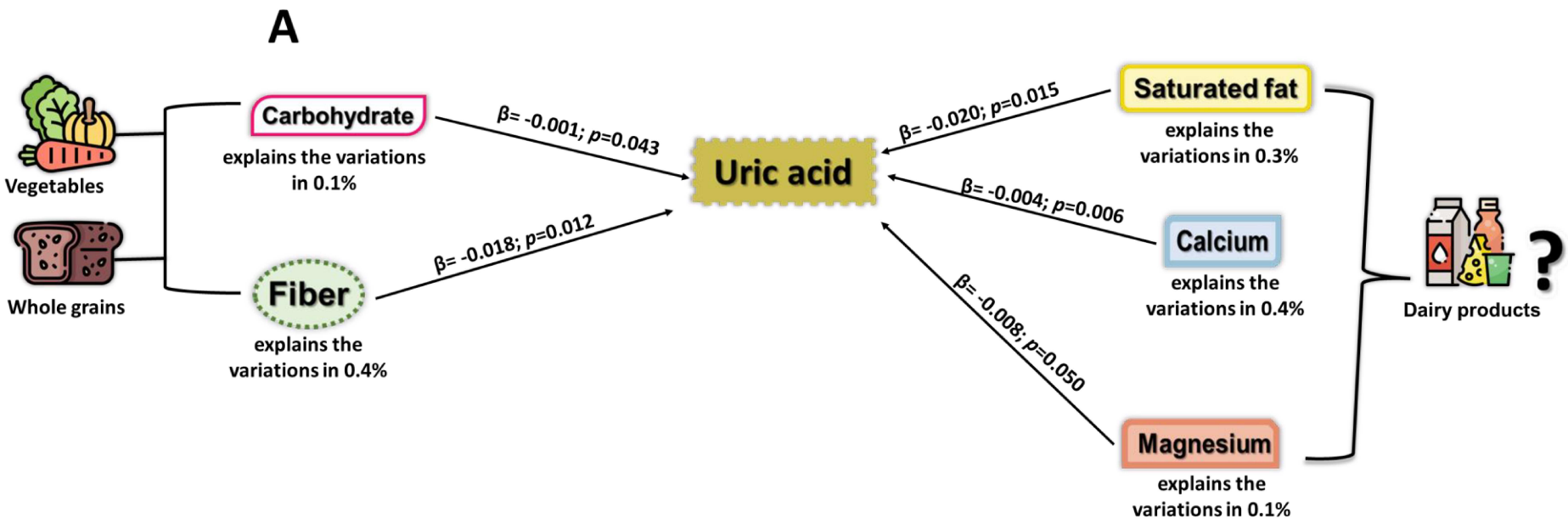
Each variable adjusted for age, sex, race/ethnicity, education level, marital status, annual family income, diabetes, hypertension, smoking status, physical activity, allopurinol use, body mass index (kg/m²), estimated glomerular filtration rate (ml/min/173m^2), serum triglyceride (mg/dL), and energy intake (kcal). When energy intake (kcal) was analyzed, energy (kcal) was removed from the analyzes.

Table 5. Logistic regression analysis of presence of hyperuricemia and alcohol intake according to the servings*. NHANES, 2011-2012.

Alcohol intake	Unadjusted		Adjusted	
	OR	***CI (95%)***	**OR**	***CI (95%)***
< 1 serving	REF		REF	
≥ 1 and < 2 servings	0.88	(0.586 - 1.317)	1.14	(0.785 - 1.655)
≥ 2 servings and < 3 servings	2.17	(1,226 – 3.849)	3.11	(1.892 – 5.125)
≥ 3 servings	2.37	(0.795 – 7.072)	3.48	(1.954 – 11.103)

*One serving equals 14g of alcohol

Each variable adjusted for age, sex, race/ethnicity, education level, marital status, annual family income, diabetes, hypertension, smoking status, physical activity, allopurinol use, body mass index (kg/m²), estimated glomerular filtration rate (ml/min/173m^2), serum triglyceride (mg/dL), and energy intake (kcal). When energy intake (kcal) was analyzed, energy (kcal) was removed from the analyzes


A
Vegetables
Whole grains
Carbohydrate
explains the variations in 0.1%
Fiber
explains the variations in 0.4%
β= -0.001; p=0.043
β= -0.018; p=0.012
Uric acid
β= -0.020; p=0.015
β= -0.004; p=0.006
β= -0.008; p=0.050
Saturated fat
explains the variations in 0.3%
Calcium
explains the variations in 0.4%
Magnesium
explains the variations in 0.1%
Dairy products
?

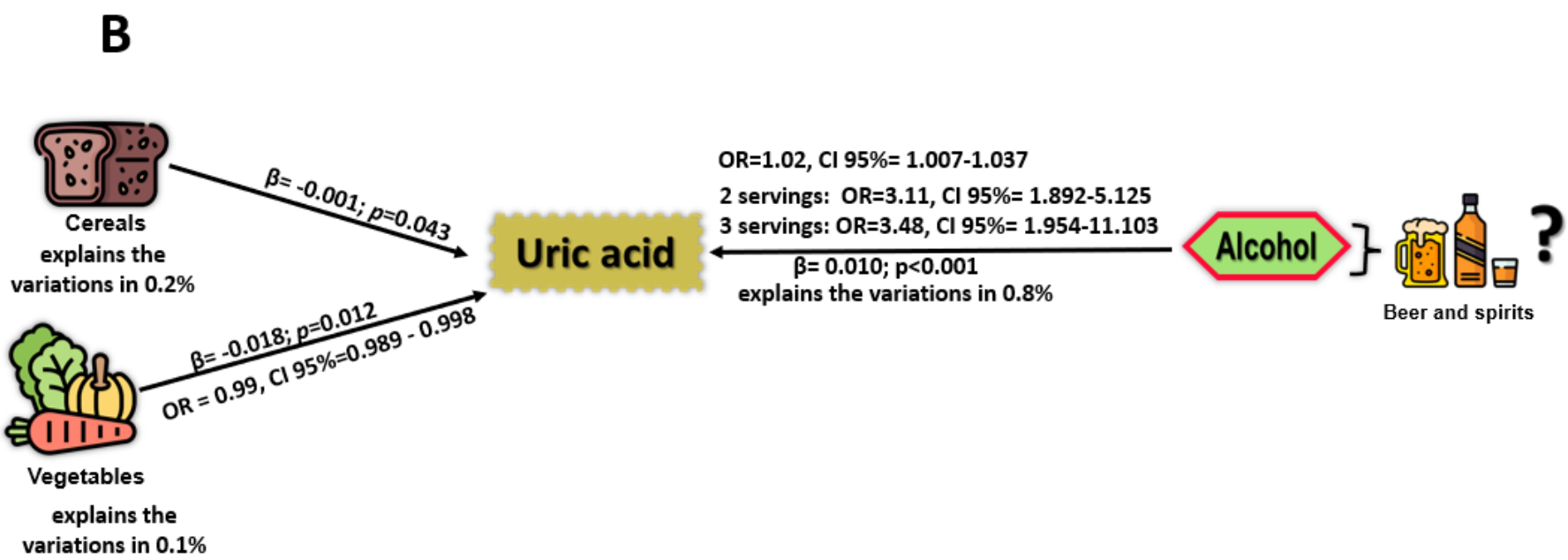


Figure 2. Summary of associations of hyperuricemia (logistic regression), serum uric acid levels (linear regression) and dietary intake. Associations of serum uric acid levels and hyperuricemia and nutrients (A) and dietary factors (B). The percentage values represent how much dietary factors explain variations in serum uric acid levels. *One serving equals 14g of alcohol

Artigo 2: Association of caffeine and caffeine metabolites in the urine with serum uric acid levels and hyperuricemia. NHANES 2011-2012

Original Article

Association between caffeine metabolites in urine and serum uric acid levels in USA population. NHANES 2011-2012

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Abstract

Objective: To associate caffeine and caffeine metabolites with serum UA levels. **Methods:** A Cross-sectional study was performed evaluating a subsample of 1252 individuals aged over 20 years with data on caffeine and its metabolites in urine from National Health and Nutrition Examination Survey (NHANES) 2011-2012. Caffeine and 15 of its metabolites in spot urine samples were evaluated by use of LC-tandem MS with electrospray ionization. UA was measured by the colorimetric method. Linear and logistic regression were performed for the associations. **Results:** In linear regression analyses, after adjustments, paraxanthine (β= -0.004, p= 0.006), theobromine (β= -0.004, p= <0.001), 7-methyluric acid (β= -0.003, p= 0.0033), 3,7-dimethyluric acid (β= -0.029, p= 0.024), 3-methylxanthine (β= -0.001, p= 0.038), and 7-methylxanthine (β= -0.001, p= 0.001) were inversely associated with serum U; whereas 1,3-dimethyluric acid (β= 0.001, p= 0.012) was positively associated with serum UA. In logistic regression analyses, theobromine (OR: 0.99 CI: 0.980 - 0.999), 3-methyluric acid (OR: 0.91 CI: 0.837 - 0.996), 7-methyluric acid (OR: 0.99 CI: 0.989 - 0.998), and 3-methylxanthine (OR: 0.99 CI: 0.992 - 0.999) were associated with a lower chance of hyperuricemia. **Conclusion:** Theobromine, 7-methylxanthine, 3-methyluric, 3-methylxanthine, 3,7-dimethyluric and 7-methyluric were inversely associated with serum UA and with the lower chance of having hyperuricemia, and paraxanthine was associated with lower chance of hyperuricemia. whereas 1,3-dimethyluric acid (theophylline metabolite) was positively associated with serum UA. These metabolites explained 0.04 to 1.3% of serum UA variations.

Keywords: Uric acid; hyperuricemia; caffeine, caffeine metabolites

Introduction

Caffeine is a psychoactive substance widely consumed around the world, present in beverages such as coffee, tea, soft drinks, energy drinks, in products containing cocoa or chocolate, and in medications (1). Caffeine is metabolized in the liver and transformed into metabolites, such as paraxanthine, theobromine, and theophylline (2). These metabolites are excreted through sweat, fecal excretion, and mainly renal excretion (2). The amount of caffeine metabolites may vary according to the dose and frequency of consumption, as well as individual sensitivity (2). Caffeine and its metabolites have diverse effects on the human body, including the stimulus of the central nervous system (3), a favorable effect on microvascular function (4), and may affect serum uric acid (UA) levels (5).

UA is the end product of exogenous and endogenous purine metabolism in humans (6, 7). Exogenous purines are obtained through the protein sources intake, which corresponds to one-third of the production of the UA (7, 8). Endogenous purines are derived from the decomposition of nucleoproteins, which account for two-thirds of UA production. (8-12). Reduced renal and intestinal excretion, increased production, or a combination of these factors can lead to increased UA levels and, consequently, hyperuricemia (6, 13). Hyperuricemia is described as an independent risk factor for the development of gout and is related to the pathophysiology of another comorbidity, for example, metabolic syndrome and its components (14, 15). Thus, dietary factors have been the focus of investigations due to their possible role in the management of hyperuricemia (10, 16).

Some studies have evaluated the association of caffeine, coffee tea, and chocolate consumption, which are sources that determine caffeine metabolites in urine (17), with UA levels, and most of them showed an inverse association with serum UA (18-21). However, the assessment of caffeine consumption through dietary surveys faces limitations such as imprecise food quantification and inaccurate reporting by participants (22). Furthermore, it is important to consider that the majority of individuals with hyperuricemia also have overweight and obesity (23), conditions in which underestimating food intake, including sources of caffeine, is common (24). Nevertheless, it is not clear whether dietary caffeine consumption is associated with increased levels of UA. Additionally, the evaluation of caffeine and caffeine metabolites in urine can be more reliable than consumption of food, since the product of metabolization is directly evaluated (2, 17). Nevertheless, it is not clear in the literature which isolated caffeine

metabolites are associated with serum UA concentrations. Therefore, the objective of the present study was to associate caffeine and caffeine metabolites with serum UA concentrations, as derived from the National Health and Nutrition Examination Survey (NHANES) 2011-2012.

Methods

Study Design and Subjects' Characteristics

This was a study cross-sectional design based on data from the NHANES survey conducted by The National Center for Health Statistics of the Centers for Disease Control and Prevention based on a multistage, probability, and stratified sampling design to assess the nutritional status and health of a nationally representative sample of the noninstitutionalized U.S. population.

Participants completed in-home interviews, physical examinations, biochemical tests, dietary interviews, and other examinations (25). A total of 9756 individuals were evaluated in NHANES 2011-2012. We selected a subsample of 2,398 individuals with data on caffeine and caffeine metabolites in urine. We considered for the present study adults aged over 20 years from NHANES 2011-2012. Individuals with available demographic, health conditions (diabetes, hypertension, arthritis, menopause, gout, allopurinol use) and behavior (physical activity and smoking status), anthropometric, biochemical parameters, caffeine and caffeine metabolites in urine and dietary data were included in the analyses. However, in the present study, individuals who did not have serum UA data assessment, missing information on glomerular filtration rate (eGFR), dietary data, anthropometric; women who were pregnant, and women who were breastfeeding were excluded. Thus, the present study evaluated 1252 individuals (Figure 1). NHANES is a public data set and all participants provided written informed consent, consistent with approval from the National Center for Health Statistics Research Ethics Review Board (NCHS ERB) (Protocol #2011-17 for NHANES cycle 2011-2012).

Demographic data, health conditions, and behavior

The demographic characteristics evaluated were age (years), sex (men or women), race/ethnicity (non-Hispanic white or other), marital status single/divorced/widowed/never married or married/living as married), annual family income (0 to $19,999, from $20,000 to 54,999, $55,000 to 74,999, over $75,000) and educational level (under/ high school graduate and some college or over). Health

conditions and behavior included in the present study were self-report of diabetes (no, yes, or pre-diabetes), hypertension (no or yes), menopause (only for women; no or yes), gout (no or yes), arthritis (no or yes), physical activity (no or yes), smoking status (no or yes). Medicines included were allopurinol use (no or yes), and prednisone (no or yes). Annual family income a missing variable was created.

Anthropometric measurements

Body weight and height were evaluated according to Lohman's protocol (26) and body mass index (BMI) was calculated (27). A retractable steel measuring tape was used to take circumferences. Waist circumference was measured from the point marked above the upper lateral border of the right ilium, crossing vertically with the midaxillary line, the tape was extending around the participant's waist (28).

Uric acid and biochemical analysis

Serum UA levels and plasma triglyceride levels were measured by the colorimetric method (29). Elevated UA levels were defined as > 7.0 and > 6.0 mg/dl for men and women, respectively (30). Urea was measured by the enzymatic conductivity rate method. Creatinine was measured by the Jaffe rate method (29). eGFR was estimated by the chronic kidney disease epidemiology collaboration (CKD-EPI) equation (31). Glucose was measured by the glucose oxidase method. Cholesterol and HDL-cholesterol were measured by the timed-endpoint method (through reaction specific for HDL-cholesterol) (29). LDL-cholesterol was obtained according to the Friedewald calculation: [LDL-cholesterol] = [total cholesterol] – [HDL-cholesterol] – [triglycerides/5] (29, 32).

Caffeine and caffeine metabolites in the urine

Spot urine specimens were collected from all NHANES participants from the 2011–2012 survey who could provide a specimen. The urine collection took place in the mobile examination center (MEC). Two examination sessions were conducted daily. Participants were randomly assigned to exams in the morning session, or the afternoon or evening sessions. Each participant was instructed to provide a urine sample as soon as possible upon entry to the MEC and to empty their bladder when providing the sample. Urine samples were analyzed for caffeine and caffeine metabolites by using LC-tandem MS with electrospray ionization (33). Urine concentrations were reported for the following compounds: caffeine (1,3,7-trimethylxanthine), paraxanthine (1,7-

dimethylxanthine), theobromine (3,7-dimethylxanthine), theophylline (1,3-dimethylxanthine), 1,3,7-trimethyluric acid, 1,3-dimethyluric acid, 1,7-dimethyluric acid, 3,7-dimethyluric acid, 1-methyluric acid, 3-methyluric acid, 7-methyluric acid, 1-methylxanthine, 3-methylxanthine, 7-methylxanthine, 5-acetylamino-6-amino-3-methyluracil. The limits of detection in the urine of 0.05 μmol/L were as follows. Results were reported for caffeine and caffeine metabolites in 2,398 participants (34). All reported results satisfied the requirements of a multirule quality control system that used 3 quality control pool concentrations for each analyte (35). Coefficient of variation for the study were ≤5% at analyte concentrations ≥1 μmol/L (34).

Dietary intake

Dietary intake was assessed using two 24-hour food recalls for each volunteer. The first 24-hour food recall interview was collected in person and the second was collected by call 3 to 10 days later. Individuals with one day of 24-hour food recall were considered to estimate the usual dietary intake (36). The 24-hour dietary recalls were applied according to the 5-step multiple pass method (37), which interviews 5 steps (quick list, forgotten foods, time and occasion, detail cycle, and final probe). To process dietary intake, USDA's Food and Nutrient Database for Dietary Studies (FNDDS) 2011-2012 was used for processing the 2011-2012 intakes (http://www.ars.usda.gov/ba/bhnrc/fsrg). We evaluated the intake of energy (kcal), carbohydrate (g), protein (g), protein (g/kg/day), total fat (g), total fiber (g), alcohol (g), caffeine (mg), theobromine (mg), vitamin C (mg), coffee and tea (ml) with additions (with milk, cream, sugar).

Statistical analysis

Sociodemographic data, health conditions and behavior, anthropometric data, biochemical parameters, caffeine metabolites urine, medicines, and dietary intake characteristics were described individuals according to the tertile of serum UA levels. The comparison between the tertile of serum UA levels was performed through regression analysis. The continuous variables were described as mean and standard deviation and the categorical variables were described as percentage and confidence interval.

Linear regression analysis was performed to evaluate whether serum UA was associated with caffeine and caffeine metabolites. Logistic regression analysis was performed to evaluate whether the presence of hyperuricemia was associated with caffeine and its metabolites. Analyses were performed without adjustment and adjusted

for age, sex, race/ethnicity, education level, marital status, annual family income, diabetes, hypertension, physical activity, smoking status, body mass index (kg/m²), eGFR (ml/min/173m2), serum triglyceride (mg/dL), allopurinol use, and energy intake (kcal). All analyses were performed using the "svy" command to incorporate information on the 'two-year C subsample weights' as sample weight, primary sampling units, and strata for correct variance estimation. The significance of the associations was considered when p-value <0.05. The analyses were performed using Stata software version 14.0 (StataCorp, College Station, TX, USA).

RESULTS

The characteristics of individuals by UA tertile are shown in Table 1. All individuals in the first and second tertile had adequate serum UA values, while 45.2% of individuals in the third tertile were adequate. Individuals in the higher tertile of UA levels comparing individuals with lower tertile of UA levels were older, had higher prevalence of male, hypertension, most women were in menopause, and gout. Additionally, they had higher weight, height, BMI, and waist circumference. For biochemical parameters, individuals in the third tertile of UA levels had higher creatinine, urea, triglycerides, and lower GFR, and HDL cholesterol. As for caffeine and its metabolites, individuals in the third tertile of UA levels had lower concentrations of theobromine and 7-methylxanthine in their urine. Individuals in the third tertile of UA levels ingested more energy, protein (g; g/kg); total fat, and less vitamin C, coffee, and tea.

Linear regression analyses of serum UA with caffeine and caffeine metabolites are shown in Table 2. In the unadjusted model, theobromine and 7-methylxanthine were inversely associated with serum UA, whereas theophylline and 1,3-dimethyluric acid were positively associated with serum UA levels. After adjustments, paraxanthine, theobromine, 7-methyluric acid, 3,7-dimethyluric acid, 3-methylxanthine, and 7-methylxanthine were inversely associated with serum UA levels, whereas 1,3-dimethyluric acid was positively associated with serum UA. These metabolites explained 0.04 to 1.3% of serum UA variations.

Logistic regression analyses (odds ratio) are shown in Table 3. In the unadjusted model, -acetylamino-6-amino-3-methyluracil was associated with a higher chance of hyperuricemia. In the adjusted model, theobromine, 3-methyluric acid, 7-methyluric acid, and 3-methylxanthine were associated with a lower chance of hyperuricemia.

DISCUSSION

The main findings of the present study were that theobromine and 7-methylxanthine, 3-methyluric, 3-methylxanthine, 3,7-dimethyluric and 7-methyluric were inversely associated with serum UA and with the lower chance of having hyperuricemia, and paraxanthine was associated with lower chance of hyperuricemia. These results showed that theobromine is an important component for these associations once 7-methylxanthine, 3-methyluric, 3-methylxanthine, 3,7-dimethyluric and 7-methyluric are predominantly derived from theobromine. However, it is important to highlight that caffeine also plays an important role in these inverse associations, since there was an association of paraxanthine, mainly derived from caffeine, with serum UA. In addition, 1,3-dimethyluric acid was positively associated with serum UA. This is the first study that associated caffeine and caffeine metabolites with serum UA.

To the best of our knowledge, no study has evaluated the direct comparisons direct comparisons between caffeine and caffeine metabolites in urine with serum UA. However, epidemiological studies have made associations between the consumption of caffeine-rich foods (19, 21). The study by Choi et al. (19) evaluated 14,758 NHANES III participants aged ≥ 20 years and examined the relationship between coffee, tea, and caffeine intake and serum UA level. The authors observed that serum UA showed an inverse association with regular coffee and decaffeinated coffee, showing that other components, for example, theobromine, could have a protective action for hyperuricemia and higher concentrations of serum UA, despite the small concentrations in coffee (200 mg/g) (38, 39). In our previous study (21) with 125 patients who underwent kidney transplantation, caffeine was inversely associated with serum UA levels. However, we did not evaluate caffeine in isolation, but through sources such as coffee, teas, and chocolates, which have a high theobromine content in their composition (69 mg in 100 grams of black tea extract, and ~460 mg in 100 grams of dark chocolate), which allows us to infer that there was an indirect association with the components of these foods (39). Therefore, our results confirm that these inverse associations with coffee, teas, and chocolates, observed in other studies, may be mainly due to components other than caffeine. However, we must consider that caffeine alone may have a protective action for serum UA concentrations due to the inverse association with paraxanthine, which is a direct metabolite of caffeine, which is rarely encountered as a dietary compound (2).

Theobromine and its metabolites (7-methylxanthine, 3-methyluric, 3-methylxanthine, 3,7-dimethyluric and 7-methyluric) inversely associated and 1,3-

dimethyluric acid positively associated with UA levels explained 0.04 to 1.3% of serum UA variations, which allows us to extrapolate the small relevance of the action of caffeine and caffeine metabolites on serum UA levels. The limited relevance of the association between caffeine metabolites and serum UA levels can be attributed to several factors. These metabolites, which reflect the levels of caffeine metabolites in the body, may have a relatively small effect on the modulation of serum UA. The observed percentage of variation explained by these associated metabolites, ranging from 0.04% to 1.3%, further supports the notion that their impact on serum UA levels is minimal. It is important to consider that other factors, such as genetic and physiological factors, such as body fat (2, 23), have a more significant influence on UA modulation. Therefore, while the association between caffeine metabolites and serum UA levels exists, its biological relevance is relatively small in the overall context of UA modulation.

The mechanisms that explain the inverse association of paraxanthine, theobromine and its metabolites with serum UA are not fully understood. Nonetheless, caffeine, paraxanthine, and theobromine are methylxanthines, which have an affinity to the xanthine oxidase enzyme leading to a decrease in UA production by reducing the availability of xanthine oxidase for the UA synthesis pathway (12, 40). Wu et al. (41) showed a positive correlation between paraxanthine, theobromine, and urinary flow rate, which may contribute to the uricosuric action of these metabolites. The positive association between 1,3-dimethyluric acid (theophylline metabolite) had with UA can be partially explained due to its inhibitory effect on the family of organic anion transporters (OAT), which play an important role in the urinary excretion of UA (42). However, further studies are needed to understand the action of caffeine and its metabolites on serum UA.

This study has limitations. First, caffeine and caffeine metabolites were evaluated in urine, which may not be the gold standard method of evaluating these components once the gold standard for the evaluation of caffeine metabolites is through plasma quantification, as it allows for direct measurement. However, the evaluation of metabolites is a more accurate method compared to evaluation through dietary surveys, since these metabolites were consumed, metabolized, and excreted and had their action in the organism before excretion. Second, in an observational study, we cannot rule out that part of the association found could be explained by residual confounding. However, the analyses were adjusted for important potential confounders, which reduces this possibility. Third, due to the cross-sectional design, causality cannot be established. As

strengths, we evaluated caffeine and its metabolites in urine, which provides a more precise assessment compared to dietary surveys, known to have several known limitations. Generalizability is not an issue as we evaluated a representative US sample. In addition, all analyzes were adjusted for important confounders. Our result, serum UA, was measured using a reliable method of measurement.

CONCLUSION

Theobromine, 7-methylxanthine, 3-methyluric, 3-methylxanthine, 3,7-dimethyluric and 7-methyluric were inversely associated with serum UA and with the lower chance of having hyperuricemia, and paraxanthine was associated with lower chance of hyperuricemia, whereas 1,3-dimethyluric acid (theophylline metabolite) was positively associated with serum UA. Additionally, these metabolites explained 0.04 to 1.3% of serum UA variations, therefore, these results should be interpreted with caution due to the small relevance of the action of caffeine and caffeine metabolites on serum UA levels. Further studies are needed to understand the action of caffeine and its metabolites on serum UA.

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Conflict of interest

None.

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Figures and tables

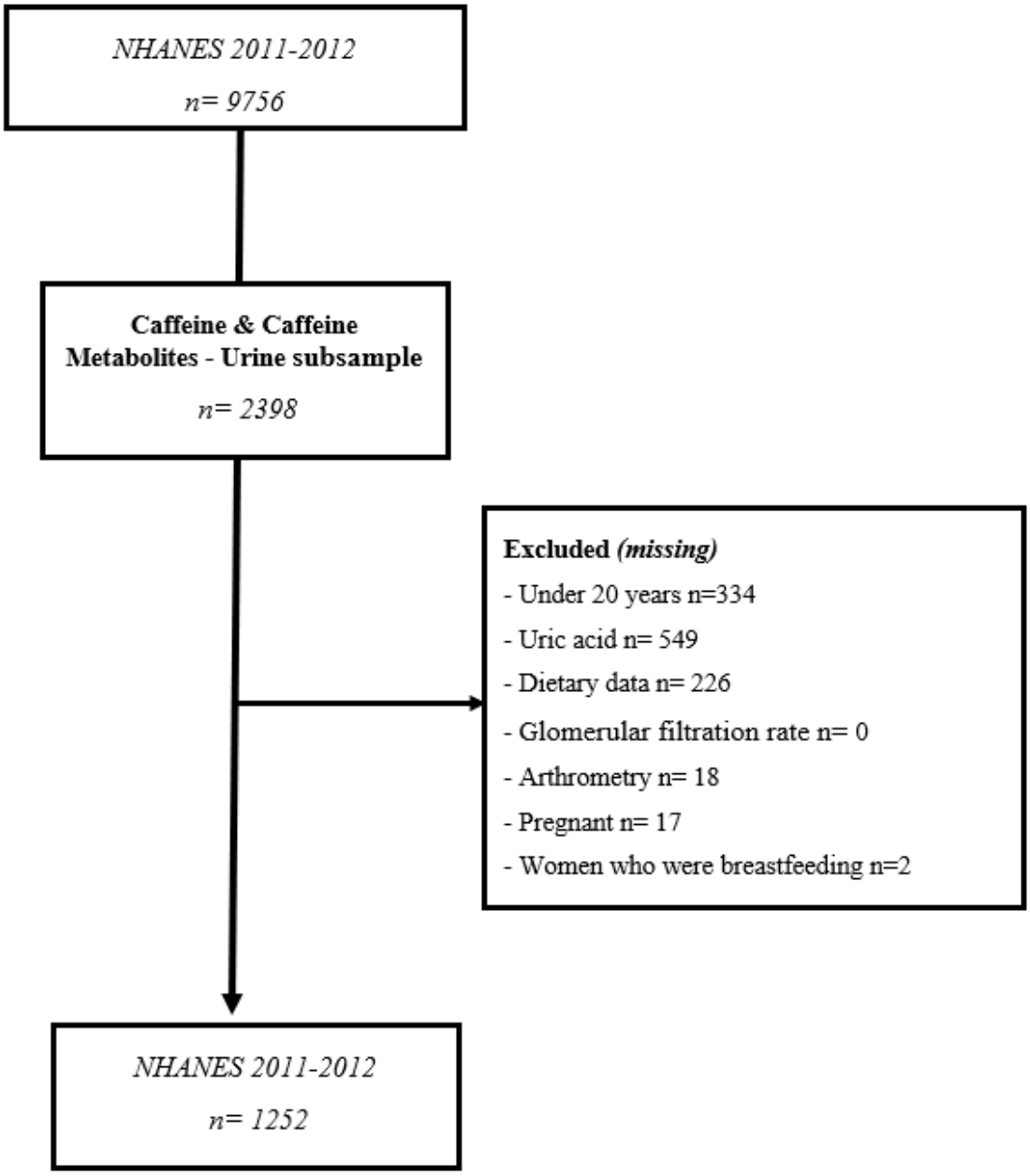

Figure 1. Flowchart of the sample selection by caffeine and caffeine metabolites in the urine subsample of NHANES 2011-2012.

Table 1. Sociodemographic, health conditions and behavior, anthropometric, and biochemical parameters by total sample and tertile of serum uric acid. NHANES, 2011-2012.

Variables	Total Sample	Tertile 1	Tertile 2	Tertile 3	*p-Value*
Uric acid, mg/dL	5.5 ± 1.4	3.9 ± 0.6	5.4 ± 0.3	7.0 ± 0.9	**<0.001**
Adequate uric acid, %	83.2 (77.9; 87.4)	100	100	45.2 (38.1; 52.5)	-
Sociodemographic					
Age, y	47.3 ± 16.4	45.0 ± 16.2	49.3 ± 15.5	49.6 ± 17.1	**0.014**
Sex, %					**<0.001**
Women	52.4 (49.5; 55.4)	79.8 (73.8; 84.7)	48.2 (43.3; 53.1)	27.3 (21.6; 34.0)	
Men	47.6 (44.6; 50.5)	20.2 (15.3; 26.2)	51.8 (46.9; 56.7)	72.7 (66.0; 78.4)	
Race/ethnicity, %					0.074
Non-Hispanic white	68.9 (59.5; 77)	63.3 (51.6; 73.6)	70.0 (57.4; 80.2)	73.8 (64.0; 81.7)	
Others	31.1 (23.0; 40.5)	36.7 (26.4; 48.4)	30.0 (19.8; 42.6)	26.2 (18.3; 36.0)	
Marital status, %					0.798
Married/Living with partner	64.0 (60.3; 67.6)	61.6 (54.6; 68.1)	67.6 (60.7; 73.8)	62.6 (56.7; 68.2)	
Single/Divorced/Widowed/Never Married	36.0 (32.4; 39.7)	38.4 (31.9; 45.4)	32.4 (26.2; 39.3)	37.4 (31.8; 43.3)	
Annual Family Income, %					0.664
$0-19,999	18.3 (15.1; 22.1)	19.0 (13.8; 25.7)	18.6 (14.5; 23.7)	17.2 (11.6; 24.9)	
$20,000-54,999	34.6 (29.9; 39.7)	37.3 (30.3; 44.8)	31.1 (25.2; 37.6)	35.9 (28.9; 43.6)	
$55,000-74,999	13.2 (11.0; 15.8)	12.7 (8.9; 17.8)	13.5 (8.7; 20.4)	13.5 (9.0; 19.7)	
Over $75,000	31.0 (24.7; 38.1)	28.3 (20.2; 38.1)	34.6 (27; 43)	29.8 (22.9; 37.8)	
Missing	2.8 (2.0 ; 4.0)	2.7 (1.6; 4.6)	2.2 (1.3; 3.7)	3.6 (2.1; 6.0)	
Educational level, %					0.482
Under high school graduate	34.0 (28.3; 40.2)	32.4 (23.3; 43.0)	34.2 (26.6; 42.7)	35.7 (30.1; 41.8)	
Some college or over	66.0 (59.8; 71.7)	67.6 (57.0; 76.7)	65.8 (57.3; 73.4)	64.3 (58.2; 69.9)	
Health Conditions and Behavior					
Diabetes, %					0.131
No	90.0 (87.7; 91.9)	93.2 (89.9; 95.5)	87.5 (82; 91.4)	89.4 (84.5; 92.9)	
Yes	7.7 (6.0; 9.9)	5.3 (3.1; 8.9)	10.3 (7.4; 14.1)	7.4 (4.4; 12.1)	

Pre-diabetes	2.2 (1.3; 3.7)	1.4 (0.6; 3.2)	2.2 (0.8; 5.7)	3.2 (1.4; 7.0)	
Hypertension, %					**<0.001**
No	68.6 (63.5; 73.3)	80.1 (72.9; 85.8)	66.2 (59.5; 72.3)	58.8 (50.3; 66.7)	
Yes	31.4 (26.7; 36.5)	19.9 (14.2; 27.1)	33.8 (27.7; 40.5)	41.2 (33.3; 49.7)	
Menopause, %					**<0.001**
No	50.0 (41.6; 58.4)	61.4 (50.9; 71.0)	42.2 (29.1; 56.6)	31.2 (17.3; 49.6)	
Yes	50.0 (41.6; 58.4)	38.6 (29.0; 49.1)	57.8 (43.4; 70.9)	68.8 (50.4; 82.7)	
Gout, %					**0.007**
No	96.4 (93.6; 98.0)	98.8 (96.8; 99.5)	95.8 (92.6; 97.7)	94.6 (88.6; 97.5)	
Yes	3.6 (2.0; 6.4)	1.2 (0.5; 3.2)	4.2 (2.3; 7.4)	5.4 (2.5; 11.4)	
Arthritis, %					0.442
No	74.7 (70.3; 78.7)	74.9 (67.9; 80.8)	71.2 (63.5; 77.8)	78.6 (70.6; 84.9)	
Yes	25.2 (21.2; 29.5)	24.8 (19; 31.7)	28.6 (22.1; 36.2)	21.4 (15.1; 29.4)	
Physical activity, %					0.485
Yes	41.6 (37.9; 45.5)	42.5 (35.5; 49.9)	37.3 (31.7; 43.3)	45.6 (38.1; 53.3)	
No	58.4 (54.5; 62.1)	57.5 (50.1; 64.5)	62.7 (56.7; 68.3)	54.4 (46.7; 61.9)	
Smoking status, %					0.882
No	82.6 (78; 86.5)	81.3 (74.4; 86.6)	85.7 (78.5; 90.8)	80.6 (75.2; 85.1)	
Yes	17.3 (13.5; 22)	18.7 (13.4; 25.6)	14.3 (9.2; 21.5)	19.2 (14.8; 24.6)	
Anthropometric data					
Weight, kg	82.5 ± 20.3	72.6 ± 17.3	84.0 ± 19.3	91.2 ± 19.8	**<0.001**
Height, m	1.69 ± 0.10	1.65 ± 0.09	1.69 ± 0.95	1.73 ± 0.10	**<0.001**
Body mass index, kg/m^2	28.7 ± 6.4	26.5 ± 5.9	29.3 ± 6.5	30.2 ± 6.1	**<0.001**
Waist Circumference, cm	98.6 ± 15.4	91.5 ± 14.1	100.1 ± 15.1	104.2 ± 14.1	**<0.001**
Biochemical parameters					
Creatinine, mg/dL	0.9 ± 0.3	0.8 ± 0.3	0.9 ± 0.2	1.0 ± 0.3	**<0.001**
Urea, mg/dl	13.1 ± 5	11.6 ± 4.1	13.1 ± 4.2	14.7 ± 6	**<0.001**
Glomerular filtration rate, ml/min/1.73^2	94.6 ± 23.2	102.6 ± 20.2	93.1 ± 22.2	88.0 ± 24.3	**<0.001**
Triglycerides, mg/dL	154.0 ± 106.7	121.6 ± 81.6	156.8 ± 109.6	184.7 ± 114.3	**<0.001**
Glucose, mg/dL	98.3 ± 32.4	95.8 ± 34.5	99.6 ± 35.4	99.5 ± 25.8	0.140

Cholesterol, mg/dL	196.7 ± 39.8	193.9 ± 42	197.3 ± 38.6	198.9 ± 38.6	0.156
HDL cholesterol, mg/dL	52.2 ± 13.9	58.3 ± 14.8	51.5 ± 12.4	46.5 ± 12.1	**<0.001**
LDL cholesterol, mg/dL	119.0 ± 34.9	116.9 ± 36.6	118.6 ± 32.9	121.3 ± 35.1	0.535
Caffeine Metabolites Urine					
Caffeine - 1,3,7-trimethylxanthine, umol/L	8.1 ± 9.5	8.3 ± 9.8	8.2 ± 9.4	7.9 ± 9.2	0.441
Paraxanthine - 1,7-dimethylxanthine, umol/L	28.8 ± 32.9	27.8 ± 26.9	32.0 ± 39.8	26.4 ± 28.8	0.440
Theobromine - 3,7-dimethylxanthine, umol/L	30.2 ± 41.5	32.1 ± 39.6	33.4 ± 49.2	24.6 ± 31.6	**0.017**
Theophylline - 1,3-dimethylxanthine, umol/L	4.1 ± 26.0	2.9 ± 3.1	3.1 ± 3.4	6.5 ± 45.3	0.372
1-methyluric acid, umol/L	106.8 ± 138.8	91.1 ± 106.4	110.5 ± 139.4	119.0 ± 161.5	0.195
3-methyluric acid, umol/L	1.2 ± 2.1	1.1 ± 1.5	1.2 ± 2.1	1.2 ± 2.6	0.405
7-methyluric acid, umol/L	26.9 ± 40.7	26.2 ± 37.5	30.1 ± 49.5	24.1 ± 31	0.405
1,3-dimethyluric acid, umol/L	16.4 ± 99.0	10.3 ± 12	12.5 ± 14.4	27.2 ± 172.1	0.276
1,7-dimethyluric acid, umol/L	50.6 ± 61.4	44.2 ± 57.7	52.3 ± 63.9	55.5 ± 61.2	0.226
3,7-dimethyluric acid, umol/L	1.8 ± 2.7	1.8 ± 3.0	1.9 ± 2.9	1.6 ± 2.1	0.400
1,3,7-trimethyluric acid, umol/L	3.2 ± 4.2	2.9 ± 3.9	3.2 ± 4.1	3.6 ± 4.6	0.507
1-methylxanthine, umol/L	58.1 ± 72.2	56.2 ± 69.3	60.5 ± 74.0	57.5 ± 72.5	0.968
3-methylxanthine, umol/L	53.7 ± 84	55.8 ± 74.6	56.1 ± 84.3	48.8 ± 91.4	0.418
7-methylxanthine, umol/L	82.6 ± 111.2	94.6 ± 136.7	85.9 ± 114.1	66.3 ± 71.8	**0.024**
5-acetylamino-6-amino-3-methyluracil	110.4 ± 138	96.7 ± 130.8	112.3 ± 155.5	122.6 ± 120.5	0.229
Medicines					
Allopurinol, n (%)					0.244
No	99.3 (98.4; 99.7)	99.4 (97.6; 99.8)	98.7 (96.5; 99.5)	99.9 (99.3; 100)	
Yes	0.7 (0.3; 1.6)	0.6 (0.2; 2.4)	1.3 (0.5; 3.5)	0.1 (0.0; 0.7)	
Prednisone, n (%)					0.562
No	98.6 (97.8; 99.2)	98.7 (94.7; 99.7)	98.0 (95.6; 99.1)	99.3 (98.3; 99.7)	
Yes	1.4 (0.8; 2.2)	1.3 (0.3; 5.3)	2.0 (0.9; 4.4)	0.7 (0.3; 1.7)	
Dietary intake					
Energy, kcal/day	2126.7 ± 510.3	2065.5 ± 474.8	2092.3 ± 441.1	2229.4 ± 593	**0.016**
Carbohydrate, g/day	262.4 ± 64.9	258.9 ± 64.1	258.5 ± 55.9	270.5 ± 73.7	0.134
Protein, g/day	82.6 ± 19.5	79.6 ± 19	81.5 ± 17.9	86.9 ± 20.8	**0.001**

Protein, g/kg/day	1.0 ± 0.3	1.1 ± 0.3	1.0 ± 0.3	1.1 ± 0.4	**<0.001**
Total fat, g/day	79.2 ± 21.2	76.7 ± 18.9	77.8 ± 19.4	83.3 ± 24.4	**0.032**
Total Fiber, g/day	18.3 ± 5.9	18.7 ± 6.1	18.4 ± 5.6	17.9 ± 5.9	0.153
Alcohol, g/day	9.0 ± 12.7	8.6 ± 10.8	8.9 ± 13.9	9.7 ± 12.9	0.332
Caffeine, mg/day	158.09 ± 118.9	152.4 ± 112.4	150.4 ± 98.2	172.5 ± 142.4	0.080
Theobromine, mg/day	35.7 ± 20.4	37.3 ± 21.5	35.5 ± 19.0	34.2 ± 20.7	0.192
Vitamin C, mg/day	87.1 ± 39.8	89.9 ± 41.3	89.7 ± 41.5	81.2 ± 35.3	**0.029**
Coffee, tea with additions, ml	325.6 ± 280.6	356 ± 280.2	318.7 ± 267.7	301.8 ± 291.3	**0.023**

Data are described as mean ± standard deviation or percentage (confidence interval). Bold means that the p-value is statistically significant. Menopause was only analyzed for women.

Table 2. Linear regression analysis of serum uric acid with caffeine and its metabolites.

	Unadjusted		Adjusted			
	β	***p-Value***	**β**	***p-Value***	**R^2 (%) ***	**R^2 (%) †**
Caffeine - 1,3,7-trimethylxanthine, umol/L	-0.002	0.806	-0.009	0.076	42.4	-
Paraxanthine - 1,7-dimethylxanthine, umol/L	-0.002	0.283	**-0.004**	**0.006**	**43.0**	**0.9**
Theobromine - 3,7-dimethylxanthine, umol/L	-0.003	**0.035**	**-0.004**	**<0.001**	**43.4**	**1.3**
Theophylline - 1,3-dimethylxanthine, umol/L	0.001	**0.001**	0.001	0.232	42.1	-
1-methyluric acid, umol/L	0.000	0.253	0.000	0.563	42.1	-
3-methyluric acid, umol/L	0.017	0.294	-0.02	0.144	42.2	-
7-methyluric acid, umol/L	-0.001	0.360	**-0.003**	**0.003**	**42.8**	**0.7**
1,3-dimethyluric acid, umol/L	0.001	**0.001**	**0.001**	**0.012**	**42.1**	**0.04**
1,7-dimethyluric acid, umol/L	0.001	0.165	0.001	0.560	42.1	-
3,7-dimethyluric acid, umol/L	-0.018	0.347	**-0.029**	**0.024**	**42.5**	**0.4**
1,3,7-trimethyluric acid, umol/L	0.016	0.308	-0.010	0.408	42.2	-
1-methylxanthine, umol/L	0.000	0.752	-0.001	0.193	42.3	-
3-methylxanthine, umol/L	-0.001	0.260	**-0.001**	**0.038**	**42.5**	**0.4**
7-methylxanthine, umol/L	-0.001	**0.011**	**-0.001**	**<0.001**	**43.1**	**1.1**
5-acetylamino-6-amino-3-methyluracil	0.000	0.244	0.000	0.416	42.1	-

Each variable was adjusted for age, sex, race/ethnicity, education level, marital status, annual family income, diabetes, hypertension, physical activity, smoking status, body mass index (kg/m^2), eGFR ($ml/min/1.73\ m^2$), serum triglyceride (mg/dL), allopurinol use, and energy intake (kcal).

***R^2 value:** uric acid as a dependent variable. Independent variables were: caffeine and each caffeine metabolites urine plus adjustments (age, sex, race/ethnicity, education level, marital status, annual family income, diabetes, hypertension, physical activity, smoking status, body mass index (kg/m^2), glomerular filtration rate ($ml/min/1.73m^2$), serum triglyceride (mg/dL), allopurinol use, and energy intake (kcal))

†**R^2:** the difference between R^2 (dietary component plus adjustments) and R^2 (adjustments without dietary component).

Table 3. Logistic regression analysis of presence of hyperuricemia with caffeine and caffeine metabolites.

	Unadjusted		Adjusted	
	OR	***CI (95%)***	**OR**	***CI (95%)***
Caffeine - 1,3,7-trimethylxanthine, umol/L	1.00	(0.971 - 1.027)	0.98	(0.960 - 1.006)
Paraxanthine - 1,7-dimethylxanthine, umol/L	0.99	(0.98 - 1.007)	0.99	(0.983 - 1.001)
Theobromine - 3,7-dimethylxanthine, umol/L	0.99	(0.982 - 1.001)	**0.99**	**(0.980 - 0.999)**
Theophylline - 1,3-dimethylxanthine, umol/L	0.98	(0.883 - 1.085)	0.96	(0.878 - 1.053)
1-methyluric acid, umol/L	1.00	(0.999 - 1.002)	1.00	(0.999 - 1.001)
3-methyluric acid, umol/L	0.99	(0.925 - 1.060)	**0.91**	**(0.837 - 0.996)**
7-methyluric acid, umol/L	1.00	(0.993 - 1.002)	**0.99**	**(0.989 - 0.998)**
1,3-dimethyluric acid, umol/L	1.00	(0.999 - 1.001)	1.00	(0.998 - 1.000)
1,7-dimethyluric acid, umol/L	1.00	(0.999 - 1.005)	1,00	(0.998 - 1.003)
3,7-dimethyluric acid, umol/L	0.97	(0.899 - 1.053)	0.94	(0.851 - 1.033)
1,3,7-trimethyluric acid, umol/L	1.03	(0.975 - 1.085)	0.99	(0.94 - 1.047)
1-methylxanthine, umol/L	1.00	(0.996 - 1.004)	1.00	(0.996 - 1.002)
3-methylxanthine, umol/L	1.00	(0.994 - 1.000)	**0.99**	**(0.992 - 0.999)**
7-methylxanthine, umol/L	1.00	(0.995 - 1.000)	1.00	(0.994 - 1.000)
5-acetylamino-6-amino-3-methyluracil	**1.00**	**(1.000 - 1.002)**	1.00	(0.999 - 1.002)

Each variable was adjusted for age, sex, race/ethnicity, education level, marital status, annual family income, diabetes, hypertension, physical activity, smoking status, body mass index (kg/m²), glomerular filtration rate (ml/min/1.73m^2), serum triglyceride (mg/dL), allopurinol use, and energy intake (kcal)

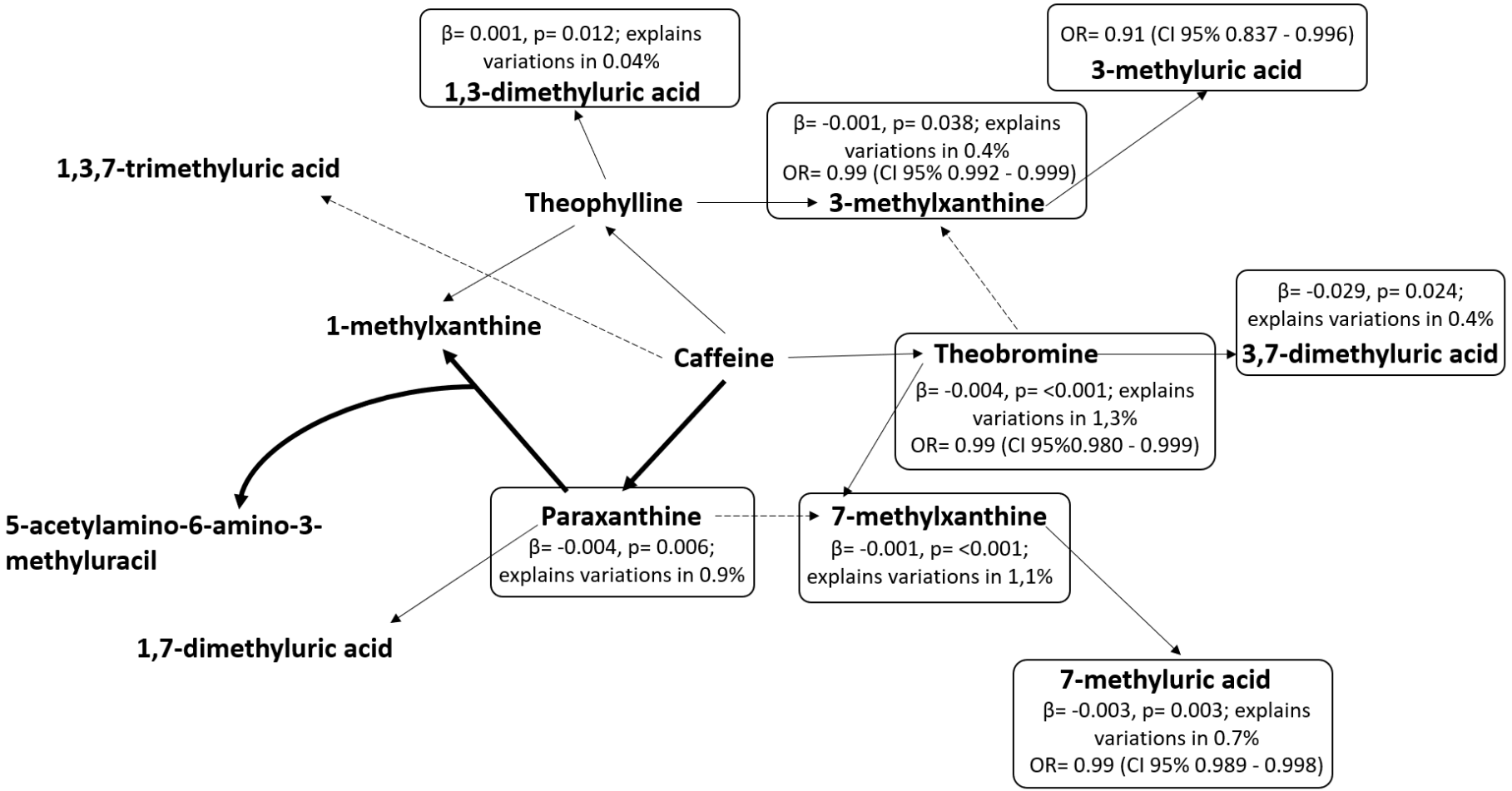

Figure 2. Summary of associations of serum uric acid (linear regression) and hyperuricemia (logistic regression, odds ratio) with caffeine and caffeine metabolites according to caffeine metabolism in humans. The percentage values represent the percentage of chance of hyperuricemia, as

well as the predicted value of serum uric acid in relation caffeine and caffeine metabolites.

5. CONCLUSÃO

Os resultados mostraram que a ingestão dietética de carboidratos, gordura saturada, fibras, cálcio, magnésio e cereais foi inversamente associada aos níveis séricos de AU, enquanto o consumo de álcool mostrou uma associação positiva com UA e com a maior chance de hiperuricemia, enquanto o consumo de vegetais com adições foi associado a uma menor chance de hiperuricemia. Por outro lado, a análise dos metabólitos de cafeína revelou que a teobromina, 7-metilxantina, 3-metilúrico, 3-metilxantina, 3,7-dimetilúrico e 7-metilúrico apresentaram associação inversa com o ácido úrico sérico e menor probabilidade de hiperuricemia e a paraxantina esteva associada a uma menor chance de hiperuricemia, enquanto o ácido 1,3-dimetilúrico (metabólito da teofilina) estava positivamente associado ao AU sérico.

Os mecanismos subjacentes a essas associações não são completamente compreendidos. Em adição, é importante ressaltar que as variações explicadas pelos nutrientes e metabólitos são baixas, indicando uma relevância clínica limitada.

Portanto, embora existam associações significativas entre a ingestão dietética, incluindo nutrientes específicos, e os metabólitos de cafeína com os níveis séricos de AU, é necessário realizar futuros ensaios clínicos randomizados para investigar se o consumo desses nutrientes, bem como a cafeína na urina e seus metabólitos tem efeitos clínicos importantes nos níveis de AU.

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