

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

**ASSOCIAÇÃO DOS METABÓLITOS DA CAFEÍNA NA URINA E ÁCIDO ÚRICO  
SÉRICO COM A FORÇA MUSCULAR: DADOS DO NATIONAL HEALTH AND  
NUTRITION EXAMINATION SURVEY (NHANES) 2011 – 2012 & 1999 – 2002**

**BRENO BATISTA DA SILVA**

**UBERLÂNDIA**

**2024**

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SÉRICO COM A FORÇA MUSCULAR: DADOS DO NATIONAL HEALTH AND  
NUTRITION EXAMINATION SURVEY (NHANES) 2011 – 2012 & 1999 – 2002**

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

**Área de concentração: Ciências da Saúde.**

**Orientador: Prof. Dr. Erick Prado de Oliveira**

**Co-orientadora: Prof<sup>a</sup>. Dr<sup>a</sup>. Larissa Silva Limirio**

**UBERLÂNDIA**

**2024**

Ficha Catalográfica Online do Sistema de Bibliotecas da UFU  
com dados informados pelo(a) próprio(a) autor(a).

S586  
2024

Silva, Breno Batista da, 1996-  
Associação dos metabólitos da cafeína na urina e ácido  
úrico sérico com a força muscular: Dados do National  
Health and Nutrition Examination Survey (NHANES) 2011 –  
2012 & 1999 – 2002 [recurso eletrônico] / Breno Batista  
da Silva. - 2024.

Orientador: Erick Prado de Oliveira.

Coorientadora: Larissa Silva Limirio.

Tese (Doutorado) - Universidade Federal de Uberlândia,  
Pós-graduação em Ciências da Saúde.

Modo de acesso: Internet.

Disponível em: <http://doi.org/10.14393/ufu.te.2024.643>

Inclui bibliografia.

Inclui ilustrações.

1. Ciências médicas. I. Oliveira, Erick Prado de, 1983-  
, (Orient.). II. Limirio, Larissa Silva, 1993-,  
(Coorient.). III. Universidade Federal de Uberlândia.  
Pós-graduação em Ciências da Saúde. IV. Título.

CDU: 61

Bibliotecários responsáveis pela estrutura de acordo com o AACR2:

Gizele Cristine Nunes do Couto - CRB6/2091  
Nelson Marcos Ferreira - CRB6/3074



## ATA

|                                    |                                                                                                                                                                                        |                 |        |                       |        |
|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|--------|-----------------------|--------|
| Programa de Pós-Graduação em:      | Ciências da Saúde                                                                                                                                                                      |                 |        |                       |        |
| Defesa de:                         | Defesa de Tese Doutorado Nº 14/PPGCSAUDE                                                                                                                                               |                 |        |                       |        |
| Data:                              | 04.09.2024                                                                                                                                                                             | Hora de início: | 08:00h | Hora de encerramento: | 12:00h |
| Matrícula do Discente:             | 12213CSD003                                                                                                                                                                            |                 |        |                       |        |
| Nome do Discente:                  | Breno Batista da Silva                                                                                                                                                                 |                 |        |                       |        |
| Título do Trabalho:                | ASSOCIAÇÃO DOS METABÓLITOS DA CAFEÍNA NA URINA E ÁCIDO ÚRICO SÉRICO COM A FORÇA MUSCULAR: DADOS DO NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES) 2011 - 2012 & 1999 - 2002 |                 |        |                       |        |
| Área de concentração:              | Ciências da Saúde                                                                                                                                                                      |                 |        |                       |        |
| Linha de pesquisa:                 | 2: Diagnóstico, Tratamento e Prognóstico das Doenças e Agravos à Saúde                                                                                                                 |                 |        |                       |        |
| Projeto de Pesquisa de vinculação: | Nutrição e Exercício Físico Aplicados à Saúde e Desempenho Humano                                                                                                                      |                 |        |                       |        |

Reuniu-se em sala virtual, em web conferência pela plataforma Zoom, a Banca Examinadora, designada pelo Colegiado do Programa de Pós-graduação em Ciências da Saúde, assim composta: Professores Doutores: Bryan Saunders (USP), Fabio Lera Orsatti (UFTM), Ana Elisa Madalena Rinaldi (UFU), Nadia Carla Cheik (UFU) e Erick Prado de Oliveira (UFU), orientador do candidato.

Iniciando os trabalhos o(a) presidente da mesa, Dr. Erick Prado de Oliveira, apresentou a Comissão Examinadora e o candidato(a), agradeceu a presença dos membros da banca, e concedeu ao Discente a palavra para a exposição do seu trabalho. A duração da apresentação do Discente e o tempo de arguição e resposta foram conforme as normas do Programa.

A seguir o senhor(a) presidente concedeu a palavra, pela ordem sucessivamente, aos(às) examinadores(as), que passaram a arguir o(a) candidato(a). Ultimada a arguição, que se desenvolveu dentro dos termos regimentais, a Banca, em sessão secreta, atribuiu o resultado final, considerando o(a) candidato(a):

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Nada mais havendo a tratar foram encerrados os trabalhos. Foi lavrada a presente ata que após lida e achada conforme foi assinada pela Banca Examinadora.



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Documento assinado eletronicamente por **Ana Elisa Madalena Rinaldi, Professor(a) do Magistério Superior**, em 04/09/2024, às 11:58, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do [Decreto nº 8.539, de 8 de outubro de 2015](#).



Documento assinado eletronicamente por **Bryan Saunders, Usuário Externo**, em 04/09/2024, às 11:58, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do [Decreto nº 8.539, de 8 de outubro de 2015](#).



Documento assinado eletronicamente por **Fábio Lera Orsatti, Usuário Externo**, em 04/09/2024, às 12:05, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do [Decreto nº 8.539, de 8 de outubro de 2015](#).



Documento assinado eletronicamente por **Nadia Carla Cheik, Professor(a) do Magistério Superior**, em 04/09/2024, às 14:45, conforme horário oficial de Brasília, com fundamento no art. 6º, § 1º, do [Decreto nº 8.539, de 8 de outubro de 2015](#).



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## DEDICATÓRIA

*À minha mãe e ao meu pai, por serem meus pilares de força e inspiração ao longo  
desta jornada*

## **AGRADECIMENTOS**

Agradeço a Deus, cuja constante fortaleza me sustentou em meio aos desafios que surgiram em meu caminho. Quero estender meus agradecimentos especiais aos meus pais, cujo apoio amoroso e educação foram fundamentais para minha jornada até aqui. Sem eles, é improvável que eu estivesse neste ponto.

À minha noiva, Julia Buiatte Tavares, que tem sido uma presença constante e solidária em todos os momentos difíceis da minha vida acadêmica e pessoal, meu sincero agradecimento.

Agradeço de coração aos meus colegas do Laboratório de Nutrição, Exercício e Saúde (LaNES) pelos bons momentos de aprendizagem, troca de conhecimento e descontração. Destaco especialmente a Profa. Dra. Larissa Limirio, cuja prontidão em auxiliar-me na compreensão do banco de dados e na elaboração de ambos os artigos da tese foi fundamental.

Meus professores do programa da pós-graduação em Ciências da Saúde merecem uma menção especial, assim como meu orientador, Prof. Dr. Erick Prado de Oliveira, cuja dedicação e apoio foi crucial para o sucesso deste trabalho. Sem sua experiência e orientação, essa conquista não seria possível. Expresso também minha gratidão por me receber em meados de 2019, enquanto ainda estava no mestrado, para participar das reuniões científicas organizadas pelo seu grupo de estudo.

## RESUMO

**Introdução:** Tanto o estresse oxidativo quanto a hiperglicemia estão associados ao declínio da força muscular. Compostos com propriedades antioxidantes, como os metabólitos de cafeína e o ácido úrico (AU), podem desempenhar um papel protetor prevenindo a diminuição da força muscular. No entanto, a associação específica desses compostos com a força muscular em diferentes faixas etárias e estados glicêmicos permanece incerta. **Objetivo:** O primeiro estudo teve como objetivo investigar se os metabólitos da cafeína na urina estão associados com a força muscular em jovens e idosos. O segundo estudo, por sua vez, objetivou investigar se existe associação entre níveis de AU sérico e força muscular em idosos, estratificados pelos níveis de hemoglobina glicada. **Métodos:** Dois estudos transversais foram conduzidos utilizando dados do National Health and Nutrition Examination Survey (NHANES). O primeiro estudo, utilizou dados do biênio 2011-2012, incluiu 1145 indivíduos com mais de 20 anos e avaliou a associação entre os metabólitos de cafeína na urina e a força muscular usando análise de regressão linear. O segundo estudo, utilizou dados dos biênios 1999-2000 e 2001-2002, envolveu 2380 indivíduos com idades entre 50 e 85 anos e examinou a relação entre os níveis séricos de AU e a força muscular de acordo com o status glicêmico, também utilizando análise de regressão linear. Análises de regressão linear em ambos os estudos foram ajustadas por fatores de confusão. **Resultados:** No primeiro estudo, foram observadas associações positivas entre os metabólitos da cafeína e a força muscular, como ácido 7-metilúrico ( $\beta = 0.029$ ;  $p = 0.021$ ), ácido 1,3-dimetilúrico ( $\beta = 0.008$ ;  $p = 0.004$ ), ácido 3,7-dimetilúrico ( $\beta = 0.645$ ;  $p = 0.012$ ), 3-metilxantina ( $\beta = 0.020$ ;  $p = 0.002$ ), 7-metilxantina ( $\beta = 0.020$ ;  $p = 0.006$ ), 1,3-dimetilxantina (teofilina) ( $\beta = 0.030$ ;  $p = 0.004$ ) e 3,7-dimetilxantina (teobromina) ( $\beta = 0.035$ ;  $p = 0.029$ ) em idosos. Em contraste, nenhuma dessas associações foi observada em jovens. No segundo estudo, por sua vez, o tercil dos níveis de AU mostrou uma associação positiva com o pico de força em indivíduos com hiperglicemia ( $p$ -tendência = 0.013), mas não naqueles com normoglicemia ( $p$ -tendência = 0.077). Além disso, valores contínuos de AU foram positivamente associados à força muscular em idosos com hiperglicemia ( $\beta = 5.2$  (CI = 0.6; 9.8);  $p = 0.027$ ), enquanto nenhuma associação foi observada naqueles com glicemia normal ( $\beta = 2.4$  (CI = -2.1; 6.9);  $p = 0.282$ ). **Conclusão:** O primeiro estudo indica uma associação positiva entre certos metabólitos da cafeína na urina e a força

muscular em idosos, mas não em indivíduos mais jovens. No segundo estudo, por sua vez, foi observado que o AU sérico apresenta uma associação positiva com a força muscular em idosos com hiperglicemia, no entanto, essa associação não é observada em indivíduos com níveis normais de glicose. Os resultados de ambos os estudos sugerem que compostos antioxidantes, como os metabólitos da cafeína e o ácido úrico, desempenham um papel importante na manutenção da força muscular em populações cuja perda de força está associada ao estresse oxidativo, como em idosos e indivíduos com hiperglicemia.

**Palavras-chave:** Cafeína, ácido úrico, antioxidante, envelhecimento.

## ABSTRACT

**Background:** Both oxidative stress and hyperglycemia are implicated in the decline of muscle strength. Compounds with antioxidant properties, such as certain caffeine metabolites and uric acid (UA), have shown potential in mitigating this decline. However, the specific association of these compounds with muscle strength in different age groups and glycemic statuses remains unclear. **Aim:** The first study aimed to investigate whether caffeine metabolites in urine are associated with muscle strength in both young and older adults. The second study, in turn, aimed to examine whether there is an association between serum uric acid levels and muscle strength in the older adults, stratified by glycated hemoglobin levels. **Methods:** Two cross-sectional studies were conducted using data from the National Health and Nutrition Examination Survey (NHANES). The first study, utilizing data from the 2011-2012 biennium, included 1,145 individuals aged over 20 years and evaluated the association between caffeine metabolites in urine and muscle strength using linear regression analysis. The second study, using data from the 1999-2000 and 2001-2002 biennia, involved 2,380 individuals aged 50 to 85 years, examining the relationship between serum uric acid levels and muscle strength according to glycemic status, also employing linear regression analysis. Linear regression analyses in both studies were adjusted for confounders. **Results:** In the first study, positive associations were observed between caffeine metabolites and muscle strength, such as 7-methyluric acid ( $\beta = 0.029$ ;  $p = 0.021$ ), 1,3-dimethyluric acid ( $\beta = 0.008$ ;  $p = 0.004$ ), 3,7-dimethyluric acid ( $\beta = 0.645$ ;  $p = 0.012$ ), 3-methylxanthine ( $\beta = 0.020$ ;  $p = 0.002$ ), 7-methylxanthine ( $\beta = 0.020$ ;  $p = 0.006$ ), 1,3-dimethylxanthine (theophylline) ( $\beta = 0.030$ ;  $p = 0.004$ ), and 3,7-dimethylxanthine (theobromine) ( $\beta = 0.035$ ;  $p = 0.029$ ) in older adults. In contrast, none of these associations were observed in young individuals. In the second study, the tertile of uric acid levels showed a positive association with peak strength in individuals with hyperglycemia ( $p$ -trend = 0.013), but not in those with normoglycemia ( $p$ -trend = 0.077). Additionally, continuous uric acid values were positively associated with muscle strength in elderly individuals with hyperglycemia ( $\beta = 5.2$ ; (IC = 0.6; 9.8);  $p = 0.027$ ), while no association was observed in those with normal glycemia ( $\beta = 2.4$  (IC = -2.1; 6.9);  $p = 0.282$ ). **Conclusion:** The first study indicates a positive association between certain caffeine metabolites in urine and muscle strength in older adults, but not in younger individuals. Conversely, the second study observed that serum UA shows a

positive association with muscle strength in older adults with hyperglycemia; however, this association is not observed in individuals with normal glucose levels. The findings from both studies suggest that antioxidants, such as caffeine metabolites and uric acid, play an important role in maintaining muscle strength in populations where strength loss is associated with oxidative stress, such as older adults and individuals with hyperglycemia.

**Keywords:** Caffeine, uric acid, antioxidant, aging.

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## LISTA DE ABREVIATURAS E SÍMBOLOS

|                |                                                      |
|----------------|------------------------------------------------------|
| AFMU           | Uracil metabolite                                    |
| AU             | Ácido úrico                                          |
| BMI            | Body mass index                                      |
| CDC            | Centers for Disease Control and Prevention           |
| CKD-EPI        | Chronic kidney disease epidemiology collaboration    |
| CRP            | C-reactive protein                                   |
| dl             | Deciliter                                            |
| DNA            | Ácido desoxirribonucleico                            |
| eGFR           | Glomerular filtration rate                           |
| EROs           | Espécies reativas de oxigênio                        |
| EWGSOP         | European Working Group on Sarcopenia in Older People |
| g              | Gram                                                 |
| HbA1c          | Glycated hemoglobin                                  |
| HDL            | High density lipoprotein                             |
| HPLC           | High-performance liquid chromatography               |
| IBGE           | Instituto Brasileiro de Geografia e Estatística      |
| kcal           | Calorie                                              |
| kg             | Kilogram                                             |
| m <sup>2</sup> | Square meter                                         |
| mcg            | Microgram                                            |
| mg             | Milligram                                            |
| min            | Minute                                               |
| ml             | Milliliter                                           |

|          |                                                                    |
|----------|--------------------------------------------------------------------|
| N        | Newtons                                                            |
| NCHS     | National Center for Health Statistics                              |
| NCHS ERB | National Center for Health Statistics Research Ethics Review Board |
| NHANES   | National Health and Nutrition Examination Survey                   |
| ROS      | Reactive oxygen species                                            |
| UA       | Uric acid                                                          |
| USA      | United States of America                                           |
| y        | Years                                                              |

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## 1. INTRODUÇÃO

Diversas mudanças fisiológicas ocorrem durante o envelhecimento, como a redução da massa e da força muscular (MCGREGOR; CAMERON-SMITH; POPPITT, 2014). Essas mudanças têm sido associadas à diminuição da capacidade funcional e a um aumento no risco de quedas e fraturas (UUSI-RASI; KARINKANTA; TOKOLA; KANNUS *et al.*, 2019; WANG; MA; WANG; HAN *et al.*, 2016). Apesar da natureza multifatorial, vários fatores têm potencial para contribuir para o declínio da força muscular em idosos (BARTELS; ROBERTSON; DANNESKIOLD-SAMSØE; APPLEBYARD *et al.*, 2018; LANGHAMMER; BERGLAND; RYDWIK, 2018; LEE; JUNG; BANG; KIM *et al.*, 2018; MAINOUS; TANNER; ANTON; JO, 2015). O aumento do estresse oxidativo pode acelerar essa condição, uma vez que o desequilíbrio redox pode afetar tanto a massa muscular quanto a ativação das fibras musculares e os processos de excitação-contratação (FULLE; PROTASI; DI TANO; PIETRANGELO *et al.*, 2004). Além disso, a condição de hiperglicemia tem sido correlacionada com a diminuição da força muscular, um fenômeno atribuído à sua capacidade de induzir o aumento do estresse oxidativo por meio da produção exarcebada de espécies reativas de oxigênio (EROs) (PARK; GOODPASTER; LEE; KULLER *et al.*, 2009). Portanto, espera-se que compostos com propriedades antioxidantes possam potencialmente conferir efeitos protetores à força muscular, mitigando o impacto do estresse oxidativo.

O ácido úrico (AU) é o produto final do metabolismo de purinas e ácidos nucleicos em humanos e é um importante antioxidante, contribuindo com mais de cinquenta por cento da capacidade antioxidante total do plasma (DE OLIVEIRA; BURINI, 2012). Embora o AU tenha sido associado com a força muscular em determinadas populações (GARCÍA-ESQUINAS; RODRÍGUEZ-ARTALEJO, 2018; KAWAMOTO; NINOMIYA; KASAI; KUSUNOKI *et al.*, 2016; LEE; JUNG; BANG; KIM *et al.*, 2018), há uma lacuna substancial no entendimento de como essa substância se comporta em populações clínicas onde o estresse oxidativo é identificado como uma das causas subjacentes da perda de força. Por exemplo, HOU; ZENG; CHEN; HAN *et al.* (2022) em um estudo transversal utilizando o banco de dados KNHANES com uma amostra de 5247 pessoas observaram uma correlação inversa entre os níveis séricos de AU e a força de preensão manual em mulheres, e sua significância foi mantida mesmo após ajuste para idade e componentes da síndrome metabólica. Por outro lado, nosso grupo de pesquisa avaliou uma amostra semelhante de adultos

mais velhos do NHANES (1999-2002) e mostrou que os níveis de ácido úrico estavam positivamente associados à força muscular após ajustes para vários fatores de confusão em homens e mulheres (NAHAS; ROSSATO; DE BRANCO; AZEREDO *et al.*, 2021).

Além do AU, pesquisas recentes sugerem que a Cafeína (1,3,7-trimetilxantina) também possui propriedades antioxidantes que podem ajudar a proteger contra danos celulares e promover efeitos positivos para a saúde (MARTINI; DEL BO; TASSOTTI; RISO *et al.*, 2016; RATHOD; PATEL; DAS; TIPPARAJU *et al.*, 2013). Este efeito benéfico pode ser atribuído aos metabólitos primários da cafeína, que são potentes antioxidantes capazes de reduzir a peroxidação lipídica nas membranas celulares (BHAT; SRIDHAR; MADYASTHA, 2001; STADLER; FAY; CHEMISTRY, 1995). No entanto, no que se refere a populações clínicas que frequentemente apresentam declínio de força devido ao estresse oxidativo excessivo, como é observado em idosos, a associação entre cafeína e força muscular ainda não foi investigada.

Portanto, é plausível especular que maiores níveis de AU, cafeína e de seus metabólitos, poderiam conferir uma maior proteção da força e função muscular, consequentemente melhorando a experiência do envelhecimento e reduzindo a incidência de condições relacionadas com a idade.

## **2. FUNDAMENTAÇÃO TEÓRICA**

### **2.1. Envelhecimento**

Devido aos avanços nos cuidados com a saúde, dieta e infraestrutura a expectativa de vida no mundo tem aumentado (CHRISTENSEN; DOBLHAMMER; RAU; VAUPEL, 2009; VAUPEL; VILLAVICENCIO; BERGERON-BOUCHER, 2021). Globalmente, a expectativa de vida aumentou em mais de 6 anos entre 2000 e 2019 passando de 66,8 anos em 2000 para 73,4 anos em 2019 de acordo com dados da Organização Mundial da Saúde (WHO, 2023). No contexto americano, dados divulgados pelo National Institutes of Health indicaram um aumento da expectativa de vida de 2,3 anos entre 2000 e 2019 (NIH, 2019).

Entretanto, há uma lacuna na literatura em relação a esse cenário, ainda não está claro se o aumento da expectativa de vida está associado a um adiamento simultâneo das limitações funcionais, capacidades físicas e cognitivas. Dados do estudo nacional de centenários realizado em New England nos Estados Unidos indicam que indivíduos longevos têm um início tardio para várias doenças crônicas, como câncer, doenças cardiovasculares, hipertensão e diabetes mellitus, doenças nas quais são conhecidas como determinantes de dependência (TERRY; WILCOX; MCCORMICK; PERLS, 2004). Adicionalmente, um estudo epidemiológico transversal conduzido na província de Zhejiang, China, entre 2013 e 2017, envolvendo uma amostra de 271 indivíduos centenários e 570 não-centenários, indicou uma possível correlação entre a longevidade dos centenários e um estado de saúde superior. Os autores do estudo sugerem que esta correlação pode ser um fator contribuinte para a longevidade observada nesta população. Eles observaram uma menor taxa de prevalência de tumor, úlcera gástrica e duodenal, diabetes, asma brônquica e doença pulmonar obstrutiva crônica, tuberculose entre os centenários comparado aos não-centenários (RONG; SHEN; XIAO; HUANG *et al.*, 2019).

Por outro lado, evidências de um estudo sobre mudanças na expectativa de vida e anos vividos com saúde, que analisou indivíduos com mais de 70 anos em 33 países ao longo de três décadas, de 1990 a 2019, indicam que, embora tenha havido um aumento significativo na expectativa de vida para pessoas de 70 a 74 anos em todas as nações examinadas, também se observou um aumento na prevalência de anos vividos com a saúde comprometida. Isso aponta para uma persistente carga de morbidade entre a população em processo de envelhecimento (CHOI; SEMPUNGU; LEE; LEE, 2024). Além disso, em um estudo populacional longitudinal conduzido na Dinamarca e que envolveu a avaliação de 207 centenários, os pesquisadores chegaram à conclusão de que, devido à elevada prevalência de diversas doenças comuns e condições crônicas, os centenários dinamarqueses não apresentavam um estado de saúde ótimo (ANDERSEN-RANBERG; SCHROLL; JEUNE, 2001).

Condições crônicas de saúde que comumente acompanham o envelhecimento, como doenças cardiovasculares, metabólicas e musculoesqueléticas, podem agravar o processo de envelhecimento levando à incapacidade física, comprometimento da mobilidade, quedas e diminuição da independência e qualidade de vida (XU; OU; LI, 2022). Mesmo em condições de envelhecimento 'saudável', há um declínio

progressivo na qualidade do músculo esquelético, devido a várias mudanças na estrutura, mecânica e função muscular (WEBBER; PORTER; MENEZES, 2010). A condição conhecida como perda de massa muscular relacionada à idade, originalmente denominada sarcopenia (CRUZ-JENTOFT; BAHAT; BAUER; BOIRIE *et al.*, 2019) apresenta uma prevalência significativa em populações idosas. Estudos indicam que aproximadamente 10% dos adultos com mais de 60 anos são afetados por essa condição (SHAFIEE; KESHTKAR; SOLTANI; AHADI *et al.*, 2017). Entretanto, essa prevalência aumenta substancialmente com o avanço da idade, atingindo cerca de 50% dos adultos com mais de 80 anos (BAUMGARTNER; KOEHLER; GALLAGHER; ROMERO *et al.*, 1998).

Além disso, associado ao processo de envelhecimento, diversos fatores atuam em conjunto para a diminuição da força muscular. Entre esses fatores, destacam-se a inatividade física (BOWDEN DAVIES; PICKLES; SPRUNG; KEMP *et al.*, 2019), a ingestão inadequada de nutrientes (LENGELÉ; BRUYÈRE; BEAUDART; REGINSTER *et al.*, 2021) e as alterações hormonais (CHO; LEE; SONG, 2022). Esses elementos colaboram para a diminuição da eficiência da junção neuromuscular, comprometem o fluxo sanguíneo para os músculos e reduzem a capacidade regenerativa muscular. Além disso, há uma propensão à infiltração de células inflamatórias e ao aumento do estresse oxidativo, somando-se para o agravamento da condição muscular relacionada ao envelhecimento (CHEN; WANG; DENG; LIAN *et al.*, 2022).

Essas observações corroboram diversas teorias que visam explicar o processo de envelhecimento. A teoria do encurtamento dos telômeros, por exemplo, sugere que o envelhecimento celular é acelerado pelo encurtamento gradual dos telômeros, que são estruturas protetoras localizadas nas extremidades dos cromossomos (ROSSIELLO; JURK; PASSOS; D'ADDA DI FAGAGNA, 2022). Esse encurtamento progressivo limita o número de divisões celulares possíveis e reduz a capacidade regenerativa dos tecidos (JIANG; JU; RUDOLPH, 2007). Evidências indicam que o encurtamento dos telômeros está diretamente associado à deterioração da função celular e ao surgimento de doenças relacionadas ao envelhecimento (LANSDORP, 2022). A teoria do dano mitocondrial, por sua vez, argumenta que as mitocôndrias, responsáveis pela produção de energia celular, sofrem danos acumulativos ao longo do tempo, comprometendo sua função e contribuindo para a deterioração celular e o envelhecimento (SANZ; STEFANATOS, 2008). Estudos mostram que o declínio na

função mitocondrial está associado a várias condições degenerativas relacionadas ao envelhecimento (BARJA, 2014). Por fim, a teoria do dano oxidativo, proposta por Denham Harman, sugere que o envelhecimento é resultado do acúmulo de danos causados por radicais livres e espécies reativas de oxigênio, levando ao estresse oxidativo e à deterioração celular (BECKMAN; AMES, 1998). Além disso, estudos reforçam o impacto do estresse oxidativo na aceleração do envelhecimento e na exacerbação de doenças relacionadas (LIGUORI; RUSSO; CURCIO; BULLI *et al.*, 2018; SALMON; RICHARDSON; PÉREZ, 2010).

## **2.2. Estresse Oxidativo e Força Muscular**

O estresse oxidativo é caracterizado como um distúrbio no equilíbrio do estado pró-oxidante/antioxidante que é prejudicial às células pois envolve a produção exacerbada de espécies reativas de oxigênio (EROs) (LIGUORI; RUSSO; CURCIO; BULLI *et al.*, 2018). Nesse cenário há um aumento na infiltração inflamatória de neutrófilos, na secreção de proteases e geração de uma ampla gama de intermediários oxidativos, com efeitos prejudiciais, tais como a peroxidação dos lipídios de membrana e agressão às proteínas dos tecidos e das membranas, às enzimas, aos carboidratos e ao DNA (MALDONADO; MORALES-PISON; URBINA; SOLARI, 2023).

Ao longo do processo de envelhecimento, observa-se uma deterioração na capacidade do tecido muscular em lidar eficientemente com níveis elevados de EROs, (JACKSON; MCARDLE, 2011), com um aumento da apoptose e morte celular, assim como uma redução na diferenciação de mioblastos, resultando em uma falha no processo de reparo muscular (LIAN; CHEN; WU; DENG *et al.*, 2022). Nesse contexto, a capacidade comprometida das células musculares em eliminar mitocôndrias disfuncionais também pode contribuir para o aumento da produção de EROs (CARTER; CHEN; HOOD, 2015). Além disso, estudos prévios indicam que o declínio das fibras musculares do tipo II relacionado à idade pode, pelo menos em parte, estar associado a uma maior incidência de injúria oxidativa e apoptose (LEXELL; TAYLOR; SJÖSTRÖM, 1988; PHILLIPS; LEEUWENBURGH, 2005). Isso decorre do fato de que esse tipo de fibra possui um menor conteúdo mitocondrial e é mais suscetível à atrofia em comparação com as fibras do Tipo I, que possuem um alto conteúdo mitocondrial (DONG; TSAI, 2023).

Ademais, durante o envelhecimento, estudos indicam que a redução da força muscular se correlaciona com a fragilidade, perda de independência e incapacidade física (BATISTA; GOMES; NERI; GUARIENTO *et al.*, 2012; JANSSEN; BUSSMANN; STAM, 2002). Estudos longitudinais observaram diminuições na força muscular de aproximadamente ~2-4% ao ano (DELMONICO; HARRIS; VISSER; PARK *et al.*, 2009; FRONTERA; HUGHES; FIELDING; FIATARONE *et al.*, 2000), valores esses superiores quando comparados a declínios na massa muscular (~1 ano) (MCGREGOR; CAMERON-SMITH; POPPITT, 2014). O European Working Group on Sarcopenia in Older People (EWGSOP) revisou recentemente suas recomendações para enfatizar que os menores níveis de força muscular são a principal característica da sarcopenia e que se deve empregar a avaliação da quantidade e qualidade muscular reduzidas para confirmar o diagnóstico da sarcopenia (CRUZ-JENTOFT; BAHAT; BAUER; BOIRIE *et al.*, 2019).

Estudos recentes têm destacado a importância da força muscular na saúde e longevidade dos idosos. LI; XIA; ZHANG; GATHIRUA-MWANGI *et al.* (2018) conduziram um estudo prospectivo utilizando uma amostra de 4.449 indivíduos com 50 anos ou mais, utilizando dados do National Health and Nutrition Examination Survey (NHANES) 1999–2002. O objetivo foi investigar as associações entre os menores níveis de força muscular e a mortalidade por todas as causas em uma amostra nacionalmente representativa dos Estados Unidos. Eles observaram que a prevalência de menores níveis de força muscular foi de 19,4%. Além disso, constatou-se que esses níveis menores estavam significativamente correlacionados de forma independente com um aumento substancial no risco de mortalidade por todas as causas entre idosos norte-americanos, mesmo após ajustes para fatores como massa muscular, síndrome metabólica, tempo sedentário e atividade física. Isso sugere a importância da força muscular na previsão de resultados de saúde relacionados ao envelhecimento em idosos.

### **2.3. Antioxidantes**

O estresse oxidativo pode ser prevenido pela neutralização de EROs por meio do sistema antioxidante. Esse sistema atua no sentido de restabelecer o equilíbrio e assim minimizar os danos decorrentes da intensificação do estresse oxidativo

(IRSHAD; CHAUDHURI, 2002). O sistema antioxidante possui diversos mecanismos para regular os efeitos danosos dos radicais livres, como a doação de elétrons, remoção catalítica, ou ligação aos radicais e/ou regulação da expressão gênica (JANCIAUSKIENE, 2020). Adicionalmente, o efeito na saúde de uma substância antioxidante está condicionado à sua biodisponibilidade sistêmica, à concentração do composto que pode ser transportado para sítios específicos nos órgãos, e à capacidade deste antioxidante em desempenhar a função esperada (ALI; AHSAN; ZIA; SIDDIQUI *et al.*, 2020).

Os antioxidantes podem ser endógenos, produzidos pelo próprio organismo, ou adquiridos exogenamente através da dieta ou de suplementos alimentares (WAHLQVIST, 2013). Alguns antioxidantes endógenos incluem enzimas como a superóxido dismutase, catalase e glutathione peroxidase, cada uma com papéis específicos na neutralização de radicais livres e peróxidos (ALKADI, 2020). Os antioxidantes não enzimáticos compreendem uma variedade de compostos essenciais para a proteção contra o estresse oxidativo, entre eles estão a vitamina E e vitamina C, antioxidantes tiólicos como glutathione, tioredoxina e ácido lipóico, melatonina, carotenoides, flavonoides naturais e outros compostos incluindo o ácido úrico e os metabolitos da cafeína (BHAT; SRIDHAR; MADYASTHA, 2001; DE OLIVEIRA; BURINI, 2012; KURUTAS, 2016).

### **2.3.1. Ácido Úrico**

O ácido úrico (AU) é o produto final do metabolismo das purinas e ácidos nucleicos no corpo humano, desempenhando um papel significativo e complexo nos processos oxidativos e antioxidantes (GLANTZOUNIS; TSIMOYIANNIS; KAPPAS; GALARIS, 2005). Ao longo do processo evolutivo, humanos e outros primatas desenvolveram múltiplas mutações no gene responsável pela expressão da enzima uricase, resultando na perda de sua funcionalidade (WU; MUZNY; LEE; CASKEY, 1992). Como consequência, a espécie humana apresenta concentrações mais elevadas de ácido úrico e urato em comparação com mamíferos não primatas, devido à ausência da atividade da enzima uricase, que catalisa a conversão do ácido úrico em alantoína (ODA; SATTA; TAKENAKA; TAKAHATA, 2002). Isso sugere que os humanos desenvolveram a capacidade de manter concentrações elevadas de ácido úrico, possivelmente como resultado da seleção natural que confere certas vantagens

biológicas (AMES; CATHCART; SCHWIERS; HOCHSTEIN, 1981). Além disso, o AU é responsável por contribuir em mais de 50% da capacidade antioxidante do plasma, o AU possui propriedades quelantes de metais, além de eliminar radicais de oxigênio, nitrogênio e superóxido no plasma, que auxiliam na inibição do oxidante peroxinitrito (DE OLIVEIRA; BURINI, 2012).

Com base em pesquisas realizadas nas últimas décadas, categorizar o ácido úrico como benéfico ou patológico continua sendo uma tarefa desafiadora. Há evidências que associam níveis elevados de AU ao desenvolvimento de diversas complicações como doenças cardiovasculares, hipertensão arterial e diabetes mellitus (FEIG; KANG; JOHNSON, 2008; LV; MENG; HE; CHEN *et al.*, 2013). No entanto, uma relação causal definitiva ainda não foi plenamente estabelecida. Por outro lado, alguns estudos têm demonstrado que níveis mais elevados de AU podem ser protetores na síndrome metabólica (YU; JIN; JEE; BAE *et al.*, 2019), câncer (MI; GONG; SUI, 2020) e até mesmo apresentando uma associação com a força muscular em idosos (NAHAS; ROSSATO; DE BRANCO; AZEREDO *et al.*, 2021).

### **2.3.2. Cafeína e seus metabólitos**

A cafeína (1,3,7-trimetilxantina) comumente encontrada em bebidas como café, chá e energéticos (HECKMAN; WEIL; GONZALEZ DE MEJIA, 2010) representa a substância psicoativa mais difundida globalmente, com dados estimativos sugerindo que mais de 80% dos americanos a consomem diariamente (CAPPELLETTI; PIACENTINO; SANI; AROMATARIO, 2015). O interesse a respeito da cafeína e seus metabólitos tem aumentado ao longo dos anos, principalmente devido a exposição populacional à cafeína, levando a sua aplicabilidade em estudos cinéticos e de metabolismo envolvendo enzimas do tipo CYP450, bem como sua utilização em estudos *in vivo* para avaliar a associação da cafeína com desfechos de saúde (LUDWIG; CLIFFORD; LEAN; ASHIHARA *et al.*, 2014; RANHEIM; HALVORSEN, 2005).

A cafeína é absorvida pelo estômago e intestino delgado em até 45 minutos (NEWTON; BROUGHTON; LIND; MORRISON *et al.*, 1981) e apresenta uma meia-vida média de eliminação de aproximadamente 5 horas, sendo amplamente metabolizada no organismo humano, com apenas uma fração mínima de 3% ou menos sendo excretada sem sofrer alterações na urina (BEGAS; KOUVARAS;

TSAKALOF; PAPAKOSTA *et al.*, 2007). A metabolização da cafeína é predominantemente mediada pelas enzimas do citocromo P450 no fígado (CYP1A2) em 3 importantes dimetilxantinas: paraxantina, teobromina e teofilina (KOT; DANIEL, 2008). A principal via de metabolização em humanos ocorre através da N-3-demetilação para paraxantina (~84%), também conhecida como 1,7-dimetilxantina. A N-1 demetilação da cafeína para teobromina (3,7-dimetilxantina) representa aproximadamente 12% do metabolismo da cafeína, e a N-7 demetilação para teofilina (1,3-dimetilxantina) representando cerca de 4% (GATES; MINERS, 1999; ROBERTS; FURUYA; TANG; KALOW, 1994; ULLRICH; COMPAGNONE; MÜNCH; BRANDES *et al.*, 1992).

A Cafeína também possui propriedades antioxidantes que podem ajudar a proteger contra danos celulares e promover efeitos positivos para a saúde (MARTINI; DEL BO; TASSOTTI; RISO *et al.*, 2016; RATHOD; PATEL; DAS; TIPPARAJU *et al.*, 2013; VIEIRA; GASPAR; SANTOS, 2020). Este efeito benéfico pode ser atribuído aos principais metabólitos da cafeína, que são potentes antioxidantes capazes de reduzir a peroxidação lipídica nas membranas celulares (BHAT; SRIDHAR; MADYASTHA, 2001; STADLER; FAY; CHEMISTRY, 1995). Embora já estabelecido seu potencial considerável em aumentar a força e potência muscular como um auxílio ergogênico (GRGIC; MIKULIC; SCHOENFELD; BISHOP *et al.*, 2019), quando se trata de populações específicas, como os idosos, que frequentemente experimentam declínio da força devido ao estresse oxidativo excessivo, a associação entre cafeína e força muscular permanece não esclarecida. Adicionalmente, há uma lacuna na literatura científica que tenha investigado de maneira específica o efeito da cafeína e de seus metabólitos sobre a força muscular em idosos.

## **2.4. National Health and Nutrition Examination Survey**

O National Health and Nutrition Examination Survey (NHANES) é uma pesquisa de amostragem estratificada e em múltiplos estágios, cuidadosamente elaborada para avaliar o estado de saúde e nutrição da população não institucionalizada, representativa nacionalmente, dos Estados Unidos, sendo realizada pelo National Center for Health Statistics (NCHS), o qual faz parte do Centers for Disease Control and Prevention (CDC) (NHANES, 2024).

O programa NHANES teve seu início em 1960. Desde 1999, a pesquisa tem examinado cerca de 5.000 pessoas em 15 condados diferentes por todo o país, se tornou um programa contínuo, o qual é realizado bienalmente, cujo foco abrange inúmeras variáveis demográficas, socioeconômicas, dietéticas e relacionadas à saúde, com o intuito de responder às demandas emergentes. Cada participante realiza uma contribuição relevante para o estudo, representando aproximadamente outras 65.000 pessoas no país que compartilham características semelhantes. Os Estados Unidos têm experimentado um rápido aumento na proporção da população idosa ao longo das últimas décadas. Diante das crescentes demandas por cuidados de saúde relacionadas ao envelhecimento, o NHANES desempenha um papel crucial na ampliação do conhecimento sobre o estado de saúde dos idosos americanos. Em geral, à medida que a idade do indivíduo avança, a abrangência dos exames realizados tende a aumentar. As entrevistas de saúde são realizadas nas residências dos entrevistados. As exames de saúde são realizadas em centros móveis especialmente projetados e equipados, que viajam para locais em todo o país. A equipe de estudo é composta por um médico, técnicos médicos e de saúde, além de entrevistadores de saúde e dietéticos (NHANES, 2024).

Além disso, as organizações de pesquisa, universidades, provedores de cuidados de saúde se beneficiam das informações da pesquisa. Os principais usuários dos dados são agências federais que colaboraram no design e desenvolvimento da pesquisa. O Departamento de Agricultura dos Estados Unidos e o NCHS cooperam no planejamento e na divulgação de informações dietéticas e nutricionais da pesquisa (NHANES, 2024).

E espera-se que os resultados das avaliações sejam utilizados para determinar a prevalência de doenças importantes além de seus fatores de risco. Os achados do NHANES também servem de base para os padrões nacionais de medições como altura, peso e pressão arterial. Esses bancos de dados são utilizados em estudos epidemiológicos e pesquisas em ciências da saúde, que ajudam a desenvolver políticas de saúde pública sólidas, direcionar e projetar programas e serviços de saúde, e ampliar o conhecimento em saúde (NHANES, 2024).

Para o presente estudo foram selecionados os biênios 1999-2000 e 2001-2002 (analisados de forma conjunta) e 2011-2012.

### **3. OBJETIVOS**

#### **3.1. Objetivo Geral**

Foram realizados dois estudos transversais usando dados populacionais para americanos (National Health and Nutrition Examination Survey – NHANES). No primeiro estudo, foi verificada a associação entre os metabólitos da cafeína na urina com a força muscular em jovens e idosos utilizando dados do biênio 2011-2012. No segundo estudo, o objetivo foi verificar a relação entre os níveis séricos de AU e a força muscular de acordo com o status glicêmico em idosos, utilizando os biênios 1999-2000 e 2001-2002.

#### **3.2. Objetivos Específicos**

Avaliou-se os aspectos demográficos, condições de saúde e comportamentos dos indivíduos estudados.

Avaliou-se os parâmetros antropométricos, a força muscular e os parâmetros bioquímicos e dietéticos dos indivíduos estudados.

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## 5. ARTIGOS CIENTÍFICOS

**Artigo 1:** Batista-da-Silva B, Limirio LS, de Oliveira EP. Association between caffeine metabolites in urine and muscle strength in young and older adults: A cross-sectional study from NHANES 2011-2012. Clin Nutr. 2024 Jun;43(6):1584-1592. doi: 10.1016/j.clnu.2024.05.004. Epub 2024 May 7. PMID: 38759491.

**Artigo 2:** Batista-da-Silva, B., Nahas, P.C., Limirio, L.S. et al. Association between serum uric acid and muscle strength according to glycemic status in older adults: NHANES 1999–2002. Nutrire 49, 27 (2024). <https://doi.org/10.1186/s41110-024-00269-4>



Contents lists available at ScienceDirect

## Clinical Nutrition

journal homepage: <http://www.elsevier.com/locate/clnu>

## Original article

# Association between caffeine metabolites in urine and muscle strength in young and older adults: A cross-sectional study from NHANES 2011–2012



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## ARTICLE INFO

## Article history:

Received 10 February 2024

Accepted 3 May 2024

## Keywords:

Coffee

Antioxidant

Muscle mass

Elderly

Tea

## SUMMARY

**Background:** Elevated levels of reactive oxygen species may contribute to the gradual decline in muscle strength over time. Although caffeine and its metabolites have antioxidant properties that can mitigate oxidative stress, the association of caffeine and its metabolites with muscle strength remains unknown. **Aim:** To investigate whether caffeine metabolites in urine are associated with muscle strength in young and older adults.

**Methods:** A cross-sectional study was conducted with 1145 individuals aged over 20 years ( $n = 801 < 60$  years and  $n = 344 \geq 60$  years) from the National Health and Nutrition Examination Survey (NHANES) 2011–2012. Muscle strength was assessed using a handgrip dynamometer, and combined grip strength was determined by summing the highest value from each hand. Caffeine and its metabolites in urine were quantified using ultra-high-performance liquid chromatography–electrospray ionization–tandem mass spectrometry (1-methyluric acid, 3-methyluric acid, 7-methyluric acid, 1,3-dimethyluric acid, 1,7-dimethyluric acid, 3,7-dimethyluric acid, 1,3,7-trimethyluric acid, 1-methylxanthine, 3-methylxanthine, 7-methylxanthine, 1,3-dimethylxanthine, 1,7-dimethylxanthine, 3,7-dimethylxanthine, 1,3,7-trimethylxanthine, 5-acetylamino-6-amino-3-methyluracil). Linear regression analyses were performed to determine the association of caffeine and its metabolites with muscle strength in young and older adults, adjusting for confounders.

**Results:** Positive associations between muscle strength and levels of 7-methyluric acid ( $\beta = 0.029$ ;  $p = 0.021$ ), 1,3-dimethyluric acid ( $\beta = 0.008$ ;  $p = 0.004$ ), 3,7-dimethyluric acid ( $\beta = 0.645$ ;  $p = 0.012$ ), 3-methylxanthine ( $\beta = 0.020$ ;  $p = 0.002$ ), 7-methylxanthine ( $\beta = 0.020$ ;  $p = 0.006$ ), 1,3-dimethylxanthine (theophylline) ( $\beta = 0.030$ ;  $p = 0.004$ ) and 3,7-dimethylxanthine (theobromine) ( $\beta = 0.035$ ;  $p = 0.029$ ) were observed in older adults. In contrast, no such associations were noted in young adults.

**Conclusion:** Our study indicates a positive association between certain caffeine metabolites in urine and muscle strength in older adults, but not in younger individuals. These findings indicate that specific caffeine metabolites may contribute to an antioxidant role especially in older adults.

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## 1. Introduction

The cumulative cellular damage induced by elevated levels of reactive oxygen species (ROS) is widely acknowledged as a contributing factor to aging and its associated complications, including the decline in skeletal muscle strength [1]. Low muscle strength is a crucial predictor of an elevated risk of falls [2],

fractures [3,4], and mortality [5–8]. Thus, it is important to prevent the decline in muscle strength over the years; hence, compounds with antioxidant properties may have the potential to protect against the decline in muscle strength due to decreases in oxidative stress [9–12].

Caffeine (1,3,7-trimethylxanthine) is a widely consumed substance found in common beverages such as coffee, tea, and energy drinks [13]. It is considered the most used psychoactive substance worldwide, with an estimated daily intake accounting for approximately 80% of the population [14,15]. Caffeine is metabolized in the liver in humans, resulting in the generation of several metabolites excreted mainly in the urine [16]. It is suggested that approximately

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84% of ingested caffeine is metabolized into paraxanthine, 12% into theobromine and 4% into theophylline, leading to the generation of several other metabolites [16]. Consequently, when caffeine is consumed from dietary sources, the urine typically contains low concentrations of caffeine, and the primary method for evaluating caffeine intake is through the assessment of its metabolites. Several studies suggest that caffeine and some of its metabolites have antioxidant properties, which can help protect against cellular damage and promote positive health effects [17–19]. This beneficial effect may be attributed to the primary metabolites of caffeine, which are potent antioxidants capable of reducing lipid peroxidation in cell membranes [20,21].

While acute caffeine supplementation has been extensively studied for its ergogenic effects in sports nutrition [22], including its impact on muscle strength [23], only a limited number of studies have explored the association between habitual consumption of caffeine from food sources and muscle strength/function in general population [24–27]. A higher frequency of coffee intake has been linked to a decreased risk of falls and improved functional capacity in older adults [24,26]. However, contrasting findings from other studies indicate no association with strength and the risk of functional impairment [25,27]. Therefore, the association between caffeine intake and muscle strength/function remains uncertain, warranting further studies. Moreover, since all these studies [24–27] primarily assessed coffee intake without specific focus on caffeine and its metabolites, the relationship between caffeine metabolites in urine and muscle strength is unknown. Understanding this association is crucial because caffeine metabolites in urine serve as reliable markers for assessing caffeine intake from food sources [28]. Unlike food questionnaires, which are known to have limitations [29], urine markers present fewer challenges in estimating caffeine intake. Therefore, the aim of this study was to assess whether caffeine and its metabolites in urine are associated with muscle strength in both young and older adults. We hypothesized that several caffeine metabolites would be positively associated with muscle strength, particularly in older adults, given their experience of elevated oxidative stress that is a contributing factor to strength loss [30]. In contrast, this association would not be observed in young adults, as they generally do not undergo significant declines in muscle strength [31].

## 2. Methods

### 2.1. Study design and population

This is a cross-sectional study utilizing data from National Health and Nutrition Examination Survey (NHANES) 2011–2012. NHANES is a stratified, multistage probability sampling survey meticulously crafted to evaluate the health and nutritional status of the noninstitutionalized, nationally representative population of the United States. The sample for the present study consisted of individuals aged over 20 years and was selected through NHANES 2011–2012 biennium [32]. The analyses included individuals from “caffeine and caffeine metabolites-urine subsample” ( $n = 2397$ ; Fig. 1) with complete data on caffeine and its metabolites in urine, available demographic information, health details (including diabetes, arthritis, hypertension, and use of medications), behavioral conditions (such as physical activity and smoking), anthropometric data, biochemical markers, dietary data, and those who participated in the strength tests. However, in the present study, individuals lacking dietary data assessment, with missing information on glomerular filtration rate (eGFR), serum uric acid, or anthropometric measurements, as well as pregnant and breastfeeding women, were excluded. Thus, a total of 1145 individuals were evaluated, stratified by age cut-off point ( $n = 801 < 60$  years

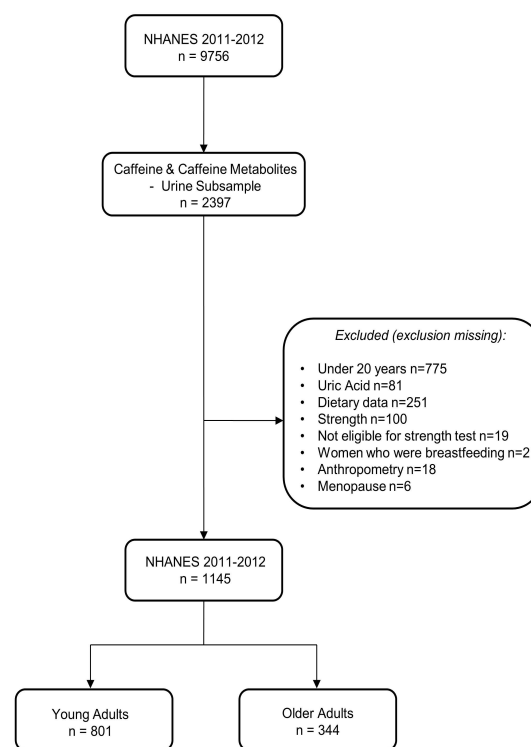


Fig. 1. Flowchart of the sample selection from NHANES 2011–2012.

(young adults) and  $n = 344 \geq 60$  years (older adults) (Fig. 1)). The NHANES data collection protocols are approved by the ethics review board of the National Center for Health Statistics (NCHS ERB) under Protocol #2011-17 for NHANES cycle 2011–2012, with informed consent obtained from all participants.

### 2.2. Caffeine and its metabolites in urine

Quantification of caffeine and its metabolites in urine was conducted using ultra-high-performance liquid chromatography electrospray ionization–tandem mass spectrometry (UHPLC–ESI–MS/MS) with stable isotope-labeled internal standards. A 50- $\mu$ L aliquot of urine was initially diluted with 450  $\mu$ L of water. Following this, 100  $\mu$ L of the diluted urine was combined with 120  $\mu$ L of a 0.2 N NaOH solution containing stable isotope-labeled internal standards. The mixture was left to incubate for at least 30 min at room temperature to facilitate the conversion of an unstable uracil metabolite (AFMU) into a more stable form (AAMU). Subsequently, 30  $\mu$ L of 2.0 N HCl and 250  $\mu$ L of a 10% methanol solution containing 0.1% formic acid were added to acidify the samples, ensuring the matrix of the sample was similar to the starting mobile phase composition of the initial analysis step. After filtration, the samples were analyzed using UHPLC–ESI–MS/MS with polarity switching. Quantitation was based on peak area ratios interpolated against an 11-point calibration curve derived from calibrators in synthetic urine.

The caffeine metabolites measured in urine included 1-methyluric acid, 3-methyluric acid, 7-methyluric acid, 1,3-dimethyluric acid, 1,7-dimethyluric acid, 3,7-dimethyluric acid, 1,3,7-trimethyluric acid, 1-methylxanthine, 3-methylxanthine, 7-

methyloxanthine, 1,3-dimethyloxanthine (theophylline), 1,7-dimethyloxanthine (paraxanthine), 3,7-dimethyloxanthine (theobromine), 1,3,7-trimethyloxanthine (caffeine), 5-acetylamino-6-amino-3-methyluracil. Additional details of laboratory methodology can be found in the caffeine and caffeine metabolites–urine lab procedure manual [32].

### 2.3. Biochemical parameters

Serum uric acid and triglyceride levels were assessed through the colorimetric method. Blood urea levels were determined using the enzymatic conductivity rate method. Serum creatinine was measured by the Jaffe rate method, and eGFR was estimated using the CKD epidemiology collaboration (CKD-EPI) equation [33]. Cholesterol and HDL-cholesterol levels were determined using the timed-endpoint method (with a reaction specific for HDL-cholesterol).

### 2.4. Muscle strength

Muscle strength was assessed using a grip test, which involved participants using a handgrip dynamometer. In the present study, we used the combined grip strength, which was determined by summing the highest value from each hand, expressed in kilograms. This variable was not calculated for participants who only performed the test on one hand. Participants were randomly assigned to initiate the test with either their dominant or non-dominant hand. Any extreme values were thoroughly reviewed and cross-checked with other available data.

### 2.5. Anthropometry

Body weight and height measurements followed Lohman's established protocol [34], and the body mass index (BMI) was subsequently calculated. Participants were instructed to wear a disposable shirt, pants, and slippers for these measurements.

### 2.6. Dietary intake

The assessment of dietary intake was conducted by a trained interviewer, administering two 24-h dietary recalls for each participant. The first 24-h food recall interview was conducted in-person, followed by the second recall through a phone call 3–10 days later. The NHANES survey conducted during 2011–2012 underwent evaluation using a structured five-step multiple-pass approach. This approach involves a systematic interview process in five steps: quick list, forgotten foods, time and occasion, detail cycle, and final probe. The processing of dietary intake utilized the USDA's Food and Nutrient Database.

### 2.7. Statistical analyses

Sociodemographic data, health status and behavior, anthropometric measurements, strength, biochemical markers, and dietary intake were described for the total sample and stratified by age (<60 years and ≥60 years). Group comparisons were conducted using linear regression analyses. Continuous variables were described using mean and standard deviation, while categorical variables were presented as percentages with confidence intervals.

Linear regression analysis was employed to assess the association between caffeine metabolites in urine and muscle strength. Analyses were initially conducted for the entire sample and then stratified by age (young or older adults). No adjustments were made in the initial analyses, and subsequently, adjustments were introduced for various covariates, including age (in years), sex (men

or women), race/ethnicity (non-Hispanic white or other), BMI (kg/m<sup>2</sup>), educational level (classified as under/high school graduate and some college or over or missing), marital status (single, divorced, widowed, never married, or married/living as married), annual family income (categorized as 0–\$19,999, \$20,000–\$54,999, or over \$55,000, or missing), diabetes (no or yes), hypertension (no or yes), arthritis (no or yes), physical activity (no or yes; as previously described [35]), smoking status (no or yes), eGFR (ml/min/1.73 m<sup>2</sup>), serum uric acid (mg/dL), gamma glutamyl transferase (U/L), as well as the intake of energy (kcal), protein (g/day), and alcohol (g/day). The analyses for total sample and young adults were additionally adjusted for menopausal status.

The analyses were conducted using Stata 14.0 software (Stata-Corp, College Station, TX, USA). All analyses were performed using the 'svy' command to incorporate information on the 'wtsc2yr' sample weight, primary sampling units, and strata for correct variance estimation. A significance level of  $p < 0.05$  was considered statistically significant.

## 3. Results

### 3.1. Individual's characteristics

Table 1 presents the characteristics of individuals in the total sample and categorized by age into groups of young and older adults. In comparison to young individuals, older adults had lower levels of 3,7-dimethyluric acid and 3,7-dimethyloxanthine. Additionally, a higher proportion of non-Hispanic white individuals was observed, along with a higher prevalence of diabetes, hypertension, arthritis among older adults. Furthermore, they had lower body weight, height, strength, and glomerular filtration rate, but higher serum levels of uric acid, creatinine, urea, and HDL. In terms of dietary intake, older adults consumed lower amounts of energy (kcal/day), protein (g/day), total fat (g/day), saturated, mono-unsaturated, and polyunsaturated fats (g/day), and sugar (g/day).

### 3.2. Association between caffeine metabolites in urine and muscle strength

#### 3.2.1. Total sample

In the crude analysis, levels of 1,3-dimethyluric acid and 1,3-dimethyloxanthine (theophylline) were positively associated with strength in the total sample. Furthermore, after adjusting for confounders, these metabolites maintained a positive association with strength (Table 2).

#### 3.2.2. Young adults

All the caffeine metabolites in urine had no association with muscle strength among adults. This lack of association was observed both in crude and adjusted analysis (Table 3).

#### 3.2.3. Older adults

In the unadjusted analyses, several caffeine metabolites, including 1-methyluric acid, 1,3-dimethyluric acid, 3,7-dimethyluric acid, 1-methyloxanthine, 3-methyloxanthine, 7-methyloxanthine, 1,3-dimethyloxanthine (theophylline), 1,7-dimethyloxanthine (paraxanthine), and 3,7-dimethyloxanthine (theobromine), exhibited positive associations with strength. After adjusting for confounders, 7-methyluric acid, 1,3-dimethyluric acid, 3,7-dimethyluric acid, 3-methyloxanthine, 7-methyloxanthine, 1,3-dimethyloxanthine (theophylline) and 3,7-dimethyloxanthine (theobromine) demonstrated positive associations with strength. Conversely, 1,3,7-trimethyloxanthine (caffeine) showed an inverse association with strength after adjustments for confounding factors (Table 4).

**Table 1**

Sociodemographic, health status and behavior, anthropometry, strength, biochemical markers, and dietary intake according to total, young and older adults groups. NHANES, 2011–2012.

| Variables                                             | Total sample      | Young adults      | Older adults      | p-value          |
|-------------------------------------------------------|-------------------|-------------------|-------------------|------------------|
| <b>Sociodemographic</b>                               |                   |                   |                   |                  |
| Age, y                                                | 48.2 ± 16.6       | 40.5 ± 11.4       | 69.2 ± 6.9        | <b>0.001</b>     |
| Sex, %                                                |                   |                   |                   | 0.248            |
| Women                                                 | 48.6 (45.5; 51.7) | 50 (45.7; 54.3)   | 44.8 (38.2; 51.7) |                  |
| Men                                                   | 51.4 (48.3; 54.5) | 50 (45.7; 54.3)   | 55.2 (48.3; 61.8) |                  |
| Race/ethnicity, %                                     |                   |                   |                   | <b>0.001</b>     |
| Non-Hispanic white                                    | 69.3 (59.3; 77.7) | 64.5 (53.4; 74.3) | 82.3 (73.8; 88.5) |                  |
| Others                                                | 30.7 (22.3; 40.7) | 35.5 (25.7; 46.6) | 17.7 (11.5; 26.2) |                  |
| Marital status, %                                     |                   |                   |                   | <b>0.014</b>     |
| Married/living with partner                           | 63.4 (59.2; 67.3) | 60.9 (55.7; 65.8) | 70.1 (64.9; 74.9) |                  |
| Single/divorced/widowed/never married                 | 36.6 (32.7; 40.8) | 39.1 (34.2; 44.3) | 29.9 (25.1; 35.1) |                  |
| Annual family income, %                               |                   |                   |                   | 0.506            |
| \$0–19,999                                            | 17.2 (13.8; 21.2) | 18 (13.8; 23.1)   | 15 (9; 23.8)      |                  |
| \$20,000–54,999                                       | 35.5 (30.3; 41.1) | 34.3 (27.8; 41.4) | 38.8 (28.4; 50.4) |                  |
| \$55,000–74,999                                       | 44.4 (37.7; 51.3) | 45 (38.4; 51.7)   | 42.9 (33.1; 53.4) |                  |
| Missing                                               | 2.9 (2; 4.1)      | 2.7 (1.7; 4.4)    | 3.3 (2; 5.3)      |                  |
| Educational level, %                                  |                   |                   |                   | 0.872            |
| Under high school graduate                            | 33.6 (27.8; 40)   | 33.4 (25.5; 42.4) | 34.3 (28.6; 40.5) |                  |
| Some college or over                                  | 66.3 (59.9; 72.2) | 66.6 (57.6; 74.5) | 65.6 (59.3; 71.3) |                  |
| Missing                                               | 0 (0; 0.3)        | 0 (0; 0)          | 0.1 (0; 1.1)      |                  |
| <b>Health status and behavior</b>                     |                   |                   |                   |                  |
| Diabetes, %                                           |                   |                   |                   | <b>&lt;0.001</b> |
| No                                                    | 89.6 (87.3; 91.6) | 94.3 (91.8; 96)   | 76.9 (71.3; 81.6) |                  |
| Yes                                                   | 10.4 (8.4; 12.7)  | 5.7 (4; 8.2)      | 23.1 (18.4; 28.7) |                  |
| Hypertension, %                                       |                   |                   |                   | <b>&lt;0.001</b> |
| No                                                    | 68.4 (63.8; 72.7) | 76.4 (72.6; 79.9) | 46.6 (38.2; 55.2) |                  |
| Yes                                                   | 31.6 (27.3; 36.2) | 23.6 (20.1; 27.4) | 53.4 (44.8; 61.8) |                  |
| Arthritis, %                                          |                   |                   |                   | <b>&lt;0.001</b> |
| No                                                    | 75.6 (71; 79.6)   | 83.3 (78.3; 87.4) | 54.4 (48.2; 60.5) |                  |
| Yes                                                   | 24.3 (20.3; 28.8) | 16.5 (12.5; 21.4) | 45.6 (39.5; 51.8) |                  |
| Missing                                               | 0.2 (0; 0.6)      | 0.2 (0; 0.9)      | 0 (0; 0)          |                  |
| Menopause, % <sup>a</sup>                             |                   |                   |                   | —                |
| No                                                    | 47.6 (39; 56.4)   | 66.9 (57.5; 75.1) | —                 |                  |
| Yes                                                   | 48.7 (39.9; 57.5) | 28 (20.1; 37.5)   | 99.7 (97.7; 100)  |                  |
| Missing                                               | 3.7 (2.3; 5.9)    | 5.1 (3.1; 8.2)    | 0.3 (0; 2.3)      |                  |
| Physical activity, %                                  |                   |                   |                   | 0.234            |
| Yes                                                   | 47 (42.2; 51.9)   | 48.5 (42.9; 54)   | 42.9 (35.2; 51)   |                  |
| No                                                    | 53 (48.1; 57.8)   | 51.5 (46; 57.1)   | 57.1 (49; 64.8)   |                  |
| Smoking status, %                                     |                   |                   |                   | 0.075            |
| No                                                    | 82 (77.2; 86)     | 79.9 (73.9; 84.9) | 87.7 (79.8; 92.8) |                  |
| Yes                                                   | 17.9 (14; 22.7)   | 20 (15.1; 26)     | 12.3 (7.2; 20.2)  |                  |
| Missing                                               | 0.1 (0; 0.4)      | 0.1 (0; 0.6)      | —                 |                  |
| <b>Anthropometric and strength</b>                    |                   |                   |                   |                  |
| Weight, kg                                            | 82.8 ± 20.4       | 83.8 ± 20.7       | 79.9 ± 18.6       | <b>0.018</b>     |
| Height, cm                                            | 169.4 ± 10.1      | 170.4 ± 9.8       | 166.5 ± 10.4      | <b>0.001</b>     |
| Body mass index, kg/m <sup>2</sup>                    | 28.8 ± 6.4        | 28.8 ± 6.4        | 28.8 ± 6.3        | 0.994            |
| Handgrip strength, kg (sum of both hands)             | 72.9 ± 22.6       | 77.2 ± 21.7       | 61 ± 20.2         | <b>&lt;0.001</b> |
| <b>Biochemical markers</b>                            |                   |                   |                   |                  |
| Uric acid, mg/dL                                      | 5.4 ± 1.4         | 5.4 ± 1.4         | 5.7 ± 1.5         | <b>&lt;0.001</b> |
| Creatinine, mg/dL                                     | 0.9 ± 0.3         | 0.86 ± 0.2        | 0.99 ± 0.4        | <b>0.001</b>     |
| Urea, mg/dL                                           | 13.2 ± 5.2        | 12.1 ± 3.9        | 16.2 ± 7.1        | <b>&lt;0.001</b> |
| Glomerular filtration rate, ml/min/1.73m <sup>2</sup> | 93.3 ± 23.6       | 100.9 ± 19.8      | 72.5 ± 20.4       | <b>&lt;0.001</b> |
| Triglycerides, mg/dL                                  | 150 ± 108.2       | 148.6 ± 107.9     | 153.8 ± 107.9     | 0.536            |
| Cholesterol, mg/dL                                    | 195.2 ± 39.9      | 194.1 ± 38.2      | 198.1 ± 44.3      | 0.327            |
| HDL cholesterol, mg/dL                                | 52.6 ± 14.2       | 51.4 ± 13.4       | 56 ± 15.8         | <b>0.016</b>     |
| Gamma glutamyl transferase (U/L)                      | 25.2 ± 27.1       | 25.1 ± 25.5       | 25.4 ± 31.4       | 0.901            |
| <b>Caffeine metabolites in urine</b>                  |                   |                   |                   |                  |
| 1-Methyluric acid, μmol/L                             | 111.6 ± 159.2     | 105.8 ± 146.6     | 127.7 ± 191.8     | 0.137            |
| 3-Methyluric acid, μmol/L                             | 1.3 ± 2.4         | 1.1 ± 1.8         | 1.7 ± 3.5         | 0.088            |
| 7-Methyluric acid, μmol/L                             | 29 ± 46.5         | 27.7 ± 44         | 32.6 ± 53         | 0.335            |
| 1,3-Dimethyluric acid, μmol/L                         | 18.5 ± 115.1      | 12.4 ± 15.6       | 35 ± 232.4        | 0.294            |
| 1,7-Dimethyluric acid, μmol/L                         | 52.6 ± 67.2       | 51.1 ± 66.3       | 56.8 ± 69.1       | 0.402            |
| 3,7-Dimethyluric acid, μmol/L                         | 1.9 ± 2.9         | 2.0 ± 3.0         | 1.5 ± 2.4         | <b>0.044</b>     |
| 1,3,7-Trimethyluric acid, μmol/L                      | 3.3 ± 4.3         | 3.3 ± 4.3         | 3.3 ± 4.1         | 0.969            |
| 1-Methylxanthine, μmol/L                              | 58.3 ± 79         | 60.6 ± 82.4       | 51.9 ± 65.8       | 0.169            |
| 3-Methylxanthine, μmol/L                              | 57.2 ± 95.4       | 55 ± 81.2         | 63.4 ± 129.8      | 0.546            |
| 7-Methylxanthine, μmol/L                              | 86.3 ± 120.5      | 91.1 ± 126.1      | 73.1 ± 97.8       | 0.067            |
| 1,3-Dimethylxanthine (theophylline), μmol/L           | 4.5 ± 30.2        | 3.1 ± 3.2         | 8.6 ± 61.2        | 0.336            |
| 1,7-Dimethylxanthine (paraxanthine), μmol/L           | 28.2 ± 31.2       | 29 ± 31.4         | 26 ± 30.1         | 0.304            |
| 3,7-Dimethylxanthine (theobromine), μmol/L            | 30.6 ± 42.8       | 32.7 ± 42.8       | 25 ± 41.9         | <b>0.042</b>     |
| 1,3,7-Trimethylxanthine (caffeine), μmol/L            | 8.1 ± 9.6         | 7.8 ± 9           | 9 ± 11.1          | 0.205            |
| 5-Acetyl amino-6-amino-3-methyluracil, μmol/L         | 115.7 ± 155.9     | 111.1 ± 155.3     | 128.1 ± 155.4     | 0.232            |

(continued on next page)

Table 1 (continued)

| Variables                        | Total sample      | Young adults      | Older adults      | p-value          |
|----------------------------------|-------------------|-------------------|-------------------|------------------|
| <b>Medicines and supplements</b> |                   |                   |                   |                  |
| Aspirin, n (%)                   |                   |                   |                   | 0.139            |
| No                               | 99.1 (98; 99.6)   | 99.5 (97.4; 99.9) | 97.9 (95.1; 99.1) |                  |
| Yes                              | 0.9 (0.4; 2)      | 0.5 (0.1; 2.6)    | 2.1 (0.9; 4.9)    |                  |
| Prednisone, n (%)                |                   |                   |                   | <b>0.010</b>     |
| No                               | 98.8 (97.6; 99.4) | 99.5 (98.8; 99.8) | 96.6 (92.4; 98.5) |                  |
| Yes                              | 1.2 (0.6; 2.4)    | 0.5 (0.2; 1.2)    | 3.4 (1.5; 7.6)    |                  |
| <b>Dietary intake</b>            |                   |                   |                   |                  |
| Energy, kcal/day                 | 2089.8 ± 777.9    | 2187 ± 777.6      | 1824.9 ± 697.8    | <b>&lt;0.001</b> |
| Protein, g/day                   | 81.2 ± 32.9       | 84 ± 33.4         | 73.7 ± 29.2       | <b>0.010</b>     |
| Total fat, g/day                 | 81.5 ± 45         | 86.1 ± 46.2       | 69.1 ± 37.8       | <b>0.010</b>     |
| Cholesterol, mg/day              | 195.2 ± 39.9      | 194.1 ± 38.2      | 198.1 ± 44.3      | 0.327            |
| Saturated fat, g/day             | 25.2 ± 12.7       | 26.5 ± 12.8       | 21.8 ± 11.5       | <b>&lt;0.001</b> |
| Monounsaturated fat, g/day       | 28.2 ± 14         | 29.2 ± 13.5       | 25.3 ± 14.7       | <b>0.032</b>     |
| Polysaturated fat, g/day         | 18.5 ± 9.7        | 19.3 ± 9.8        | 16.2 ± 9          | <b>0.003</b>     |
| Fiber, g/day                     | 18.1 ± 9.6        | 18.3 ± 9.2        | 17.6 ± 10.6       | 0.487            |
| Alcohol, g/day                   | 9.6 ± 24          | 10.2 ± 25.5       | 8 ± 17.8          | 0.144            |
| Sugar, g/day                     | 112.7 ± 61.8      | 118.1 ± 62.9      | 98.2 ± 54.6       | <b>0.004</b>     |
| Caffeine, mg/day                 | 172.2 ± 181.4     | 164 ± 160.4       | 194.7 ± 233.2     | 0.279            |

Values are presented as mean ± standard deviation or percentage (confidence interval).

Bold font indicates that the p-value is statistically significant.

<sup>a</sup> Data described only for women.

Table 2

Linear regression analysis between caffeine metabolites in urine and strength in the total sample, NHANES 2011–2012.

| Variables                                   | Total sample |                 |                  |          |                 |                  |
|---------------------------------------------|--------------|-----------------|------------------|----------|-----------------|------------------|
|                                             | Unadjusted   |                 |                  | Adjusted |                 |                  |
|                                             | β            | CI (95%)        | p-value          | β        | CI (95%)        | p-value          |
| 1-Methyluric acid, μmol/L                   | 0.005        | (−0.006; 0.016) | 0.377            | 0.003    | (−0.004; 0.010) | 0.402            |
| 3-Methyluric acid, μmol/L                   | −0.317       | (−0.991; 0.357) | 0.335            | 0.033    | (−0.569; 0.635) | 0.909            |
| 7-Methyluric acid, μmol/L                   | −0.016       | (−0.039; 0.008) | 0.183            | −0.005   | (−0.024; 0.014) | 0.574            |
| 1,3-Dimethyluric acid, μmol/L               | 0.010        | (0.008; 0.013)  | <b>&lt;0.001</b> | 0.007    | (0.004; 0.010)  | <b>&lt;0.001</b> |
| 1,7-Dimethyluric acid, μmol/L               | −0.004       | (−0.026; 0.017) | 0.669            | 0.000    | (−0.015; 0.016) | 0.954            |
| 3,7-Dimethyluric acid, μmol/L               | 0.118        | (−0.355; 0.591) | 0.606            | −0.074   | (−0.430; 0.281) | 0.664            |
| 1,3,7-Trimethyluric acid, μmol/L            | −0.029       | (−0.563; 0.506) | 0.912            | 0.080    | (−0.175; 0.335) | 0.517            |
| 1-Methylxanthine, μmol/L                    | 0.014        | (−0.004; 0.032) | 0.126            | 0.007    | (−0.003; 0.017) | 0.155            |
| 3-Methylxanthine, μmol/L                    | 0.005        | (−0.011; 0.021) | 0.541            | 0.006    | (−0.007; 0.020) | 0.338            |
| 7-Methylxanthine, μmol/L                    | 0.004        | (−0.008; 0.016) | 0.471            | 0.002    | (−0.007; 0.012) | 0.605            |
| 1,3-Dimethylxanthine (theophylline), μmol/L | 0.041        | (0.033; 0.048)  | <b>&lt;0.001</b> | 0.028    | (0.017; 0.038)  | <b>&lt;0.001</b> |
| 1,7-Dimethylxanthine (paraxanthine), μmol/L | 0.040        | (−0.019; 0.098) | 0.168            | 0.020    | (−0.013; 0.053) | 0.222            |
| 3,7-Dimethylxanthine (theobromine), μmol/L  | 0.017        | (−0.013; 0.046) | 0.252            | 0.001    | (−0.026; 0.029) | 0.924            |
| 1,3,7-Trimethylxanthine (caffeine), μmol/L  | −0.159       | (−0.380; 0.063) | 0.149            | 0.014    | (−0.092; 0.120) | 0.778            |
| 5-Acetylamin-6-amino-3-methyluracil, μmol/L | 0.002        | (−0.006; 0.011) | 0.564            | −0.001   | (−0.008; 0.006) | 0.748            |

Adjusted for age, sex, race/ethnicity, body mass index, educational level, marital status, annual family income, menopause, diabetes, hypertension, arthritis, smoking status, physical activity, eGFR, serum uric acid, gamma glutamyl transferase, energy, protein and alcohol intake.

A positive β coefficient value indicates that individuals with higher caffeine metabolite levels exhibited higher muscle strength. Conversely, a negative β coefficient suggests that individuals with lower caffeine metabolite levels demonstrated higher muscle strength.

Bold font indicates that the p-value is statistically significant.

## 4. Discussion

The main finding of the present study was that certain caffeine metabolites (1,3-dimethyluric acid and 1,3-dimethylxanthine) in urine were positively associated with muscle strength in the total sample. However, upon further analysis stratified by age-range, an age-dependent association between caffeine metabolites in urine and muscle strength was observed. Several caffeine metabolites in urine, including 7-methyluric acid, 1,3-dimethyluric acid, 3,7-dimethyluric acid, 3-methylxanthine, 7-methylxanthine, 1,3-dimethylxanthine (theophylline) and 3,7-dimethylxanthine (theobromine), were positively associated with muscle strength in older adults, but not in younger individuals. These results suggest that the antioxidant function of some caffeine metabolites may play a crucial role in muscle strength among older adults, a population characterized by increased oxidative stress, which is a significant factor contributing to muscle strength loss [30]. Conversely, as

young adults do not typically experience elevated levels of oxidative stress as a primary cause of strength loss [31], no association was observed between caffeine metabolites and muscle strength for this age group.

To the best of our knowledge, this study is the first to assess the association between caffeine metabolites in urine and muscle strength in both young and older adults. However, previous studies have explored the relationship of coffee intake (a dietary source of these metabolites) with muscle strength and function, and the results are mixed [24–27]. Consuming coffee more frequently has been associated with a reduced risk of falls and enhanced functional capacity [24,26]. However, conflicting findings indicate no association with handgrip strength [27]. The reasons for the conflicting results among these studies [24–27] are not entirely clear, but they are likely attributed to variations in the dietary assessment methods used to estimate coffee intake (e.g., food frequency questionnaire, 24-h recall), as well as differences in the methods

**Table 3**

Linear regression analysis between caffeine metabolites in urine and strength in young adults. NHANES, 2011–2012.

| Variables                                               | Young Adults |                 |         |          |                 |         |
|---------------------------------------------------------|--------------|-----------------|---------|----------|-----------------|---------|
|                                                         | Unadjusted   |                 |         | Adjusted |                 |         |
|                                                         | $\beta$      | CI (95%)        | p-value | $\beta$  | CI (95%)        | p-value |
| 1-Methyluric acid, $\mu\text{mol/L}$                    | –0.001       | (–0.011; 0.009) | 0.841   | –0.001   | (–0.008; 0.006) | 0.857   |
| 3-Methyluric acid, $\mu\text{mol/L}$                    | –0.728       | (–1.960; 0.503) | 0.229   | –0.332   | (–1.058; 0.394) | 0.348   |
| 7-Methyluric acid, $\mu\text{mol/L}$                    | –0.027       | (–0.063; 0.010) | 0.138   | –0.022   | (–0.046; 0.003) | 0.081   |
| 1,3-Dimethyluric acid, $\mu\text{mol/L}$                | –0.015       | (–0.139; 0.109) | 0.801   | –0.010   | (–0.102; 0.082) | 0.820   |
| 1,7-Dimethyluric acid, $\mu\text{mol/L}$                | –0.004       | (–0.025; 0.018) | 0.734   | –0.002   | (–0.021; 0.017) | 0.797   |
| 3,7-Dimethyluric acid, $\mu\text{mol/L}$                | –0.319       | (–0.798; 0.161) | 0.179   | –0.234   | (–0.623; 0.155) | 0.222   |
| 1,3,7-Trimethyluric acid, $\mu\text{mol/L}$             | –0.071       | (–0.610; 0.468) | 0.785   | 0.115    | (–0.173; 0.403) | 0.410   |
| 1-Methylxanthine, $\mu\text{mol/L}$                     | –0.001       | (–0.015; 0.014) | 0.940   | 0.004    | (–0.009; 0.016) | 0.554   |
| 3-Methylxanthine, $\mu\text{mol/L}$                     | –0.014       | (–0.032; 0.005) | 0.135   | –0.005   | (–0.023; 0.013) | 0.566   |
| 7-Methylxanthine, $\mu\text{mol/L}$                     | –0.009       | (–0.020; 0.003) | 0.132   | –0.002   | (–0.014; 0.009) | 0.674   |
| 1,3-Dimethylxanthine (theophylline), $\mu\text{mol/L}$  | –0.222       | (–0.852; 0.408) | 0.467   | 0.099    | (–0.283; 0.482) | 0.591   |
| 1,7-Dimethylxanthine (paraxanthine), $\mu\text{mol/L}$  | 0.004        | (–0.058; 0.066) | 0.900   | 0.010    | (–0.030; 0.049) | 0.605   |
| 3,7-Dimethylxanthine (theobromine), $\mu\text{mol/L}$   | –0.019       | (–0.052; 0.013) | 0.230   | –0.013   | (–0.047; 0.021) | 0.433   |
| 1,3,7-Trimethylxanthine (caffeine), $\mu\text{mol/L}$   | –0.115       | (–0.309; 0.080) | 0.232   | 0.034    | (–0.084; 0.152) | 0.551   |
| 5-Acetylamino-6-amino-3-methyluracil, $\mu\text{mol/L}$ | 0.001        | (–0.009; 0.011) | 0.790   | –0.003   | (–0.011; 0.005) | 0.502   |

Adjusted for age, sex, race/ethnicity, body mass index, educational level, marital status, annual family income, menopause, diabetes, hypertension, arthritis, smoking status, physical activity, eGFR, serum uric acid, gamma glutamyl transferase, energy, protein and alcohol intake.

A positive  $\beta$  coefficient value indicates that individuals with higher caffeine metabolite levels exhibited higher muscle strength. Conversely, a negative  $\beta$  coefficient suggests that individuals with lower caffeine metabolite levels demonstrated higher muscle strength.

**Table 4**

Linear regression analysis between caffeine metabolites in urine and strength in older adults. NHANES, 2011–2012.

| Variables                                               | Older Adults |                 |                  |          |                  |              |
|---------------------------------------------------------|--------------|-----------------|------------------|----------|------------------|--------------|
|                                                         | Unadjusted   |                 |                  | Adjusted |                  |              |
|                                                         | $\beta$      | CI (95%)        | p-value          | $\beta$  | CI (95%)         | p-value      |
| 1-Methyluric acid, $\mu\text{mol/L}$                    | 0.023        | (0.015; 0.032)  | <b>&lt;0.001</b> | 0.007    | (–0.001; 0.016)  | 0.081        |
| 3-Methyluric acid, $\mu\text{mol/L}$                    | 0.643        | (–0.406; 1.692) | 0.213            | 0.475    | (–0.040; 0.989)  | 0.068        |
| 7-Methyluric acid, $\mu\text{mol/L}$                    | 0.032        | (–0.022; 0.087) | 0.229            | 0.029    | (0.005; 0.052)   | <b>0.021</b> |
| 1,3-Dimethyluric acid, $\mu\text{mol/L}$                | 0.016        | (0.015; 0.018)  | <b>&lt;0.001</b> | 0.008    | (0.003; 0.013)   | <b>0.004</b> |
| 1,7-Dimethyluric acid, $\mu\text{mol/L}$                | 0.009        | (–0.026; 0.044) | 0.600            | –0.006   | (–0.029; 0.017)  | 0.613        |
| 3,7-Dimethyluric acid, $\mu\text{mol/L}$                | 1.297        | (0.554; 2.040)  | <b>0.002</b>     | 0.645    | (0.163; 1.127)   | <b>0.012</b> |
| 1,3,7-Trimethyluric acid, $\mu\text{mol/L}$             | 0.132        | (–0.483; 0.747) | 0.656            | –0.247   | (–0.536; 0.042)  | 0.089        |
| 1-Methylxanthine, $\mu\text{mol/L}$                     | 0.059        | (0.037; 0.081)  | <b>&lt;0.001</b> | 0.005    | (–0.010; 0.020)  | 0.511        |
| 3-Methylxanthine, $\mu\text{mol/L}$                     | 0.034        | (0.020; 0.048)  | <b>&lt;0.001</b> | 0.020    | (0.009; 0.032)   | <b>0.002</b> |
| 7-Methylxanthine, $\mu\text{mol/L}$                     | 0.047        | (0.022; 0.073)  | <b>0.001</b>     | 0.020    | (0.007; 0.034)   | <b>0.006</b> |
| 1,3-Dimethylxanthine (theophylline), $\mu\text{mol/L}$  | 0.063        | (0.056; 0.070)  | <b>&lt;0.001</b> | 0.030    | (0.011; 0.049)   | <b>0.004</b> |
| 1,7-Dimethylxanthine (paraxanthine), $\mu\text{mol/L}$  | 0.122        | (0.080; 0.163)  | <b>&lt;0.001</b> | 0.008    | (–0.020; 0.036)  | 0.563        |
| 3,7-Dimethylxanthine (theobromine), $\mu\text{mol/L}$   | 0.079        | (0.044; 0.115)  | <b>&lt;0.001</b> | 0.035    | (0.004; 0.065)   | <b>0.029</b> |
| 1,3,7-Trimethylxanthine (caffeine), $\mu\text{mol/L}$   | –0.117       | (–0.338; 0.104) | 0.278            | –0.127   | (–0.222; –0.031) | <b>0.012</b> |
| 5-Acetylamino-6-amino-3-methyluracil, $\mu\text{mol/L}$ | 0.015        | (–0.008; 0.039) | 0.183            | –0.002   | (–0.015; 0.011)  | 0.758        |

Adjusted for age, sex, race/ethnicity, body mass index, educational level, marital status, annual family income, diabetes, hypertension, arthritis, smoking status, physical activity, eGFR, serum uric acid, gamma glutamyl transferase, energy, protein and alcohol intake.

A positive  $\beta$  coefficient value indicates that individuals with higher caffeine metabolite levels exhibited higher muscle strength. Conversely, a negative  $\beta$  coefficient suggests that individuals with lower caffeine metabolite levels demonstrated higher muscle strength.

Bold font indicates that the p-value is statistically significant.

used to evaluate muscle strength and function, such as handgrip strength, risk of falls, and functional capacity. While our study also exhibits several differences compared to these previous studies [24–27], including variations in study design (longitudinal versus cross-sectional), methods for assessing caffeine intake (dietary versus urinary metabolites), differences in muscle function/strength assessment, and the type of populations studied, our findings are consistent with the majority of studies [24–26] that have evaluated the association of coffee intake with muscle strength and function in older adults.

In our study, several caffeine metabolites including 7-methyluric acid, 1,3-dimethyluric acid, 3,7-dimethyluric, 3-methylxanthine, 7-methylxanthine, 1,3-dimethylxanthine and 3,7-dimethylxanthine showed positive associations with muscle strength in older adults. These findings suggest that caffeine metabolites present in urine could potentially act as protective factors

for muscle strength in this population. However, an unexpected inverse association was observed between 1,3,7-trimethylxanthine (caffeine) and strength. Although it is not fully clear, these findings could be related to caffeine metabolism. For instance, when caffeine-containing foods like coffee and tea are consumed, only small quantities of caffeine are excreted in urine [16]. This occurs because caffeine undergoes metabolism in the liver, leading to the production of various other metabolites. Approximately 84% of ingested caffeine is metabolized into paraxanthine, ~12% into theobromine, and ~4% into theophylline, resulting in the generation of several other metabolites (Fig. 2) [16]. Consequently, as caffeine undergoes hepatic metabolism and its concentrations diminish in the bloodstream, leading to reduced levels excreted in urine, it gives rise to various metabolites. Several of these metabolites exhibited positive associations with strength in our study. This sequence of events suggests a potential indirect inverse

relationship with strength, as caffeine is metabolized to produce the metabolites that displayed positive associations with strength in our study. In our descriptive results (Table 1), we observed relatively low levels of caffeine in urine ( $\sim 9 \mu\text{mol/L}$ ) compared to other caffeine metabolites. This observation supports our hypothesis that caffeine undergoes further metabolism to generate additional metabolites, which may potentially elucidate the inverse association observed in our study. However, this hypothesis remains speculative, and further studies are warranted to confirm whether caffeine in urine is directly and inversely associated with strength in older adults. To date, there are no established mechanisms that can explain potential direct effects of caffeine on strength reduction. Therefore, we cannot discount the possibility that the observed inverse association between caffeine in urine and strength may have been spurious, despite adjusting for important confounding variables in our analyses. Further investigation is needed to elucidate the precise relationship between caffeine in urine and muscle strength in older adults. Conversely, several metabolites, including 7-methylxanthine, showed a positive association with strength. This metabolite is derived from paraxanthine and theobromine, with  $\sim 84\%$  and  $\sim 12\%$  of caffeine metabolizing into these compounds, respectively (Fig. 2). Among the metabolites analyzed, 7-methylxanthine exhibited one of the highest concentrations in our study ( $\sim 73 \mu\text{mol/L}$ ), indicating a notable biological significance for the observed positive association with strength. Additionally, we observed positive associations of theobromine and theophylline, as well as some of their metabolites, with strength, but no association was observed with paraxanthine (Fig. 2). Given the lower conversion of caffeine to theophylline and theobromine compared to paraxanthine, it is possible to suggest that sources other than coffee may have also contributed to the levels of these caffeine metabolites in the present study. For instance, various teas and cocoa are known sources of theophylline and theobromine [36], suggesting that these metabolites in urine may, at least in part, reflect intake from these sources in addition to coffee and caffeine consumption.

The mechanisms underlying the positive association between several caffeine metabolites in urine and strength in older adults are not fully elucidated, but are likely related to their antioxidant effects. Some studies suggest that various caffeine metabolites may

exert direct beneficial effects on redox balance [20,37–41], reducing inflammation [42], inhibiting the DNA damage response, regulating cell proliferation and death, and promoting DNA repair [18,43]. Given that elevated oxidative stress can impact the activation of muscle fibers and modulate excitation–contraction processes [44], caffeine metabolites appear to counteract the detrimental effects of elevated oxidative stress by reducing free radical generation and protecting muscle cells against oxidative damage. This preservation of muscle strength seems to be particularly notable in populations experiencing high oxidative stress, such as older adults [30]. Additionally, it cannot be ruled out that other factors might have also influenced these associations. For instance, Liu et al. [45], also analyzing NHANES data, observed that 1-methyluric acid, 7-methylxanthine, theophylline, and paraxanthine were associated with better cognitive function in older adults. Since cognitive function is linked to muscle strength [46], it remains unclear whether the positive association between caffeine metabolites and strength is (partially) influenced by improved cognitive function.

The present study has several limitations that should be acknowledged. Firstly, the cross-sectional design utilized in this study prevents the inference of causality. As an observational study, there is a possibility that the observed associations may be influenced by residual confounding factors that were not fully accounted for in the analyses. While efforts were made to adjust for important confounders, the presence of residual confounding cannot be entirely ruled out. Furthermore, it is important to note that our results may not be directly generalizable to other populations, as the NHANES survey focuses on a representative sample of the United States. Although the United States is a diverse and scientifically advanced country, caution should be exercised when extrapolating our findings to other populations with different demographic characteristics and lifestyle behaviors. Additionally, establishing precise dosage recommendations for caffeine sources based on our findings proves challenging. While our findings suggest a potential benefit for older adults from consuming caffeine sources such as coffee, tea, and other beverages, further research is needed to establish clear guidelines regarding the appropriate doses of these beverages. Moreover, it is essential to recognize that the estimation of caffeine metabolites provides insight into short-

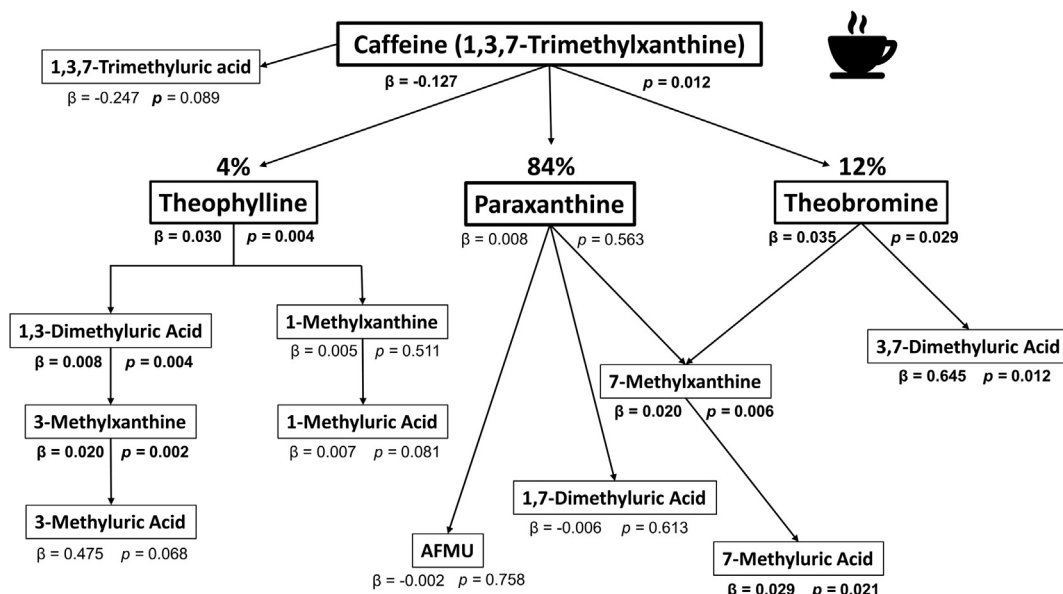


Fig. 2. Associations between caffeine metabolites in urine and muscle strength in older adults in the present study.

term caffeine intake rather than long-term consumption patterns [47]. Therefore, our results should not be extrapolated to long-term caffeine intake behaviors. Given the non-normal distribution of the caffeine metabolites in urine data, it is important to exercise caution when interpreting the beta values. We recommend focusing solely on whether the associations are positive or negative rather than placing emphasis on the magnitude of the beta values. Despite these limitations, our study is the first to demonstrate an association between caffeine metabolites and muscle strength in a representative sample of the United States. By providing valuable insights into the relationship between caffeine metabolites and muscle strength, our findings contribute to the existing body of literature on this topic and highlight the importance of further research in this area.

In conclusion, our study demonstrates a positive association between specific caffeine metabolites in urine and muscle strength among older adults, while no such association was observed in younger individuals. Additional research is warranted to comprehensively elucidate the mechanisms by which caffeine metabolites impact muscle metabolism and to delineate how these effects manifest in human overall muscle health.

## Authorship

BBS contributed to data interpretation, conducted statistical analysis, and wrote the manuscript; LSL conducted statistical analysis, participated in data interpretation, and contributed to manuscript revisions; EPO served as the mentor of the study, wrote and reviewed the manuscript, and contributed to data interpretation. All authors reviewed and approved the final version of the manuscript.

## Conflict of interest

The authors declare no conflicts of interest.

## Acknowledgment

No sources of funding were used to assist in the article preparation. EPO would like to thank The Brazilian National Council for Scientific and Technological Development (CNPq, Brazil, 307786/2022-6).

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RESEARCH



# Association between serum uric acid and muscle strength according to glycemic status in older adults: NHANES 1999–2002

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Received: 1 December 2023 / Accepted: 7 May 2024  
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## Abstract

**Background** Hyperglycemia induces heightened oxidative stress, potentially leading to reduced muscle strength. Consequently, compounds with antioxidant properties could potentially offer protection against this decline. Uric acid (UA) is known for its antioxidant effects and has shown a positive association with muscle strength in older adults. However, whether this association extends to older adults with hyperglycemia remains unknown.

**Aim** To assess the association between UA levels and muscle strength in older adults, stratified by glycosylated hemoglobin levels.

**Methods** A cross-sectional study was conducted, involving 2380 individuals aged 50 to 85 years (1500 normoglycemic and 880 hyperglycemic), selected from a subsample of the National Health and Nutrition Examination Survey (NHANES) 1999–2002. Hyperglycemia was defined as glycosylated hemoglobin levels  $\geq 5.7\%$ . Muscle strength was assessed using a kinetic communicator isokinetic dynamometer. Serum UA levels were measured using a colorimetric method. Linear regression analyses were employed to examine the association of continuous UA values and tertiles of UA levels with muscle strength based on glycemic status, adjusting for potential confounding factors.

**Results** Tertiles of UA levels showed a positive association with peak force in individuals with hyperglycemia ( $p$ -trend = 0.013), but not in those with normoglycemia ( $p$ -trend = 0.077). Moreover, continuous UA values were positively associated with muscle strength in older adults with hyperglycemia ( $\beta = 5.2$  (0.6; 9.8);  $p = 0.027$ ), whereas no association was observed in those with normal glycemia ( $\beta = 2.4$  (− 2.1; 6.9);  $p = 0.282$ ).

**Conclusion** Serum UA exhibits a positive association with muscle strength in older adults with hyperglycemia; however, this association is not observed in individuals with normal glucose levels. These results suggest that UA levels may play a crucial role in muscle strength, particularly in older adults experiencing heightened oxidative stress induced by hyperglycemia.

**Keywords** Oxidative stress · Antioxidant · Muscle mass · Glucose levels

## Introduction

The aging process is marked by various physiological changes, including reductions in muscle mass and strength [1]. These alterations have been linked to declines in functional capacity and an elevated risk of falls and fractures [2, 3]. While multifaceted in nature, several factors may

potentially contribute to the decline in muscle strength observed in older adults [4–10]. Elevated oxidative stress represents one such factor that can hasten this decline, as the imbalance in redox status may affect not only muscle mass but also the activation of muscle fibers and excitation–contraction processes [11].

Hyperglycemia has likewise been linked to the loss of muscle strength [12–14], attributed to its ability to heighten oxidative stress through the overproduction of reactive oxygen species (ROS) [15]. This exacerbation of oxidative stress can amplify the detrimental effects of aging alone [15, 16]. Consequently, compounds with antioxidant properties could potentially confer protective effects on muscle strength by mitigating the impact of oxidative stress [9, 17].

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Uric acid (UA) is the final product of purine and nucleic acid metabolism in humans, playing a pivotal role as an antioxidant and contributing to over 50% of the total antioxidant capacity of plasma [18]. Previous studies have consistently shown a positive association between serum UA levels and muscle strength, particularly among older adults and clinical populations where oxidative stress significantly contributes to strength loss [19–26]. Conversely, in populations where increased oxidative stress is not a prominent factor in strength loss, such as healthy adults, UA does not appear to be associated with muscle mass or strength [27, 28]. These findings suggest that the relationship between UA and muscle strength may be influenced, at least partially, by oxidative stress. Therefore, it is reasonable to speculate that higher UA levels may correlate with greater muscle strength, especially in individuals experiencing conditions characterized by heightened oxidative stress, such as hyperglycemia. The antioxidant properties of UA may serve to counteract the detrimental effects of elevated glucose levels on muscle strength. However, despite these insights, the specific association between UA levels and muscle strength in older adults with hyperglycemia remains unexplored. Hence, the aim of this study was to investigate the association between UA levels and muscle strength in older adults, stratified by glycosylated hemoglobin levels. We hypothesized that UA would demonstrate a positive association with muscle strength in older adults across both normal and altered glycemic levels, with a potentially stronger association observed in those with hyperglycemia.

## Methods

### Study design and population

This cross-sectional study utilized data from the National Health and Nutrition Examination Survey (NHANES) conducted between 1999 and 2002. NHANES employs a stratified, multistage probability sampling method to evaluate the health and nutritional status of the noninstitutionalized, nationally representative population of the United States. The current study focused on individuals from NHANES cycles spanning 1999 to 2000 and 2001 to 2002 [29]. Eligibility for inclusion in the study required subjects to have available serum UA data and undergo assessment of isokinetic strength of the knee extensors. Muscle strength assessments in NHANES 1999–2000 and 2001–2002 were restricted to individuals aged 50 years and older. Additionally, we selected individuals within this age range because significant strength loss is already evident after 50 years of age [30]. Subjects with available demographic profiles, health-related factors (including hypertension, arthritis, diabetes, and allopurinol usage),

behavioral conditions (smoking habits and physical activity data), anthropometric measurements, biochemical indicators, and dietary information were included in the present study. Additionally, only individuals who successfully completed the strength tests were considered for analysis. Exclusion criteria encompassed amputees, pregnant women, subjects with implausible peak velocity strength [31], and those who failed to execute a minimum of four trials during the isokinetic strength assessment (Fig. 1). Participants with recent medical history, such as myocardial infarction within the preceding 6 weeks, recent knee surgery or knee replacement surgery, recent chest or abdominal surgery within the last 3 weeks, a prior history of brain aneurysm or stroke, or severe back pain, were ineligible to undergo the muscle strength test and were consequently excluded from the analysis. As a result, a total of 2380 individuals (1500 normoglycemic and 880 hyperglycemic, stratified according to glycosylated hemoglobin (GHb) cut-off point [32]) were included in the present study's analysis.

NHANES data collection protocols are approved by the ethics review board of the National Center for Health Statistics (NCHS ERB) (protocol #98–12 for NHANES cycle 1999–2002). Prior to participation, informed consent was obtained from all participants.

### Glycosylated hemoglobin, UA, and other biochemical markers

Glycosylated hemoglobin levels were assessed using boronate affinity high-performance liquid chromatography (HPLC) with Primus CLC330 and Primus CLC 385. Hyperglycemia was defined as glycosylated hemoglobin levels  $\geq 5.7\%$  [32]. Serum UA and triglycerides were quantified via a colorimetric method, while creatinine levels were measured photometrically. Glomerular filtration rate (eGFR) was calculated using the equation developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [33]. Serum C-reactive protein (CRP) was quantified using latex-enhanced nephelometry.

### Muscle strength

The assessment of knee extensor strength was conducted utilizing the Kinetic Communicator isokinetic dynamometer. Muscle strength, represented as peak force, was quantified in Newtons and targeted the quadriceps muscles, executing movements at a velocity of 60 degrees per second. Participants exhibiting outlier values in peak force velocity ( $< 55$  degrees per second or  $> 65$  degrees per second) were excluded from the analysis [31]. Six measurements of muscle strength were acquired: three warm-up/learning trials and three outcome measurements. During the warm-up phase,

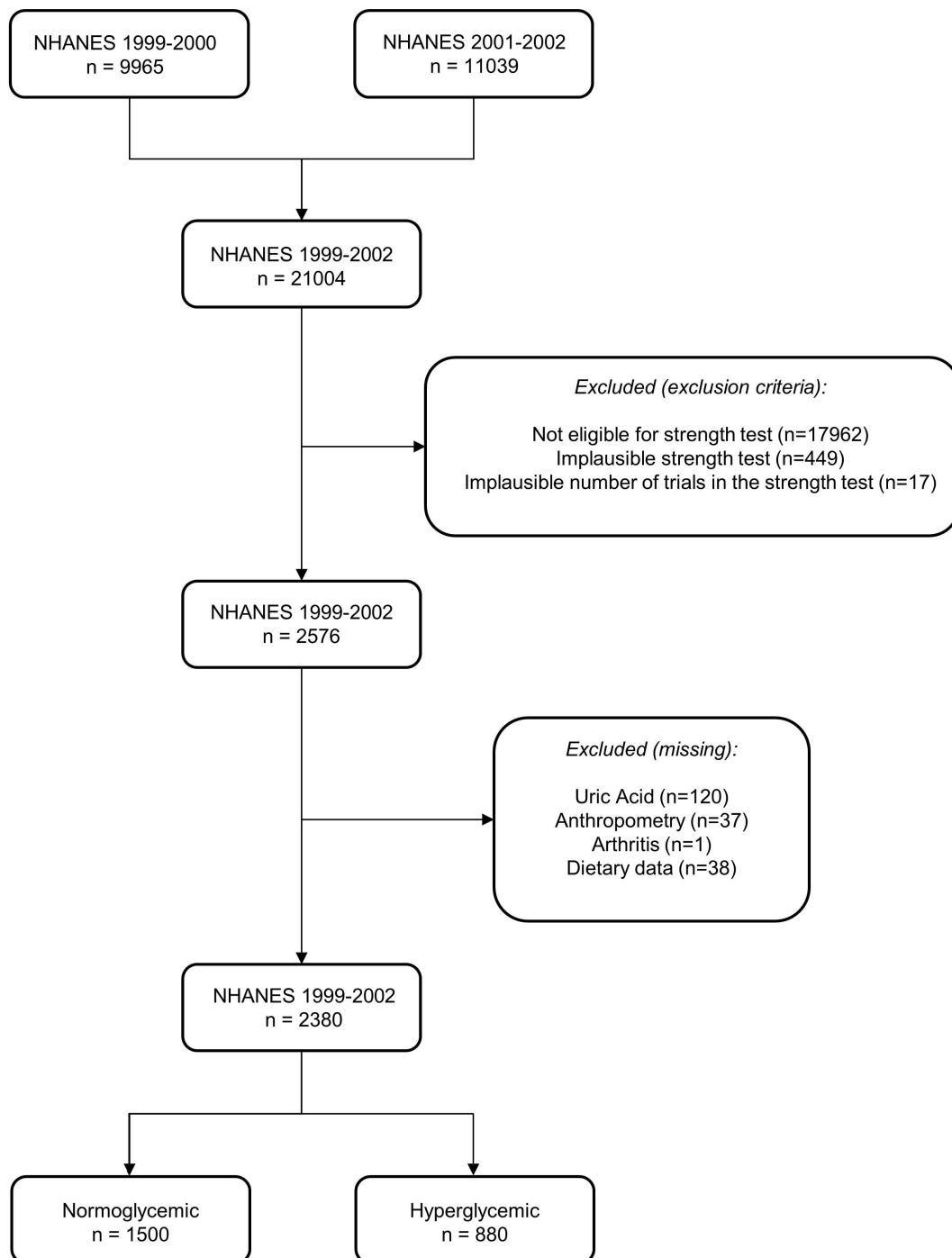


**Fig. 1** Flowchart of the sample selection from NHANES 1999–2002

participants were instructed to exert submaximal effort to familiarize themselves with the movement and to prepare physically. Subsequently, in the three outcome trials, participants were encouraged to exert maximal effort to accurately quantify muscle strength. Following completion of the 4–6 trials, the peak force value obtained from the highest trial was selected for further analysis.

### Anthropometry

Body weight and height were measured following Lohman's established protocol [34], and subsequently, the body mass index (BMI) was calculated [35]. Participants were instructed to wear disposable attire consisting of a shirt, pants, and slippers during the measurements.

### Dietary intake

Dietary intake was assessed by a trained interviewer using a 24-h dietary recall for each participant. The NHANES surveys conducted during 1999–2000 and 2001 utilized a structured four-step multiple-pass approach, while the 2002 survey employed the US Department of Agriculture Automated five-step multiple-pass method for comprehensive dietary intake assessment [36, 37]. The intake of energy (kcal/day), protein (g/day and g/kg), lipid (g/day), carbohydrate (g/day), alcohol (g/day), and several micronutrients was evaluated.

### Covariates of interest

Several covariates of interest were evaluated, encompassing demographic data such as sex (men or women), age (in years), marital status (categorized as single, divorced, widowed, never married, or married/living as married), race/ethnicity (non-Hispanic white or other), annual household income (stratified into intervals of \$0 to \$19,999, \$20,000 to \$54,999, or exceeding \$55,000), and educational level (classified as under or high school graduate and some college or above). Health conditions and behavioral aspects were also assessed, including self-reported diabetes diagnosis (classified as no, pre-diabetes, or yes), hypertension status (classified as no or yes), arthritis presence (classified as no or yes), allopurinol usage (classified as no or yes), metformin usage (classified as no or yes), glipizide usage (classified as no or yes), smoking status (categorized as no or yes), and physical activity level (classified as no or yes), as previously detailed [38]. Additionally, eGFR (mL/min/1.73 m<sup>2</sup>), triglycerides (mg/dL), and CRP (mg/dL) levels, as well as total energy intake (kcal/day) and protein intake (g/day), were assessed as confounders.

### Statistical analyses

Sociodemographic data, anthropometry, health status and behavior, muscle strength, biochemical markers, and dietary intake were described for the total sample, normoglycemic, and hyperglycemic individuals. The comparisons of these variables were made using linear regression. The continuous variables were characterized using mean and standard deviation, whereas the categorical variables were delineated through percentage and confidence interval. Linear regression analysis was performed to evaluate whether muscle strength (expressed in Newtons) was associated with the tertiles of UA for normoglycemic and hyperglycemic samples. The analytical procedures were executed in two statistical models: without any covariate adjustments (model 1), and adjusted for several covariates, such as age, educational level, sex, BMI, race/ethnicity, annual household income, marital status, presence of hypertension, arthritis, utilization of allopurinol, metformin and glipizide, physical activity, smoking behavior, eGFR, CRP, and triglyceride levels, as well as energy and protein intake (model 2). The selection of these variables was based on their biological influence on strength and/or UA levels [4–8, 39]. Furthermore, linear regression analysis was also conducted to assess the relationship between continuous values of UA and muscle strength according to the glycemic levels.

Analyses were conducted using Stata 14.0 software (StataCorp, College Station, TX, USA). The “svy” command was utilized to incorporate information on the “wtmec4yr” sample weight, primary sampling units, and strata for accurate variance estimation [29]. A significance level of  $p < 0.05$  was considered statistically significant.

### Results

The characteristics of individuals in the total sample, as well as those classified as normoglycemic and hyperglycemic, are presented in Table 1. Compared to the normoglycemic group, individuals in the hyperglycemic group exhibited a lower proportion of non-Hispanic white participants, lower annual household income, and lower educational level. Additionally, the hyperglycemic group had a higher prevalence of diabetes, hypertension, arthritis, and allopurinol usage, along with a higher prevalence of individuals with physical inactivity and higher body weight and BMI. Regarding biochemical parameters, individuals in the hyperglycemic group showed higher levels of serum UA, triglycerides, and CRP. Regarding dietary intake, the hyperglycemic group had lower energy, protein, and alcohol consumption, as well as lower selenium intake.

**Table 1** Sociodemographic data, health status and behavior, anthropometry, strength, biochemical parameters, and dietary intake according to total, normoglycemic, and hyperglycemic sample. NHANES, 1999–2002

|                                       | Total             | Normoglycemic     | Hyperglycemic     | <i>p</i> -value   |
|---------------------------------------|-------------------|-------------------|-------------------|-------------------|
| Glycosylated hemoglobin (%)           | 5.6 ± 0.9         | 5.3 ± 0.2         | 6.5 ± 1.4         | <b>&lt; 0.001</b> |
| Uric acid, mg/dL                      | 5.6 ± 1.4         | 5.4 ± 1.4         | 5.8 ± 1.6         | <b>&lt; 0.001</b> |
| Demographic                           |                   |                   |                   |                   |
| Age, y                                | 62.1 ± 9.5        | 61.3 ± 8.9        | 64 ± 10.4         | <b>&lt; 0.001</b> |
| Sex                                   |                   |                   |                   | 0.653             |
| Men                                   | 50.4 (48.6; 52.2) | 51.5 (49.7; 53.3) | 47.9 (43.5; 52.3) |                   |
| Women                                 | 49.6 (47.8; 51.4) | 48.5 (46.7; 50.3) | 52.1 (47.7; 56.5) |                   |
| Race/ethnicity, %                     |                   |                   |                   | <b>&lt; 0.001</b> |
| Non-Hispanic white                    | 81.6 (77.4; 85.1) | 86 (82.6; 88.8)   | 71.2 (63.3; 78)   |                   |
| Marital status, %                     |                   |                   |                   | 0.502             |
| Single/divorced/widowed/never married | 69.1 (65.3; 72.6) | 69.6 (65.5; 73.4) | 67.8 (62.3; 72.9) |                   |
| Married/living with partner           | 25.6 (22.8; 28.7) | 24.4 (21.1; 28.1) | 28.5 (24; 33.4)   |                   |
| Missing                               | 5.3 (2.8; 9.7)    | 6 (3.1; 11.1)     | 3.7 (1.7; 7.8)    |                   |
| Annual household income, %            |                   |                   |                   | <b>&lt; 0.001</b> |
| \$0–19,999                            | 21.2 (18.2; 24.6) | 16.8 (13.7; 20.6) | 31.6 (27.7; 35.8) |                   |
| \$20,000–54,999                       | 41.9 (38.5; 45.3) | 41.7 (37.7; 45.9) | 42.3 (38.1; 46.5) |                   |
| Over \$55,000                         | 34.3 (30; 38.8)   | 39 (34.2; 44)     | 23.2 (18.6; 28.4) |                   |
| Missing                               | 2.6 (1.8; 3.7)    | 2.5 (1.8; 3.5)    | 2.9 (1.7; 5.2)    |                   |
| Educational level, %                  |                   |                   |                   | <b>&lt; 0.001</b> |
| Under high school graduate            | 48.1 (44.2; 52)   | 42.7 (38.9; 46.6) | 61 (56; 65.7)     |                   |
| Some college or over                  | 51.8 (47.9; 55.7) | 57.2 (53.3; 61.1) | 39 (34.2; 43.9)   |                   |
| Missing                               | 0.1 (0; 0.2)      | 0.1 (0; 0.4)      | 0 (0; 0.3)        |                   |
| Health conditions and behavior        |                   |                   |                   |                   |
| Diabetes, %                           |                   |                   |                   | <b>&lt; 0.001</b> |
| Yes                                   | 9.1 (7.8; 10.4)   | 1 (0.6; 1.7)      | 28 (24.5; 31.8)   |                   |
| No                                    | 88.7 (86.7; 90.5) | 98 (96.8; 98.7)   | 66.9 (62.4; 71)   |                   |
| Pre-diabetes                          | 2.2 (1.4; 3.3)    | 1 (0.5; 2.2)      | 4.9 (3.4; 6.9)    |                   |
| Hypertension, %                       |                   |                   |                   | <b>&lt; 0.001</b> |
| Yes                                   | 39.3 (36.5; 42.1) | 34.9 (31.4; 38.6) | 49.5 (45; 53.9)   |                   |
| No                                    | 60.5 (57.7; 63.1) | 64.8 (61.2; 68.3) | 50.2 (45.7; 54.7) |                   |
| Arthritis, %                          |                   |                   |                   | <b>0.003</b>      |
| Yes                                   | 37.2 (34.3; 40.1) | 35.1 (31.9; 38.5) | 42 (38.2; 45.9)   |                   |
| No                                    | 62.8 (59.9; 65.7) | 64.9 (61.5; 68.1) | 58 (54.1; 61.8)   |                   |
| Allopurinol use, %                    |                   |                   |                   | <b>0.005</b>      |
| Yes                                   | 1.4 (1; 2.1)      | 0.9 (0.6; 1.5)    | 2.6 (1.6; 4.4)    |                   |
| No                                    | 98.6 (97.9; 99)   | 99.1 (98.5; 99.4) | 97.4 (95.6; 98.4) |                   |
| Metformin use, %                      |                   |                   |                   | <b>&lt; 0.001</b> |
| Yes                                   | 3.2 (2.4; 4.2)    | 0.1 (0.01; 0.01)  | 10.4 (7.6; 14.2)  |                   |
| No                                    | 96.8 (95.8; 97.6) | 99.9 (99.5; 99.9) | 89.6 (85.8; 92.4) |                   |
| Glipizide use, %                      |                   |                   |                   | <b>&lt; 0.001</b> |
| Yes                                   | 1.8 (1.3; 2.5)    | 0.1 (0; 0.6)      | 5.6 (4.1; 7.7)    |                   |
| No                                    | 98.2 (97.5; 98.7) | 99.9 (99.4; 100)  | 94.5 (92.3; 95.9) |                   |
| Physical activity, %                  |                   |                   |                   | <b>&lt; 0.001</b> |
| Yes                                   | 7.2 (5.5; 9.3)    | 8.9 (7; 11.3)     | 3.2 (1.7; 5.8)    |                   |
| No                                    | 92.7 (90.6; 94.4) | 91 (88.7; 92.9)   | 96.7 (94.2; 98.1) |                   |
| Smoking status, %                     |                   |                   |                   | 0.122             |
| Yes                                   | 16.7 (14.6; 19)   | 15.7 (13.5; 18.2) | 18.9 (15.4; 23)   |                   |
| No                                    | 83.1 (80.8; 85.2) | 84.1 (81.6; 86.3) | 81 (76.9; 84.4)   |                   |

**Table 1** (continued)

|                                                        | Total         | Normoglycemic  | Hyperglycemic | <i>p</i> -value   |
|--------------------------------------------------------|---------------|----------------|---------------|-------------------|
| <b>Anthropometric</b>                                  |               |                |               |                   |
| Weight, kg                                             | 80.1 ± 17.8   | 78.3 ± 16.6    | 84.3 ± 20     | <b>&lt; 0.001</b> |
| Height, cm                                             | 167.9 ± 9.9   | 168.3 ± 9.4    | 167 ± 10.9    | <b>0.007</b>      |
| Body mass index, kg/m <sup>2</sup>                     | 28.3 ± 5.5    | 27.6 ± 5.1     | 30.1 ± 6      | <b>&lt; 0.001</b> |
| <b>Strength</b>                                        |               |                |               |                   |
| Peak force, Newtons                                    | 378.9 ± 124.8 | 381.2 ± 119.3  | 373.5 ± 136.1 | 0.268             |
| Time to peak force, seconds                            | 1.1 ± 0.6     | 1.1 ± 0.5      | 1.1 ± 0.7     | 0.407             |
| Peak force velocity, degree/second                     | 60.7 ± 0.6    | 60.7 ± 0.6     | 60.7 ± 0.7    | 0.567             |
| <b>Biochemical parameters</b>                          |               |                |               |                   |
| Creatinine, mg/dL                                      | 0.9 ± 0.4     | 0.9 ± 0.4      | 0.9 ± 0.4     | 0.361             |
| Glomerular filtration rate, mL/min/1.73 m <sup>2</sup> | 86.9 ± 19.3   | 87.2 ± 17.8    | 86.2 ± 23     | 0.331             |
| C-reactive protein, mg/dL                              | 0.4 ± 0.7     | 0.4 ± 0.5      | 0.6 ± 1.1     | <b>&lt; 0.001</b> |
| Triglycerides, mg/dL                                   | 160.3 ± 171   | 145.7 ± 140.3  | 194.6 ± 235.8 | <b>&lt; 0.001</b> |
| <b>Dietary intake</b>                                  |               |                |               |                   |
| Energy, kcal/day                                       | 1993 ± 914.7  | 2031.2 ± 877.6 | 1903.3 ± 981  | <b>0.007</b>      |
| Carbohydrate, g/day                                    | 244.9 ± 118   | 248.6 ± 110.3  | 236.3 ± 135   | 0.067             |
| Protein, g/day                                         | 76.1 ± 38.4   | 77.4 ± 37.4    | 73.1 ± 39.7   | <b>0.023</b>      |
| Protein, g/kg                                          | 0.97 ± 0.48   | 1.01 ± 0.47    | 0.89 ± 0.48   | <b>&lt; 0.001</b> |
| Lipids, g/day                                          | 76 ± 44.9     | 76.7 ± 42.7    | 74.5 ± 49.5   | 0.361             |
| <b>Alcohol, g/day</b>                                  |               |                |               |                   |
| Vitamin A, IU/day                                      | 9.2 ± 29.3    | 11.2 ± 30.8    | 4.5 ± 21.2    | <b>&lt; 0.001</b> |
| Vitamin C, mg/day                                      | 7001 ± 9760   | 7461 ± 9562    | 5997 ± 9945   | 0.160             |
| Vitamin E as alpha-tocopherol, mg/day                  | 97.7 ± 88.9   | 100 ± 84.3     | 92.1 ± 98.5   | 0.138             |
| Zinc, mg/day                                           | 7.1 ± 5.7     | 7.3 ± 5.4      | 6.6 ± 6.4     | 0.064             |
| Selenium, mcg/day                                      | 11.1 ± 8.1    | 11.2 ± 8       | 10.8 ± 7.9    | 0.249             |
|                                                        | 103 ± 64.6    | 104 ± 61.2     | 100 ± 71.8    | <b>0.007</b>      |

Values are presented as mean ± standard deviation or percentage (confidence interval)

Hyperglycemic group = glycosylated hemoglobin ≥ 5.7%

The *p*-value was obtained through linear regression analysis and bold indicates a statistically significant difference (*p* < 0.05)

In the unadjusted analysis, tertiles of serum UA levels showed a positive association with peak force in both normoglycemic and hyperglycemic individuals (Supplementary Table 1, model 1). However, after adjusting for confounding variables, the association remained positive only in the hyperglycemic group, while no significant association was observed in normoglycemic individuals (Fig. 2; Supplementary Table 1, model 2). Furthermore, continuous values of UA levels were positively associated with muscle strength in older adults with hyperglycemia, but not in those with normal glycemia (Table 2).

## Discussion

Our hypothesis was that UA would exhibit a positive association with muscle strength in both older adults with normal and altered glycemia, with a potentially stronger association observed in individuals with hyperglycemia.

However, our hypothesis was only partially supported by our findings. The main finding of our study was the positive association observed between serum UA levels and muscle strength solely among older adults with altered glycemia, with no such relationship in those with normal glucose levels. These results suggest that UA levels might significantly influence muscle strength primarily in older adults experiencing heightened oxidative stress induced by hyperglycemia. Importantly, to our knowledge, this study represents the first investigation of this association in hyperglycemic older adults.

The mechanisms underlying the results of the present study remain incompletely understood; however, they may be attributed to the antioxidant properties exerted by UA [18]. Hyperglycemia activates several biochemical pathways associated with the generation of ROS, leading to increased oxidative stress [40, 41]. Furthermore, ROS production increases during aging primarily due to mitochondrial dysfunction caused by numerous age-related changes, including mutations, deletions, and damage to mitochondrial

**Fig. 2** Linear regression between tertiles of serum uric acid and peak force (Newtons) in normoglycemic and hyperglycemic individuals. Adjusted for age, body mass index, estimated glomerular filtration rate, C-reactive protein, triglycerides, energy and protein intake, sex, race/ethnicity, educational level, annual household income, marital status, hypertension, arthritis, physical activity, smoking status, and allopurinol, metformin, and glipizide use. UA tertiles for normoglycemic individuals: tertile 1, 0.4–4.9; tertile 2, 5.0–6.1; tertile 3, 6.2–13.4 mg/dL. UA tertiles for hyperglycemic individuals: tertile 1, 1.6–4.9; tertile 2, 5.0–6.1; tertile 3, 6.2–12.5 mg/dL

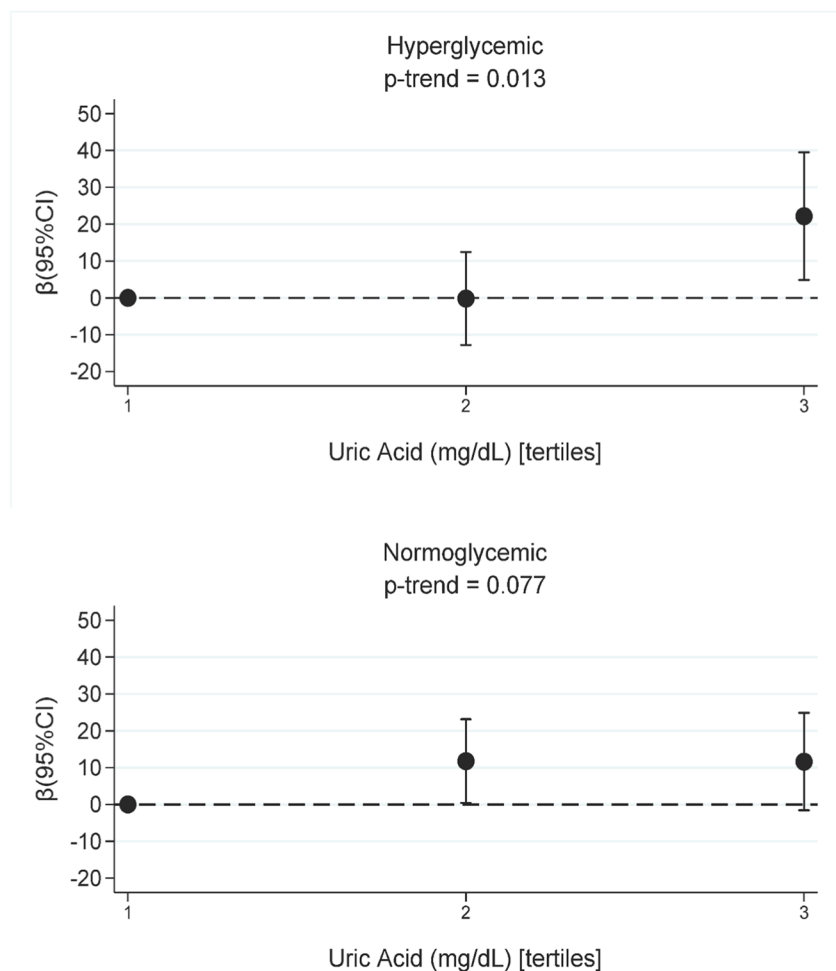


**Table 2** Linear regression analysis between continuous serum uric acid values and strength

| Model 1       | Model 2            |         |
|---------------|--------------------|---------|
|               | $\beta$ (95% CI)   | p       |
| Normoglycemic | 28.76 (22.8; 34.8) | < 0.001 |
| Hyperglycemic | 13.24 (7.9; 18.5)  | < 0.001 |

Model 1: crude analysis

Model 2: adjusted for age, body mass index, estimated glomerular filtration rate, C-reactive protein, triglycerides, energy and protein intake, sex, race/ethnicity, educational level, marital status, annual household income, hypertension, arthritis, physical activity, smoking status, and allopurinol, metformin, and glipizide use

DNA [42, 43]. Consequently, elevated oxidative stress has the potential to impact muscle mass and the activation of muscle fibers, and may also influence the excitation–contraction processes within muscle tissue, resulting in reduced muscle strength [11]. Given that hyperglycemic older adults may experience greater oxidative stress compared to older

adults with normal glycemia, these individuals may have greater protection against excess ROS when they have more antioxidants available, such as UA levels [44], consequently preserving their muscle strength. Future longitudinal studies should evaluate the effect of UA levels on muscle strength across different glycemic levels to confirm our results.

Although no study has directly examined the association of UA with strength according to glycemic levels, several studies have demonstrated that UA is positively associated with muscle strength in older adults overall [19, 21–23, 26]. For instance, our research group evaluated a similar sample of older adults from NHANES (1999–2002) and found that UA levels were positively associated with muscle strength after adjusting for various confounders, including the self-reported diagnosis of diabetes [19]. This finding partially supports our results as we observed a positive association between UA and strength in hyperglycemic older adults, but not in those with normal glycemic values. This suggests that older adults with normal glucose levels may not experience elevated oxidative stress, thus rendering UA less critical in counterbalancing excess ROS. Upon examining the characteristics

of individuals (Table 1), it becomes apparent that normoglycemic older adults lead healthier lifestyles, as evidenced by a lower prevalence of hypertension and arthritis, as well as lower BMI, triglyceride, and CRP levels. Consequently, individuals in this group appear to adopt healthier lifestyles, potentially resulting in lower oxidative stress and thus precluding an association between UA and muscle strength. However, taken together, the findings of the present study and other investigations [19, 21–23, 28] suggest that UA may play a role in muscle strength in older adults, with potentially greater significance observed in individuals experiencing higher oxidative stress, such as those with hyperglycemia.

The present study and others [19, 21–23, 28] have demonstrated that UA appears to be a protective factor for muscle strength in older adults; however, our results should be interpreted with caution as the current evidence does not definitively establish whether higher levels of UA have overall positive or negative effects on health [18]. Several studies have linked elevated UA levels to various conditions such as cardiovascular disease [45], hypertension [46], diabetes mellitus [46], and metabolic syndrome and its components [39, 47, 48]. However, it remains uncertain whether UA is increased in these situations as a protective factor or if elevated UA directly contributes to the risk of these metabolic conditions [18]. Hence, the question of whether increased UA levels should be reduced or maintained in older adults with hyperglycemia remains unanswered.

The present study has several limitations. Firstly, its cross-sectional design precludes the determination of a cause-effect relationship. In an observational investigation, there remains the possibility that the identified association may be influenced by residual confounding factors that have not been fully accounted for. Additionally, the study did not assess oxidative stress biomarkers, which could provide valuable insights into the underlying mechanisms mediating the associations between UA and strength. Furthermore, the reliance on a single 24-h dietary recall may limit the accuracy of estimating habitual dietary intake; however, this limitation may not significantly impact the results, as dietary intake was primarily used for statistical adjustment. On the other hand, the study has several strengths. The data analyzed are representative of the USA population, encompassing a substantial number of older adults (~44,559,080 older adults). Moreover, a reliable strength test, the knee extension isokinetic strength test, was employed, and glycemia was evaluated using glycosylated hemoglobin, providing a chronic assessment of hyperglycemia [49]. Additionally, adjustments for significant confounding variables were implemented in all analyses. Notably, regression analyses were conducted using both tertile categorization and continuous values, suggesting that the association between UA and muscle strength

in older adults with hyperglycemia persists regardless of the analytical approach employed.

In summary, our findings indicate a positive association between serum UA levels and muscle strength specifically in older adults with hyperglycemia, contrasting with the absence of such an association in those with normal glycemia. These results underscore the potential importance of UA levels for muscle strength, particularly among older adults experiencing heightened oxidative stress induced by hyperglycemia.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1186/s41110-024-00269-4>.

**Acknowledgements** EPO acknowledges The Brazilian National Council for Scientific and Technological Development (CNPq, Brazil, 307786/2022-6) for their support and contribution. We thank CAPES for financial support.

**Author contribution** BBS contributed to data interpretation, conducted statistical analysis, and authored the manuscript; LSL and RN conducted statistical analysis, participated in data interpretation, and contributed to manuscript revisions; PCN and FMSB were involved in dataset configuration, statistical analysis, and manuscript revisions; EPO contributed to data interpretation, manuscript writing, and manuscript revision. All authors reviewed and approved the final version of the manuscript.

**Data availability** The dataset generated and analyzed during the current study is available from the corresponding author on reasonable request.

## Declarations

**Ethical approval** NHANES data collection protocols are approved by the ethics review board of the National Center for Health Statistics.

**Consent to participate** Informed consent was obtained from all individual participants included in the study.

**Competing interests** Erick P. de Oliveira is an Associate Editor for *Nutrire* and the peer-review process for this article was independently handled by another member of the journal editorial board. The other authors declare no competing interests.

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## **6. CONCLUSÃO DA TESE**

Os resultados obtidos em ambos os estudos indicam que antioxidantes, tais como os metabólitos da cafeína e o ácido úrico, desempenham um papel crucial na preservação da força muscular, especialmente em populações onde a perda de força está intimamente associada ao estresse oxidativo. Em indivíduos idosos, por exemplo, a diminuição da força muscular, frequentemente observada com o envelhecimento, é significativamente influenciada pelo estresse oxidativo. De maneira semelhante, pessoas com hiperglicemia ou diabetes demonstram uma maior susceptibilidade a danos musculares relacionados ao estresse oxidativo. Portanto, compostos como os metabólitos da cafeína e o ácido úrico, que possuem propriedades antioxidantes e são capazes de neutralizar radicais livres, apresentam-se como estratégias promissoras para atenuar efeitos adversos.