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

ASSOCIAÇÃO DOS NÍVEIS SÉRICOS DE ÁCIDO ÚRICO COM A FORÇA MUSCULAR DE IDOSOS E COM O ÍNDICE DE MASSA MUSCULAR APENDICULAR DE INDIVÍDUOS JOVENS, MEIA-IDADE E IDOSOS PARTICIPANTES DO NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES) 1999 – 2002

PAULA CÂNDIDO NAHAS

Uberlândia/MG

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Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Faculdade de Medicina da Universidade Federal de Uberlândia, como requisito 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: Profª. Drª. Ana Elisa Madalena Rinaldi

Uberlândia/MG

2021

Dados Internacionais de Catalogação na Publicação (CIP)
Sistema de Bibliotecas da UFU, MG, Brasil.

N153a
2021

Nahas, Paula Cândido, 1992-
Associação dos níveis séricos de ácido úrico com a força muscular de idosos e com o índice de massa muscular apendicular de indivíduos jovens, meia-idade e idosos participantes do National Health and Nutrition Examination Survey (NHANES) 1999 - 2002 [recurso eletrônico] / Paula Cândido Nahas. - 2021.

Orientador: Erick Prado de Oliveira.
Coorientadora: Ana Elisa Madalena Rinaldi.
Tese (Doutorado) - Universidade Federal de Uberlândia, Programa de Pós-Graduação em Ciências da Saúde.
Disponível em: http://doi.org/10.14393/ufu.te.2021.6017
Inclui bibliografia.
Inclui ilustrações.

1. Ciências médicas. 2. Nutrição. I. Oliveira, Erick Prado de, 1983-, (Orient.). II. Rinaldi, Ana Elisa Madalena, 1982-, (Coorient.). III. Universidade Federal de Uberlândia. Programa de Pós-Graduação em Ciências da Saúde. IV. Título.

CDU: 61

Rejâne Maria da Silva – CRB6/1925
Bibliotecária

UNIVERSIDADE FEDERAL DE UBERLÂNDIA
Coordenação do Programa de Pós-Graduação em Ciências da Saúde
Av. Pará, 1720, Bloco 2H, Sala 09 - Bairro Umuarama, Uberlândia-MG, CEP 38400-902
Telefone: 34 3225-8628 - www.ppcsa.famed.ufu.br - copme@ufu.br

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Programa de Pós-Graduação em:	Ciências da Saúde				
Defesa de:	Tese de Doutorado Nº 001/PPCSA				
Data:	23.02.2021	Hora de início:	13:30h	Hora de encerramento:	16:30h
Matrícula do Discente:	11713CSD020				
Nome do Discente:	Paula Cândido Nahas				
Título do Trabalho:	Associação dos níveis séricos de ácido úrico com força muscular e Índice de Massa Muscular Apendicular de indivíduos jovens, meia-idade e idosos participantes do National Health and Nutrition Examination Survey (NHANES) 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:	Intervenções nutricionais na Sarcopenia				

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

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Referência: Processo nº 23117.009081/2021-34 SEI nº 2568959

FOLHA DE APROVAÇÃO

Paula Cândido Nahas

Associação dos níveis séricos de ácido úrico com a força muscular de idosos e com o Índice de Massa Muscular apendicular de indivíduos jovens, meia-idade e idosos participantes do National Health and Nutrition Examination Survey (NHANES) 1999 – 2002.

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

Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Faculdade de Medicina da Universidade Federal de Uberlândia, como requisito 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: Profª. Drª. Ana Elisa Madalena Rinaldi

Banca examinadora

Titular (membro externo) Prof. Dr. Fábio Lera Orsatti

Instituição: Universidade Federal do Triângulo Mineiro (UFTM)

Titular (membro externo) Prof. Dr. Gustavo Duarte Pimentel

Instituição: Universidade Federal de Goiás (UFG)

Titular (membro interno): Profª. Drª. Luciana Saraiva da Silva

Instituição: Universidade Federal de Uberlândia (UFU)

Titular (membro interno): Profª. Drª. Yara Cristina de Paiva Maia

Instituição: Universidade Federal de Uberlândia (UFU)

DEDICATÓRIA

A Deus, pelas bênçãos de cada dia, pelo suporte em cada novo desafio, pela força incessante nos dias de luta e por me carregar em seus braços durante minha jornada de vida.

Aos meus queridos pais, Verondina e William, que doaram incondicionalmente seu sangue e suor em forma de amor e trabalho por mim, despertando a sede contínua pelo conhecimento.

Ao meu amor, Guilherme, meu espelho, que me ajudou antes e durante esse percurso, compreendendo-me e principalmente ensinando-me valores profissionais e pessoais.

AGRADECIMENTOS

Agradeço à Deus, pois somente Ele soube o quão árduo, mas também satisfatório foi percorrer este caminho; estudando, trabalhando, sendo filha, namorada e amiga. Agradeço as bênçãos derramadas a cada novo desafio e incerteza, por ter me guiado e suportado para conseguir fazer o melhor de mim com grande satisfação, me tornando docente e pesquisadora.

Aos meus pais, Verondina Maria da Paixão Felício e William David Nahas, pelo apoio incessante e amor, principalmente nos dias mais difíceis.

À Guilherme Abreu de Paula, por me presentear com seu amor e estar ao meu lado independentemente da situação.

Ao meu querido orientador, Prof. Dr. Erick Prado de Oliveira, por permitir minha presença em seu grupo de pesquisa desde 2013 e posteriormente pela orientação de trabalho de mestrado e agora doutorado; agradeço pela paciência e por me ensinar valores e excelência profissional, sendo um facilitador desta jornada.

A Profª. Drª. Ana Elisa Madalena Rinaldi e Profª. Drª. Catarina Machado Azeredo, professoras de referência e que pude contar desde a época da minha graduação, por acompanharem de perto meu desenvolvimento desde então; agradeço a parceria, paciência, dedicação e auxílio em todas as partes deste trabalho.

À minha querida amiga de longa data, Nayara Bernardes da Cunha, grande companheira desde a graduação, nutricionista, pessoa que me espelho no aspecto profissional, mas principalmente no pessoal; agradeço a amizade fiel, ombro amigo e conselhos neste percurso.

Ao meu querido amigo, Alisson Nunes Silva, uma grande pessoa que tive o privilégio de ter ao meu lado desde a graduação, mas acima de tudo um amigo para todas as horas; agradeço por ser tão presente em minha vida em todas as ocasiões.

Às minhas parceiras, Luana Thomazetto Rossato e Flavia Moure Simões De Branco, agradeço o compartilhamento de conhecimentos e por serem companheiras durante esse tempo.

Aos membros do Laboratório de Nutrição, Exercício e Saúde (LaNES) e envolvidos, pelos momentos de descontração e pelo suporte acadêmico.

À atual coordenadora Yara Paiva Maia e as secretárias do Programa de Pós-Graduação em Ciências da Saúde, Gisele e Viviane, pelo apoio durante o desenvolvimento deste trabalho.

Por fim, aos meus familiares e amigos de longa data que acompanharam meu crescimento e amadurecimento, principalmente minhas tias Ângela, Tânia e minha madrinha Telma, por me tratar como filha nesses 11 anos de estudo sem a presença física dos meus pais.

“A ciência é cometida por erros, mas por erros úteis a serem cometidos, porque pouco a pouco, eles levam à verdade."

Julio Verne

RESUMO

Introdução: O envelhecimento promove redução de força e massa muscular, sendo o estresse oxidativo uma das possíveis causas. Por outro lado, o ácido úrico (AU) é um importante antioxidante do plasma que parece estar associado a força e a massa muscular, mas essas evidências ainda são limitadas. **Objetivo:** Associar o AU sérico com a força muscular de idosos e, posteriormente com o Índice de Massa Muscular Apendicular (IMMA) de indivíduos jovens, meia idade e idosos. **Metodologia:** Estudos transversais (estudo 1: n = 2361 indivíduos - 50 a 85 anos; estudo 2: n = 7149 indivíduos - 20 a 85 anos), participantes do National Health and Nutrition Examination Survey (NHANES) 1999–2000 e 2001–2002. O AU foi obtido pelo método colorimétrico; a força muscular foi aferida pelo teste isocinético de extensão do joelho; e a composição corporal foi medida por absortometria de raio-X de dupla energia, sendo que o IMMA foi calculado usando a massa magra apendicular dividida pelo quadrado da altura. Análise de regressão linear foi realizada para observar possível associação entre quintis de AU com a força muscular e quartis de AU com o IMMA, ajustado por possíveis variáveis de confusão. **Resultados:** O AU foi positivamente associado com a força muscular na amostra total (p=0,007), homens (p=0,044) e mulheres (p=0,016). Além disso, o AU também se associou positivamente com o IMMA em homens idosos (p=0,009), mas não em indivíduos jovens e de meia idade. **Conclusão:** O AU sérico está positivamente associado com a força em homens e mulheres idosos, e também positivamente associado com o IMMA em homens idosos.

Palavras-chave: Ácido Úrico, Força Muscular, Massa Muscular, Envelhecimento, Estresse Oxidativo.

ABSTRACT

Background: Aging promotes muscle strength and muscle mass loss, and oxidative stress can be one of the possible causes. On the other hand, uric acid (UA) is an important plasma antioxidant that appears to be associated with strength and muscle mass, but this evidence is still limited. **Aim:** To associate serum UA with muscle strength in older adults and, later, with the Appendicular Muscle Mass Index (AMMI) in young, middle-aged and older adults. **Methods:** Cross-sectional studies (study 1: n = 2361 individuals - 50 to 85 years; study 2: n = 7149 individuals - 20 to 85 years), from the National Health and Nutrition Examination Survey (NHANES) 1999–2000 and 2001–2002. UA was obtained by the colorimetric method; muscle strength was measured by the isokinetic knee extension test; and body composition was measured by Dual Energy X-ray absorptiometry, and AMMI was calculated using appendicular lean mass divided by the square of height. Linear regression analysis was performed to observe a possible association between UA quintiles with muscle strength and UA quartiles with AMMI, adjusted for potential confounders. **Results:** UA was positively associated with muscle strength in the total sample ($p=0.007$), men ($p=0.044$) and women ($p=0.016$). In addition, UA was also positively associated with AMMI in older men ($p=0.009$), but not for young and middle-aged individuals. **Conclusion:** Serum UA is positively associated with muscle strength in older men and women, and also positively associated with AMMI in older men.

Keywords: Uric Acid, Muscle Strength, Muscle Mass, Aging, Oxidative Stress.

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Artigo 1: "Serum uric acid is positively associated with muscle strength in older men and women: Findings from NHANES 1999 – 2002."

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LISTA DE ABREVIATURAS E SIGLAS

Fundamentação teórica

AU	Ácido úrico
EROs	Espécies reativas de oxigênio
IMMA	Índice de Massa Muscular Apendicular
NHANES	National Health and Nutrition Examination Survey

Artigos

UA	Uric Acid
NHANES	National Health and Nutrition Examination Survey
NCHS ERB	National Center for Health Statistics Research Ethics Review Board
CDC	Centers for Disease Control and Prevention
eGFR	Glomerular Filtration Rate
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
BMI	Body Mass Index
DXA	Dual-energy X-ray Absorptiometry
AMMI	Appendicular Muscle Mass Index
MMI	Muscle Mass Index
USDA	U.S. Department of Agriculture
USA	United States of America
CRP	C-Reactive Protein
CI	Confident Intervals
y	years
kcal	calorie
g	gram
kg	kilogram

mg	milligram
ml	milliliter
min	minute
m^2	square meter
dl	deciliter
N	Newtons

SUMÁRIO

1 INTRODUÇÃO

O envelhecimento promove redução de força muscular (ZAMMIT; ROBITAILLE; PICCININ; MUNIZ-TERRERA *et al.*, 2019) e massa muscular (KELLER; ENGELHARDT, 2013), as quais são associadas com desfechos negativos, tais como, maior dependência para realização das atividades de vida diária (CRUZ-JENTOFT; LANDI; SCHNEIDER; ZUNIGA *et al.*, 2014), quedas (LANDI; LIPEROTI; RUSSO; GIOVANNINI *et al.*, 2012), fraturas (FIELDING; VELLAS; EVANS; BHASIN *et al.*, 2011) e morte (LI; XIA; ZHANG; GATHIRUA-MWANGI *et al.*, 2018; LOPRINZI, 2016). O acúmulo de espécies reativas de oxigênio (EROs) parece ser uma das causas, uma vez que o estresse oxidativo interfere negativamente na fibra muscular, gerando impactos qualitativos e quantitativos (BAUMANN; KWAK; LIU; THOMPSON, 2016; FULLE; PROTASI; DI TANO; PIETRANGELO *et al.*, 2004). Neste sentido, substâncias antioxidantes pode influenciar positivamente a força e massa muscular.

O ácido úrico (AU) é o componente final do metabolism das purinas, responsável pela maior parte do poder antioxidante do plasma (ALVAREZ-LARIO; MACARRÓN-VICENTE, 2011; DE OLIVEIRA; BURINI, 2012). Apesar de o AU estar associado com diversos desfechos negativos à saúde (ROUMELIOTIS; ROUMELIOTIS; DOUNOUSI; ELEFTHERIADIS *et al.*, 2019; ZUO; LIU; JIANG; MAO *et al.*, 2016), existe um número crescente de evidências demonstrando possível efeito benéfico na força muscular (GARCÍA-ESQUINAS; RODRÍGUEZ-ARTALEJO, 2018; KAWAMOTO; NINOMIYA; KASAI; KUSUNOKI *et al.*, 2016; LEE; HONG; PARK; KANG, 2019; MACCHI; MOLINO-LOVA; POLCARO; GUARDUCCI *et al.*, 2008; MOLINO-LOVA; SOFI; PASQUINI; VANNETTI *et al.*, 2017; NAHAS; ROSSATO; DE BRANCO; AZEREDO *et al.*, 2021; WU; ZHANG; PANG; JIANG *et al.*, 2013) e na massa muscular (DONG; TIAN; HE; WANG *et al.*, 2016; XU; ZHANG; CHEN; XU *et al.*, 2018).

No entanto, é possível observar que tais evidências ainda são limitadas, uma vez que a maioria dos estudos não avaliaram homens e mulheres separadamente, já que fisiologicamente os mesmos apresentam diferenças nas concentrações de AU, de força e massa muscular (CRUZ-JENTOFT; BAHAT; BAUER; BOIRIE; BRUYÈRE *et al.*, 2019; JOHNSON; KANG; FEIG; KIVLIGHN *et al.*, 2003). Além disso, nenhum dos estudos que avaliaram a associação entre AU e massa muscular realizaram análises em relação à idade.

Portanto, o objetivo do presente estudo foi investigar se o AU sérico é associado com a força muscular em idosos; e com o Índice de Massa Muscular Apendicular (IMMA) em

indivíduos jovens, de meia-idade e idosos, homens e mulheres, participantes do National Health and Nutrition Examination Survey (NHANES) 1999-2000 and 2001-2002. O NHANES é um programa composto por entrevistas e diversos testes físicos em uma amostra representativa da população não institucionalizada dos Estados Unidos, usando um projeto de amostragem de probabilidade complexa, estratificada e de vários estágios, tendo como objetivo avaliar a saúde e o estado nutricional dos indivíduos. A hipótese deste estudo é que o AU sérico é positivamente associado com a força muscular e o IMMA em idosos.

1.1 Considerações iniciais

Esta tese foi produzida de acordo com as normas instituídas pelo Programa de Pós Graduação e Pesquisa em Ciências Saúde da Faculdade de Medicina da Universidade Federal de Uberlândia. A formatação segue o modelo alternativo de apresentação, sendo que os resultados do trabalho devem ser apresentados em formato de 2 artigos científicos.

Inicialmente, a tese foi organizada nos seguintes tópicos: **Introdução** geral que contempla os temas trabalhados neste período; **Fundamentação Teórica** composta por uma revisão da literatura; **Objetivos** em que são expostos os propósitos do estudo; os **Dois Artigos Científicos**, que são os resultados do trabalho; e por fim, **Considerações finais e Perspectivas**, que discorre sobre a síntese dos principais resultados do estudo, bem como as expectativas para estudos futuros.

O primeiro artigo, intitulado ***"Serum uric acid is positively associated with muscle strength in older men and women: Findings from NHANES 1999 – 2002",*** teve como objetivo investigar se as concentrações séricas de AU se associam com a força muscular de indivíduos idosos participantes do NHANES. Este artigo foi publicado na revista científica *Clinical Nutrition* (Fator de impacto atual = 6.77).

O segundo artigo, intitulado ***"Association between uric acid and appendicular muscle mass index in young, middle-aged and older adults: Findings from NHANES 1999 – 2002"*** teve como objetivo analisar possível associação entre as concentrações séricas de AU e o IMMA de indivíduos jovens, de meia-idade e idosos, também participantes do NHANES. Este artigo será submetido na revista científica *Clinical Nutrition* (Fator de impacto atual = 6.77).

2 FUNDAMENTAÇÃO TEÓRICA

2.1 Ácido úrico

2.1.1 Definições e propriedades

O ácido úrico (AU) é o produto final do metabolismo de purinas endógenas e dietéticas em humanos e outros primatas (RICHETTE; BARDIN, 2010; SO; THORENS, 2010). Durante o processo evolutivo, tais espécies apresentaram diversas mutações no gene que expressa a enzima uricase, tornando-a não funcional (WU; MUZNY; LEE; CASKEY, 1992). Portanto, humanos e primatas apresentam maiores níveis de concentração de AU e urato comparado à mamíferos não primatas, peixes e anfíbios, uma vez que o AU não é convertido em alantoína, pela perda da atividade da enzima uricase responsável por tal conversão (HAYASHI; FUJIWARA; NOGUCHI, 2000). Isso sugere que humanos apresentam a habilidade de manter as concentrações aumentadas de AU, sendo resultado do processo de seleção natural associado com algumas vantagens biológicas (AMES; CATHCART; SCHWIERS; HOCHSTEIN, 1981).

O principal sítio de produção endógena do AU é o fígado, sendo excretado pelos rins (~70%) e intestino delgado (ALVAREZ-LARIO; MACARRÓN-VICENTE, 2011). Já na década de 70 foi descrito que o AU era capaz de eliminar espécies reativas de oxigênio (EROs) e de proteger a membrana de eritrócitos da oxidação lipídica (KELLOGG; FRIDOVICH, 1977), e isso foi mais bem entendido na década de 80 (AMES; CATHCART; SCHWIERS; HOCHSTEIN, 1981). Atualmente, é conhecido que o AU é um componente orgânico com imporantes propriedades antioxidantes, sendo responsável por 2/3 da capacidade antioxidante do plasma (DE OLIVEIRA; BURINI, 2012).

2.1.2 Hiperuricemia

A regulação do AU sérico é complexa, uma vez que é baseada principalmente em sua produção endógena, consumo dietético e excreção renal (DOHERTY, 2009; VITART; RUDAN; HAYWARD; GRAY *et al.*, 2008). Em meados do século XX, o papel da produção excessiva de AU juntamente com sua excreção prejudicada foi relatada, o que culmina na patogênese da hiperuricemia (RICHETTE; BARDIN, 2010), definida como AU > 7mg/dL para homens e > 6 mg/dL para mulheres (JOHNSON; KANG; FEIG; KIVLIGHN *et al.*, 2003). O resultado da hiperuricemia é, na minoria dos casos, a deposição de critais de urato dentro e ao redor das articulações. Portanto, a hiperuricemia é o principal fator de risco para o desenvolvimento da gota (SINGH; REDDY; KUNDUKULAM, 2011), apesar de a minoria dos pacientes com hiperuricemia desenvolvem gota (DOHERTY, 2009; PEREZ-RUIZ, 2009).

Além da gota, as concentrações elevadas de AU são comumente associadas com diversas doenças (SO; THORENS, 2010). Atualmente, é conhecido que a hiperuricemia pode ser fator de risco para desenvolvimento de disfunção renal (LI; YANG; ZHAO; ZENG *et al.*, 2014; XU; HU; SONG; CHEN *et al.*, 2017), doenças cardiovasculares (GRAYSON; KIM; LAVALLEY; CHOI, 2011; ZUO; LIU; JIANG; MAO *et al.*, 2016) e síndrome metabólica (KING; LANASPA; JENSEN; TOLAN *et al.*, 2018; LI; HSIEH; CHANG, 2013). Um dos mecanismos que explica a associação entre hiperuricemia e o desenvolvimento destas doenças e condições descritas acima é o dano oxidativo causado pelo acúmulo excessivo de EROs (GLANTZOUNIS; TSIMOYIANNIS; KAPPAS; GALARIS, 2005). Isso porque, em concentrações acima do ideal, o AU parece apresentar características pró-oxidantes (SAUTIN; JOHNSON, 2008), sendo o oposto da sua função normal. Portanto, o estresse oxidativo pode apresentar um papel importante neste contexto.

Por outro lado, existe um crescente número de estudos que apresentam associações positivas entre o AU e a força muscular (GARCÍA-ESQUINAS; RODRÍGUEZ-ARTALEJO, 2018; KAWAMOTO; NINOMIYA; KASAI; KUSUNOKI *et al.*, 2016; LEE; HONG; PARK; KANG, 2019; MACCHI; MOLINO-LOVA; POLCARO; GUARDUCCI *et al.*, 2008; MOLINO-LOVA; SOFI; PASQUINI; VANNETTI *et al.*, 2017; NAHAS; ROSSATO; DE BRANCO; AZEREDO *et al.*, 2021; WU; ZHANG; PANG; JIANG *et al.*, 2013) e a massa muscular (DONG; TIAN; HE; WANG *et al.*, 2016; XU; ZHANG; CHEN; XU *et al.*, 2018), os quais demonstram que pode existir um possível papel protetor da hiperuricemia para a qualidade e a quantidade muscular. A explicação mais plausível para as associações de proteção é o papel antioxidante do AU, uma vez que o mesmo pode neutralizer as EROs, o que pode reduzir o estresse oxidativo, uma das causas da redução de força e massa muscular (FOUGERE; VAN KAN; VELLAS; CESARI, 2018).

2.2 Estresse oxidativo

2.2.1 Definição

O termo estresse oxidativo refere à desordem no equilíbrio dos sistemas pró-oxidante e antioxidantes (SIES, 1985). Os efeitos prejudiciais das EROs são evidentes quando a sua taxa de produção aumenta e a capacidade de defesa das células reduz (VERTUANI; ANGUSTI; MANFREDINI, 2004). Substâncias com propriedades antioxidantes são conhecidas como "varredores" de EROs, sendo um substrato oxidável e capaz de proteger contra danos oxidativos, agindo como um doador de elétrons (HALLIWELL, 1999). Porém, o aumento

excessivo das concentrações de substâncias antioxidantes apresenta propriedades pró-oxidantes, o que facilita a injúria celular (RICHETTE; BARDIN, 2010).

Portanto, em relação ao AU e demais antioxidantes, o paradoxo é que a mesma substância, em diferentes concentrações, pode apresentar importante papel protetor, mas também ações prejudiciais (SAUTIN; JOHNSON, 2008). Apesar do AU ser associado com diversas doenças e condições (SO; THORENS, 2010), um grande número de estudos tem demonstrado que sua importante ação como antioxidante pode ser viável no combate ao estresse oxidativo (GLANTZOUNIS; TSIMOYIANNIS; KAPPAS; GALARIS, 2005), desenvolvendo importante papel também na força muscular (GARCÍA-ESQUINAS; RODRÍGUEZ-ARTALEJO, 2018; KAWAMOTO; NINOMIYA; KASAI; KUSUNOKI *et al.*, 2016; LEE; HONG; PARK; KANG, 2019; MACCHI; MOLINO-LOVA; POLCARO; GUARDUCCI *et al.*, 2008; MOLINO-LOVA; SOFI; PASQUINI; VANNETTI *et al.*, 2017; WU; ZHANG; PANG; JIANG *et al.*, 2013) e na massa muscular (DONG; TIAN; HE; WANG *et al.*, 2016; XU; ZHANG; CHEN; XU *et al.*, 2018), uma vez que um dos mecanismos que explicam essas condições é o acúmulo de EROs (BAUMANN; KWAK; LIU; THOMPSON, 2016; FULLE; PROTASI; DI TANO; PIETRANGELO *et al.*, 2004).

2.2.2 Estresse oxidativo, envelhecimento e saúde muscular

Sabe-se que em diversas situações e doenças o estresse oxidativo tem efeitos na explicação dos mecanismos molecurares, sendo o envelhecimento um deles (JUNQUEIRA; BARROS; CHAN; RODRIGUES *et al.*, 2004). O envelhecimento promove acúmulo de EROs, bem como redução do poder antioxidante (FULLE; PROTASI; DI TANO; PIETRANGELO *et al.*, 2004). Portanto, desfechos musculares (qualitativos e quantitativos) podem também ser observados devido ao envelhecimento, como redução do tamanho das fibras musculares e sua ativação/contração (FULLE; PROTASI; DI TANO; PIETRANGELO *et al.*, 2004), bem como redução da força muscular (ZAMMIT; ROBITAILLE; PICCININ; MUNIZ-TERRERA *et al.*, 2019). Portanto, teoricamente, substâncias com propriedades antioxidantes podem apresentar efeitos de proteção da força muscular devido à redução no estresse oxidativo (FOUGERE; VAN KAN; VELLAS; CESARI, 2018).

2.3 Ácido úrico e força muscular

2.3.1 Estresse oxidativo e redução de força muscular

A redução de força muscular devido ao envelhecimento é associado com desfechos negativos à saúde, tais como maior risco de quedas (WANG; MA; WANG; HAN *et al.*, 2016),

fraturas (FIELDING; VELLAS; EVANS; BHASIN *et al.*, 2011; UUSI-RASI; KARINKANTA; TOKOLA; KANNUS *et al.*, 2019), hospitalização (ZHANG; ZHANG; WANG; TAO *et al.*, 2018) e morte (GARCÍA-HERMOSO; CAVERO-REDONDO; RAMÍREZ-VÉLEZ; RUIZ *et al.*, 2018; LI; XIA; ZHANG; GATHIRUA-MWANGI *et al.*, 2018). Uma vez que o envelhecimento é uma das causas da redução de força muscular (ZAMMIT; ROBITAILLE; PICCININ; MUNIZ-TERRERA *et al.*, 2019), e isto é principalmente devido ao estresse oxidativo (BAUMANN; KWAK; LIU; THOMPSON, 2016; FULLE; PROTASI; DI TANO; PIETRANGELO *et al.*, 2004), substâncias antioxidantes podem exercer um papel importante neste contexto (FOUGERE; VAN KAN; VELLAS; CESARI, 2018).

2.3.2 Propriedades antioxidantes do ácido úrico e força muscular

Diversos estudos tem demonstrado associações positivas entre a força muscular e o AU em diferentes populações, principalmente em indivíduos idosos. Até onde sabemos, o primeiro estudo que associou o AU com a força muscular foi conduzido por Macchi et al (2008); o único estudo que até então avaliou a força muscular pelo torque de extensão do joelho e também pela força de preensão manual. Os autores avaliaram idosos italianos e concluiram que os níveis séricos de AU foram positivamente associados com ambos testes de força (MACCHI; MOLINO-LOVA; POLCARO; GUARDUCCI *et al.*, 2008). Molino-Lova et al (2017) também avaliaram idosos italianos nonagenários, demonstrando uma associação positiva entre o AU e a força de preensão manual em ambos os sexos (MOLINO-LOVA; SOFI; PASQUINI; VANNETTI *et al.*, 2017). Em 2013, Wu et al avaliaram idosos chineses (50 - 74 years) e observaram associação positiva entre o AU e a força de preensão manual, bem como com a função cognitiva (WU; ZHANG; PANG; JIANG *et al.*, 2013). Em sequência, Kawamoto et al (2016) avaliaram idosos japoneses (60 - 90 years) e encontraram associação positiva entre o AU e a força de preensão manual somente para mulheres, e não para homens. Os autores explicaram este resultado pois possivelmente homens consumiam maior quantidade de álcool, bem como apresentavam maior uso de diuréticos, além da influência de hormônios sexuais (KAWAMOTO; NINOMIYA; KASAI; KUSUNOKI *et al.*, 2016).

Embora os estudos que avaliaram idosos tenham mostrado que o AU está positivamente associado à força, quando observada essa relação em outras faixas etárias não parece ser a mesma (GARCÍA-ESQUINAS; RODRÍGUEZ-ARTALEJO, 2018; HUANG; NIU; KOBAYASHI; GUAN *et al.*, 2013; LEE; HONG; PARK; KANG, 2019). García-Esquinas (2017) conduziram um estudo com uma amostra representative de americanos participantes do

National Health and Nutrition Examination Survey (NHANES 2011-2012), e foi encontrada associação inversa entre o AU e a força em pessoas com 40 anos ou menos, sem associação na faixa de idade entre 40 – 60 anos, e associação positiva para idosos (GARCÍA-ESQUINAS; RODRÍGUEZ-ARTALEJO, 2018). Mais recentemente, Lee et al (2019) também avaliaram faixas de idades, encontrando associação positiva entre o AU e a força de preensão manual apenas em idosos (LEE; HONG; PARK; KANG, 2019). Finalmente, Huang et al (2013) demonstraram um associação em forma de "J-invertido" entre o AU e a força de homens adultos japoneses (HUANG; NIU; KOBAYASHI; GUAN *et al.*, 2013).

Uma das limitações frequentes na maioria dos estudos é a medida da força pelo método de força de preensão manual (GARCÍA-ESQUINAS; RODRÍGUEZ-ARTALEJO, 2018; KAWAMOTO; NINOMIYA; KASAI; KUSUNOKI *et al.*, 2016; LEE; HONG; PARK; KANG, 2019; MOLINO-LOVA; SOFI; PASQUINI; VANNETTI *et al.*, 2017; WU; ZHANG; PANG; JIANG *et al.*, 2013), e não pelo método de torque de extensão do joelho, o qual parece ser melhor preditor (MARTIEN; DELECLUSE; BOEN; SEGHERS *et al.*, 2015). Além disso, a população estudada até o momento tem sido principalmente idosos, e ainda não é possível garantir os mesmos resultados na população jovem. Finalmente, uma vez que homens e mulheres apresentam diferentes níveis de AU e de força, observar tais variáveis por sexo é importante. Somente poucos estudos realizaram a associação entre o AU e a força muscular separadamente por sexo (KAWAMOTO; NINOMIYA; KASAI; KUSUNOKI *et al.*, 2016; MOLINO-LOVA; SOFI; PASQUINI; VANNETTI *et al.*, 2017); enquanto Kawamoto et al (2016) demonstraram associação positiva somente para mulheres, Molino-Lova et al (2017) encontraram associação para ambos sexos. Portanto, até o momento, esta evidência parece ser limitada.

2.4 Ácido úrico e massa muscular

2.4.1 Estresse oxidativo e redução de massa muscular

A massa muscular apresenta, devido ao envelhecimento, mudanças marcantes em relação à sua quantidade e função, que impactam na saúde dos indivíduos (AVERSA; ZHANG; FIELDING; LANZA *et al.*, 2019). É possível observar redução e atrofia de fibras muscular, aumento na gordura intramuscular, tecido fibroso e denervação ao comparar o músculo jovem com um envelhecido, resultando em perda de massa muscular e força muscular relacionada à idade (LEXELL; TAYLOR; SJÖSTRÖM, 1988).

A redução de massa muscular foi chamada de sarcopenia inicialmente por Rosenberg (ROSENBERG, 1997). Porém, a diretriz mais recente do Grupo de Trabalho Europeu sobre

Sarcopenia em Pessoas Idosas (CRUZ-JENTOFT; BAHAT; BAUER; BOIRIE; BRUYERE *et al.*, 2019) utiliza a baixa força muscular como componente primário para o diagnóstico de sarcopenia, pois é reconhecido que a força é melhor do que a massa muscular na predição de resultados adversos (LEONG; TEO; RANGARAJAN; LOPEZ-JARAMILLO *et al.*, 2015). No entanto, a quantidade de massa muscular é ainda importante para que o diagnóstico de sarcopenia seja confirmado, após a observação de baixa força muscular (CRUZ-JENTOFT; BAHAT; BAUER; BOIRIE; BRUYÈRE *et al.*, 2019), e está relacionado à resultados negativos. A redução de massa muscular é também associada com aumento do risco de quedas (LANDI; LIPEROTI; RUSSO; GIOVANNINI *et al.*, 2012), dificuldade na realização das atividades de vida diária (CRUZ-JENTOFT; LANDI; SCHNEIDER; ZUNIGA *et al.*, 2014) e morte (LI; XIA; ZHANG; GATHIRUA-MWANGI *et al.*, 2018).

Bem como a redução de força muscular, uma das possíveis causas da perda de massa muscular é o acúmulo de EROs, o qual promove dano tecidual (FULLE; PROTASI; DI TANO; PIETRANGELO *et al.*, 2004). Tal acúmulo ocorre porque, com o envelhecimento, acontecem mudanças nos sistemas antioxidantes, e o músculo é incapaz de neutralizar altos níveis de EROs, culminando em estresse oxidativo (BAUMANN; KWAK; LIU; THOMPSON, 2016). Desta forma, substâncias antioxidantes, como o AU, pode desenvolver um papel importante na redução de massa muscular devido ao envelhecimento (FOUGERE; VAN KAN; VELLAS; CESARI, 2018).

2.4.2 Propriedades antioxidantes do AU e massa muscular

Até o momento, existem poucos estudos na literatura que associaram a massa muscular com o AU. Dong et al (2016) avaliaram 3079 indivíduos chineses de meia-idade e idosos (40 – 75 years) e observaram uma associação entre o AU e a massa muscular apendicular (DONG; TIAN; HE; WANG *et al.*, 2016). Além disso, Xu et al (2018) avaliaram idosos chineses pacientes ambulatoriais em um hospital universitário. Os indivíduos tiveram a massa magra avaliada por densitometria por emissão de raios X de dupla energia e os resultados demonstraram associação positiva entre AU e massa magra (XU; ZHANG; CHEN; XU *et al.*, 2018). Porém, no estudo conduzido por Beavers et al (2009), o qual avaliou uma grande amostra de americanos com idade > 40 anos participantes do NHANES III (1988-1994), foi demonstrado uma associação entre os maiores níveis de AU com menor quantidade de massa muscular (BEAVERS; BEAVERS; SERRA; BOWDEN *et al.*, 2009). Com base nas poucas

evidências até o momento, os resultados da associação entre massa muscular e AU parecem ser limitados e controversos.

2.5 National Health and Nutrition Examination Survey

A amostra deste estudo foi obtida a partir do National Health and Nutrition Examination Survey (NHANES), o qual é o maior programa do National Center for Health Statistics (NCHS). Este programa é composto por entrevistas e exames físicos dos participantes, tendo como objetivo avaliar a saúde e o estado nutricional de adultos e crianças de uma amostra representativa da população não institucionalizada dos Estados Unidos, usando um projeto de amostragem de probabilidade complexa, estratificada e de vários estágios. A primeira etapa consiste na seleção das unidades primárias de amostragem por probabilidade proporcional. No estágio 2, as unidades primárias de amostragem são divididas em segmentos (por exemplo, quarteirões), que também são selecionados por probabilidade. A etapa 3 consiste no sorteio dos domicílios e, por fim, na etapa 4, a seleção probabilística dos indivíduos dentro da casa previamente selecionada (CDC, 2019).

O NHANES teve início na década de 60 e partir de 1999 se tornou um programa contínuo, o qual é realizado bienalmente, cujo foco abrange inúmeras variáveis demográficas, socioeconômicas, dietéticas e relacionadas à saúde, visando atender às necessidades emergentes. A amostra do NHANES é selecionada para representar a população dos Estados Unidos de todas as idades, inclusive idosos. Sabe-se que os Estados Unidos apresentaram um rápido crescimento do número de idosos nos últimos 100 anos, e, frente as necessidades de cuidados de saúde relacionadas ao envelhecimento, o NHANES apresenta papel fundamental no aumento o conhecimento do estado de saúde dos americanos mais velhos. Em geral, quanto mais velho o indivíduo, mais extenso é o exame (CDC, 2019).

O NHANES foi projetado para facilitar a realização das pesquisas e incentivar a participação da população, sendo que as entrevistas de saúde são realizadas nas casas dos participantes e as avaliações de saúde são realizadas em centros móveis, os quais viajam para todos os locais do país. Um sistema avançado de computadores auxilia a coleta e processa todos os dados, praticamente eliminando a necessidade de formulários em papel e operações manuais. As informações do NHANES são disponibilizadas através vários documentos, os quais são disponíveis em publicações no próprio site do programa e em artigos em revistas científicas. Os dados são publicamente disponibilizados na internet em todo o mundo (CDC, 2019).

Para o presente estudo foram selecionados os biênios 1999-2000 e 2001-2002, os quais foram analisados de forma conjunta.

3 OBJETIVOS

3.1 Objetivo Geral

Associar o ácido úrico sérico com a força muscular de idosos e com o Índice de Massa Muscular Apendicular (IMMA) de indivíduos jovens, meia idade e idosos participantes do National Health and Nutrition Examination Survey (NHANES) 1999-2000 e 2001-2002.

3.2 Objetivos Específicos

- Avaliar as características demográficas, condições de saúde e comportamento dos indivíduos avaliados;
- Avaliar a antropometria e composição corporal, força, parâmetros bioquímicos e dietéticos dos participantes dos estudos.

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4 ARTIGOS CIENTÍFICOS

Artigo 1:

"Serum uric acid is positively associated with muscle strength in older men and women: Findings from NHANES 1999 – 2002."

Artigo 2:

"Association between uric acid and appendicular muscle mass index in young, middle-aged and older adults: Findings from NHANES 1999 – 2002."

Artigo 1

Original Article

Serum uric acid is positively associated with muscle strength in older men and women: Findings from NHANES 1999 – 2002

Paula C. Nahas [1], Luana T. Rossato [1], Flávia M.S. de Branco [1], Catarina M. Azeredo [2], Ana Elisa M. Rinaldi [2], Erick P. de Oliveira [1*]

[1] Laboratory of Nutrition, Exercise and Health (LaNES), School of Medicine, Federal University of Uberlandia (UFU), Uberlandia, Minas Gerais, Brazil.

[2] School of Medicine, Federal University of Uberlandia (UFU), Uberlandia, Minas Gerais, Brazil.

* Corresponding author. Federal University of Uberlandia, School of Medicine, Av. Para, 1.720 Bloco 2U - Sala 20, Campus Umuarama, Umuarama, 38400902, Uberlandia, MG, Brazil. Fax: +55 34 32328620.
e-mail address: erick_po@yahoo.com.br, erickdeoliveira@ufu.br

ABSTRACT

Background: One of the causes of strength loss in older adults is the increased oxidative stress; thus, substances with antioxidants properties may have protective effects on muscle strength. Uric acid (UA) is an important antioxidant and it seems to be positively associated with muscle strength in older adults; however, the current evidence is still limited.

Aim: To investigate whether serum UA is associated with muscle strength in older men and women.

Methods: A cross-sectional study was performed evaluating older adults aged from 50 to 85 years, from National Health and Nutrition Examination Survey (NHANES) 1999-2000 and 2001-2002. A total of 2361 individuals (1256 men and 1105 women) were evaluated. The peak isokinetic knee extensor strength was assessed by kinetic communicator isokinetic dynamometer; while UA levels were measured by colorimetric method. Linear regression analyses were performed to estimate the coefficients and 95% confident intervals for muscle strength by quintiles of UA levels, adjusted for potential confounders.

Results: In the unadjusted analyzes, serum UA was positively associated with peak force in men and in total sample, but not for women. However, after adjustments for confounders, UA levels were positively associated with peak force in total sample (p-trend = 0.007), men (p-trend = 0.044) and women (p-trend = 0.016).

Conclusion*:* Serum UA is positively associated with muscle strength in older men and women. These results suggest that UA levels seems to be a protective factor for muscle strength in older adults independent of the sex.

Keywords: Uric acid, Muscle strength, Aging, Peak force, Oxidative stress.

1. Introduction

Aging promotes strength loss [1], which is associated with increased risk of falls [2], fractures [3, 4] and death [5-8]. Although several factors can influence the loss of muscle strength in older adults [9-13], one of the causes is the increased oxidative stress [14, 15], since excess of reactive oxygen and nitrogen species seem to affect muscle size, fiber activation, and excitation-contraction [14]. Thus, theoretically, substances with antioxidants properties may have protective effects on muscle strength due to decreases in oxidative stress [16].

Uric acid (UA) is an organic compound with important antioxidant properties, as it is responsible for 2/3 of total plasma antioxidant capacity [17]. To date, several studies have reported that UA is positively associated with muscle strength in older adults [18-23]. However, the current evidence is still limited because most studies evaluated the strength only by handgrip strength [19-23], although isokinetic knee extensor strength seems to be a better predictor of functional capacity in older adults [24], and could provide more reliable associations.

In addition, only few studies performed the association between UA and strength evaluating men and women separately [20, 21] and the results are mixed. Kawamoto et al [20] observed a positive association only in older women, while Molino-lova et al [21] noted a positive association for both sexes. It is plausible to speculate that associations would vary according to the sex because men and women have different values of muscle strength as well as of UA levels [25, 26].

Therefore, more studies are needed evaluating sex-specific associations and muscle strength using a more reliable test than handgrip strength, such as isokinetic knee extensor strength. The aim of the present study was to investigate whether serum UA is associated with muscle strength (measured by isokinetic knee extensor strength) in older men and women derived from National Health and Nutrition Examination Survey (NHANES) 1999 - 2002. We hypothesized that UA is positively associated with strength in both older men and women.

2. Methods

2.1 Survey and Participants

The NHANES is a cross-sectional survey conducted by The National Center for Health Statistics of the Centers for Disease Control and Prevention based on a multistage,

probability and stratified sampling design to assess the nutritional status and health of a nationally representative sample of the noninstitutionalized U.S. population.

The present study evaluated older adults aged from 50 to 85 years from NHANES 1999-2000 and 2001-2002. Participants completed in-home interviews, physical examinations, biochemical tests, dietary interviews and other examinations [27]. A total of 2361 individuals (1256 men and 1105 women) were evaluated and had complete serum UA and isokinetic strength of the knee extensors (peak force) data. Only the individuals aged 50 y or over were eligible to perform the strength test in NHANES 1999-2000 and 2001-2002. In addition, we also chose to evaluate the individuals in this age-range because a significant strength loss is already observed after 50 years of age [28]. Individuals with available demographic, health conditions (diabetes, arterial hypertension, arthritis, menopause, allopurinol use) and behavior (physical activity and smoking status), anthropometric, body composition, biochemical parameters and dietary data; and who performed strength tests were included in the analyzes. Pregnant women, individuals with amputation, those with implausible peak force velocity [29] and who did not perform at least 4 trials in the isokinetic strength test were excluded from the study (Figure 1). The subjects who presented history of myocardial infarction within the past six weeks, knee surgery or knee replacement surgery, chest or abdominal surgery within the past three weeks, history of brain aneurysm or stroke, or severe back pain were not able to perform the strength test; therefore, they were not included in the present study. NHANES is a public data set and all participants provided a written informed consent, consistent with approval from the National Center for Health Statistics Research Ethics Review Board (NCHS ERB) (protocol #98-12 for NHANES cycle 1999-2002).

2.2 Uric acid and other biochemical parameters

UA, creatinine and triglycerides levels were measured by colorimetric method [30, 31]. Elevated UA levels were defined as > 7.0 and > 6.0 mg/dl for men and women, respectively [25]. Glomerular Filtration Rate (eGFR) was estimated by the chronic kidney disease epidemiology collaboration (CKD-EPI) equation [32]. Serum C-reactive protein levels were measured by high-sensitivity immuno-nephelometric [30, 31].

2.3 Muscle strength

The peak isokinetic knee extensor strength was assessed by Kinetic Communicator isokinetic dynamometer (Kin Com MP, Chattecx Corp., Chattanooga,

TN). Six muscle strength measurements of the right quadriceps were performed, at a speed of 60 degrees for second (°/second). Individuals with extreme values of peak force velocity (<55°/second or >65°/second) were excluded [29, 33].

The individuals were encouraged to not perform the maximal effort in the first three trials because this part of the test was used for movement learning and warm-up. In the last three trials, they were strongly encouraged to perform the maximal effort for muscle strength measurement. If the individual completed 4-6 trials, the highest peak force value was used.

2.4 Anthropometrics and body composition

Body weight and height were evaluated according to the Lohman's protocol [34] and body mass index (BMI) was calculated. Whole body dual-energy x-ray absorptiometry (DXA) scans were taken with a Hologic QDR-4500A fan-beam densitometer (Hologic, Inc., Bedford, Massachusetts). Due to invalid and missing data (50-59 years: 75% of valid DXA; 60-69 years: 72% of valid DXA; 70-79 years: 70% of valid DXA; over 80 years: 59% of valid DXA), multiple imputation was performed by NHANES using the sequential regression imputation method [35]. Survey Methodology Program at the University of Michigan's Institute of Survey Research developed a SAS-callable imputation and variance estimation software, which was used to impute the NHANES DXA data [35]. Total lean mass, appendicular lean mass (arms and legs lean mass), Appendicular Muscle Mass Index – AMMI (appendicular lean mass divided by height squared) [26] and total fat mass (kg and %) were evaluated.

2.5 Dietary intake

Dietary intake was evaluated by an interviewer who administered one 24h dietary recall for each volunteer. NHANES 1999-2000 and 2001 survey were evaluated through a 4-step multiple pass [31, 36], while in NHANES 2002 the dietary intake was evaluated according to the U.S. Department of Agriculture (USDA) Automated 5- steps multiple-pass method [31, 36]. The intake of total energy (kcal/day), carbohydrate (g/day), protein (g/day and g/kg), lipids (g/day), alcohol (g/day), caffeine (mg/day) and total omega 3 (g/day) [33] were analyzed. Food Intake Analysis System version 3.99 with the USDA 1994-98 Survey Nutrient Database was used to code and report the NHANES 1999-2000 dietary data. The USDA Food and Nutrient Database for Dietary Study, version 1, was used for processing the intakes for 2001-2002.

2.6 Covariates of interest

The demographic characteristics evaluated were age (years), sex (men or women), race/ethnicity (non-Hispanic white or other), marital status (single/divorced/widowed/never married or married/living as married), annual family income (0 to $19999, from $20000 to 54999 or over $55000) and educational level (under/high school graduate and some college or over). Health conditions and behavior included in the present study were self-report of diabetes (no, pre-diabetes or yes), hypertension (no or yes), arthritis (no or yes), menopause (only for women; no or yes), allopurinol use (no or yes), and smoking status (no or yes). Physical activity level included moderate, vigorous or strength exercises (no or yes), as previously described [33]. Total lean mass (kg), total fat mass (kg), eGFR (ml/min/1.73m^2), C-reactive protein (CRP) (mg/dl) and triglycerides (mg/dl) levels; the intake of energy (kcal/day), protein (g/day), alcohol (g/day), caffeine (mg/day) and total omega 3 (g/day) were also assessed. For marital status, annual family income, educational level and menopause status, a missing variable was created whenever required.

2.7 Statistical analyzes

Demographic characteristics, health conditions and behavior, anthropometric and body composition, strength, and biochemical parameters, and dietary intake were compared according to the quintiles of UA using linear regression. The continuous variables were described as mean and standard error, while the categorical variables were described as percentage and confidence interval. Linear regression was used to estimate the coefficients and 95% confident intervals (95%CI) for peak force (muscle strength) by quintiles of UA. The analyses were performed without (Model 1) and with adjustments for confounders (Model 2). The variables included as adjustments were age, race/ethnicity, educational level, marital status, annual family income, diabetes, hypertension, arthritis (yes/no), allopurinol use, physical activity, smoking status, total lean mass (kg), total fat mass (kg), eGFR (ml/min/1.73m^2), CRP (mg/dl), triglycerides (mg/dl); intake of energy (kcal/day), protein (g/day), alcohol (g/day), caffeine (mg/day), and total omega 3 (g/day). For total sample, the analyses were additionally adjusted for sex. In the analyses stratified by sex, in the subgroup of women, menopausal status was added in the adjustments. Stata 14.0 software (StataCorp, College Station, TX, USA) was used for statistical analyses and $p < 0.05$ was considered as significant. All statistical analyzes were performed considering the examination sample weight [27].

3. Results

3.1 Individual characteristics

The characteristics of older men according to the quintile of UA levels are shown in Table 1. All the individuals in quintile 1 to 3 had normal values of UA, while 76.4% presented adequate UA in fourth quintile and all individuals presented elevated UA in top quintile. Older men with higher serum UA had higher prevalence of hypertension, and higher body weight, BMI, lean mass (total and appendicular), MMI, fat mass (kg and %) and muscle strength (peak force). For biochemical parameters, individuals with higher serum UA presented higher creatinine and triglycerides levels and lower glomerular filtration rate. Individuals with higher serum UA ingested lower amounts of carbohydrate (g) and protein (g/kg); and higher alcohol (g) consumption.

The characteristics of older women according to the quintile of UA levels are shown in Table 2. All the individuals in quintile 1 to 4 had normal values of UA, while all individuals presented elevated UA in the top quintile. A lower proportion of non-Hispanic white, lower annual family income and educational level were noted among the individuals with higher UA levels. Women with higher serum UA were older, had higher prevalence of hypertension, diabetes, arthritis, menopause status and physical inactivity level. Higher values of body weight, BMI, lean mass (total and appendicular), MMI and fat mass (kg and %) were observed according to the UA quintile progression. No difference was observed for strength (peak force) in older women with higher UA levels. Women with higher UA levels presented higher creatinine, C-reactive protein and triglycerides levels, and lower glomerular filtration rate and protein intake (g/kg) (Table 2).

Evaluating the total sample (men and women together; Supplementary Table 1), individuals with higher serum UA were predominantly men, married/living with partner, had higher prevalence of hypertension and smokers. Higher age, body weight, height, BMI, lean mass (total and appendicular), MMI, fat mass (kg), and strength (peak force), and lower body fat percentage were observed in the highest quintiles of UA. For biochemical parameters, it was noted higher values of creatinine and triglycerides levels; and lower glomerular filtration rate according to the UA quintile progression. Individuals with higher serum UA levels ingested more calories (kcal), protein (g), lipids (g) and alcohol (g), and lower amounts of protein in grams per kilo.

3.2 Peak force and uric acid

In the unadjusted analyzes serum UA was positively associated with peak force in total sample and in men, but not in women (Supplementary Table 2; Model 1). However, after the adjustments for confounders, UA levels were positively associated with peak force in total sample, men and women (Figure 2; Supplementary Table 2 – Model 2).

4. Discussion

The main finding of the present study was that serum UA levels were positively associated with muscle strength (peak force) in older men and women. These results suggest that UA may have a protective role in muscle strength of older adults independent of the sex. Interestingly, a higher positive association was observed mainly in the top UA quintile for both sexes, which had a totality of the individuals presenting hyperuricemia. This finding suggests that it would not be beneficial to promote reductions in UA levels, at least where muscle strength is concerned, even for older adults with elevated UA. However, since hyperuricemia is also associated with increased risk of cardiovascular disease [37], it is unknown whether the maintenance of elevated serum UA levels can be advantageous for general health in older adults.

We observed that individuals in the top quintile of UA presented approximately 22.0 N higher peak force when compared with individuals from quintile 1, which is equivalent to ~2.2 kg of strength. These associations may have important clinical relevance because an increase of 1 kg of strength can decrease the risk of multiple falls by 17% [38]. Future studies should be performed to evaluate whether older adults with higher UA levels present lower risk of falls.

Our results are in agreement with previous studies conducted with older adults [18-23]. García-Esquinas and Rodríguez-Artalejo [23] observed that UA was positively associated with handgrip strength in older adults from NHANES (2011-2012). Thus, this study [23] and ours show that UA is positively associated with strength in older adults from USA independently of the type of strength test. Several studies evaluating different populations also observed that UA was positively associated with muscle strength [18-22] in older adults from Korea [22], Japan [20], China [19], and Italy [18, 21], suggesting that this association is consistent in different population. Regarding all the studies that associated UA with strength in older adults [18-23], only one [18] evaluated the strength by knee extension torque, such as in the present study, while all the other studies evaluated

by handgrip strength [19-23]. Macchi et al [18] showed that baseline UA was positively associated with strength (at three-year follow-up) measured by handgrip strength, as well as by knee extension torque. However, the analyses were not performed separated by sex [18], which is an important knowledge gap in the literature, since men and women have different values of muscle strength and UA levels [25, 26]. To the best of our knowledge, the present study is the first todemonstrate that UA is associated with peak force in both older men and women, showing that this association does not seem to be sex-specific.

Although studies evaluating older adults show that UA is positively associated with strength, this relationship does not seem to be the same in young and middle-aged individuals [22, 23, 39]. Huang et al [39] showed an inverted J-shaped association between serum UA quartiles and muscle strength in Japanese men (mean age 46 y). In addition, in the study of García-Esquinas and Rodríguez-Artalejo [23] the association between UA and strength differed according to age. Although a positive association was observed in older adults, a negative association was noted in adults aged 20-40 y, while no association was observed in middle aged individuals (40-60 y) [23]. These results show that the association between UA and strength may be age-specific; however, we cannot exclude the possibility that different associations can be observed when different strength tests are used. For example, Floriano et al [40] noted that UA levels were not associated with handgrip strength in kidney transplant patients (mean age 47.9 y), as well as observed by other studies that evaluated middle-aged individuals [23, 39]. However, UA was associated with five times sit to stand test [40], which is another type of strength test [26]. Therefore, it is unclear whether the association between UA and strength is age-specific, whether is dependent of the strength test, or even if is different according to the type of population (for example, individuals with renal disease).

The mechanisms by which UA is positively associated with strength in older adults is not fully clear, but it is likely due to UA antioxidants properties. The excess of oxidative stress is one of the causes of low muscle strength in older adults [15, 41] due to effects in fiber activation and excitation-contraction [14]. Since UA is a powerful antioxidant [17], older adults with increased UA levels may have lower oxidative stress, which may improve the muscle strength. One additional cause for low muscle strength in older adults can be the effect of increased oxidative stress on muscle size, which can decrease the muscle strength [14]. However, the analyses were adjusted for lean mass in the present study, suggesting that the association between UA and strength are independent of the lean mass amount.

The present study has limitations. First, biomarkers of oxidative stress were not evaluated, which would help to conclude whether the associations between UA and strength are mediated by oxidative stress. Second, in an observational study, we cannot rule out that part of the association found could be explained by residual confounding. However, the analyses were adjusted by important potential confounders, which reduces this possibility. Third, due to the cross-sectional design, causality cannot be stablished. Fourth, although we observed that elevated UA was positively associated with strength, these results should not be extrapolated to the presence of gout, a type of arthritis caused by UA. As strengths, generalization is not an issue, since we evaluated a representative sample from USA. In addition, all analyzes were adjusted for important confounders. Our outcome, muscle strength, was measured by an isokinetic dynamometer that is a reliable method for strength measurement [42].

In conclusion, serum UA is positively associated with strength (peak force) in older men and women. These results suggest that UA levels seems to be a protective factor for muscle strength in older adults independently of the sex.

Funding

No sources of funding were used to assist in the article preparation.

Authorship

PCN participated in interpretation of the data, performed statistical analysis and wrote the manuscript; LTR and FMSB participated in analysis and interpretation of the data. AEMR and CMA participated in the configuration of datasets, organization of the statistical analysis and contributed with the revision of the manuscript. EPO participated in the interpretation of the data, wrote, and contributed with the revision of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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Table 1. Sociodemographic, health conditions and behavior, anthropometric and body composition, strength, biochemical parameters and dietary intake of older men by quintile of serum uric acid. NHANES, 1999-2002.

	Total	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p-value
Uric acid, mg/dl	6.1 ± 0.04	4.3 ± 0.04	5.4 ± 0.02	6.0 ± 0.01	6.8 ± 0.02	8.1 ± 0.06	**<0.001**
Adequate uric acid, %	76.9 (73.9 ; 79.6)	100	100	100	76.4 (69.5 ; 82.2)	0	-
Demographic							
Age, y	61.6 ± 0.3	60.5 ± 0.6	61.9 ± 0.6	62.3 ± 0.7	61.3 ± 0.6	62.2 ± 0.7	0.218
Race/ethnicity, %							0.335
Non-Hispanic white	83.6 (81.4 ; 85.5)	80.1 (75.2 ; 85.7)	83.7 (78.7 ; 87.7)	83.7 (78.2 ; 87.9)	85.7 (81.4 ; 89.2)	83.6 (78.5 ; 87.6)	
Marital status, %							0.269
Single/Divorced/Widowed/Never Married	14.0 (11.9 ; 16.4)	15.8 (11.1 ; 21.9)	16.8 (12.0 ; 23.0)	9.8 (6.7 ; 14.1)	10.8 (7.3 ; 15.6)	16.7 (11.9 ; 23.0)	
Married/Living with partner	80.8 (77.9 ; 83.3)	77.6 (70.5 ; 83.5)	79.4 (72.8 ; 84.7)	83.1 (76.4 ; 88.2)	82.5 (76.4 ; 87.2)	81.4 (74.7 ; 86.7)	
Missing	5.2 (3.7 ; 7.2)	6.5 (3.3 ; 12.5)	3.8 (1.8 ; 7.9)	7.0 (3.4 ; 13.8)	6.7 (3.8 ; 11.8)	1.9 (0.4 ; 7.4)	
Annual Family Income, %							0.166
$0-19,999	16.4 (14.3 ; 18.8)	18.5 (13.6 ; 24.7)	15.0 (10.9 ; 20.2)	19.7 (14.9 ; 25.5)	13.4 (9.6 ; 18.4)	16.1 (11.6 ; 21.9)	
$20,000-54,999	36.4 (33.2 ; 39.8)	40.2 (32.7 ; 48.2)	36.7 (30.1 ; 43.8)	34.8 (27.6 ; 42.7)	34.7 (28.2 ; 41.9)	35.6 (28.5 ; 43.4)	
Over $55,000	44.3 (40.9 ; 47.8)	38.9 (31.4 ; 47.1)	43.8 (36.7 ; 51.1)	45.2 (37.4 ; 53.3)	48.6 (41.2 ; 55.9)	45.1 (37.3 ; 53.2)	
Missing	2.8 (1.9 ; 4.0)	2.3 (1.0 ; 5.2)	4.5 (2.3 ; 8.4)	0.3 (0.07 ; 1.2)	3.2 (1.6 ; 6.5)	3.2 (1.4 ; 7.1)	
Educational level, %							0.504
Under high school graduate	45.4 (42.0 ; 48.8)	42.7 (35.2 ; 50.5)	46.6 (39.6 ; 53.8)	44.7 (37.1 ; 52.6)	45.0 (38.0 ; 52.3)	47.8 (40.0 ; 55.7)	
Some college or over	54.6 (51.2 ; 57.9)	57.3 (49.5 ; 64.7)	53.4 (46.2 ; 60.4)	55.3 (47.4 ; 62.9)	54.8 (47.5 ; 61.9)	52.2 (44.3 ; 60.0)	
Missing	0.02 (0.00 ; 0.18)	-	-	-	0.12 (0.02 ; 0.88)	-	
Health Conditions and Behavior							
Diabetes, %							0.089
Yes	10.2 (8.4 ; 12.3)	19.2 (13.8 ; 26.1)	7.4 (4.6 ; 11.6)	7.7 (4.7 ; 12.4)	6.1 (3.5 ; 10.7)	10.9 (7.2 ; 16.1)	
No	87.6 (85.3 ; 89.6)	78.7 (71.6 ; 84.4)	91.1 (86.7 ; 94.2)	89.8 (84.9 ; 93.3)	91.5 (86.7 ; 94.7)	86.0 (79.9 ; 90.4)	

Pre-diabetes	2.2 (1.5 ; 3.4)	2.1 (0.7 ; 6.0)	1.4 (0.5 ; 4.3)	2.4 (1.1 ; 5.2)	2.4 (1.0 ; 5.4)	3.1 (1.2 ; 8.0)	
Hypertension, %							**<0.001**
Yes	34.2 (31.1 ; 37.4)	23.4 (17.5 ; 30.5)	29.1 (23.2 ; 35.8)	31.7 (24.9 ; 39.4)	39.3 (32.5 ; 46.5)	48.8 (40.9 ; 56.7)	
No	65.8 (62.6 ; 68.9)	76.6 (69.5 ; 82.4)	70.9 (64.2 ; 76.7)	68.3 (60.6 ; 75.0)	60.7 (53.5 ; 67.5)	51.2 (43.3 ; 59.0)	
Arthritis, %							0.450
Yes	31.1 (28.0 ; 34.3)	28.1 (21.5 ; 35.7)	32.6 (26.3 ; 39.5)	33.5 (26.7 ; 41.1)	30.4 (24.1 ; 37.5)	30.6 (24.0 ; 38.2)	
No	68.9 (65.7 ; 71.9)	71.9 (64.3 ; 78.5)	67.4 (60.5 ; 73.7)	66.4 (58.8 ; 73.2)	69.6 (62.4 ; 75.9)	69.3 (61.8 ; 76.0)	
Allopurinol use, %							0.256
Yes	2.9 (2.0 ; 4.2)	4.6 (2.3 ; 8.9)	3.4 (1.7 ; 6.8)	1.7 (0.5 ; 5.9)	2.2 (0.8 ; 6.2)	2.4 (0.9 ; 6.2)	
No	97.1 (95.7 ; 98.0)	95.4 (91.0 ; 97.7)	96.6 (93.2 ; 98.3)	98.3 (94.1 ; 99.5)	97.7 (93.8 ; 99.2)	97.6 (93.8 ; 99.1)	
Physical activity, %							0.219
Yes	7.8 (6.0 ; 9.9)	10.1 (6.0 ; 16.6)	7.1 (4.2 ; 11.9)	8.3 (4.7 ; 14.1)	8.0 (4.7 ; 13.4)	5.1 (2.4 ; 10.5)	
No	92.2 (90.1 ; 93.9.0)	89.8 (83.4 ; 93.9)	92.9 (88.1 ; 95.8)	91.7 (85.8 ; 95.3)	92.0 (86.6 ; 95.3)	94.8 (89.5 ; 97.5)	
Smoking status, %							0.179
Yes	67.9 (64.6 ; 71.0)	66.4 (58.5 ; 73.4)	66.4 (59.3 ; 72.9)	64.8 (57.0 ; 72.0)	69.0 (61.8 ; 75.5)	73.1 (65.4 ; 79.6)	
No	32.1 (29.0 ; 35.4)	33.6 (26.5 ; 41.4)	33.5 (27.1 ; 40.7)	35.1 (28.0 ; 43.0)	30.9 (24.5 ; 38.2)	26.9 (20.4 ; 34.6)	
Anthropometric and Body Composition							
Weight, kg	86.7 ± 0.6	82.7 ± 1.4	84.3 ± 1.1	86.3 ± 1.2	90.9 ± 1.3	89.7 ± 1.2	**<0.001**
Height, m	1.75 ± 0.00	1.74 ± 0.01	1.76 ± 0.00	1.74 ± 0.00	1.76 ± 0.00	1.75 ± 0.00	0.669
Body mass index, kg/m²	28.2 ± 0.2	27.1 ± 0.4	27.2 ± 0.3	28.3 ± 0.3	29.4 ± 0.4	29.3 ± 0.3	**<0.001**
Total lean mass, kg	58.0 ± 0.3	56.2 ± 90.8	57.2 ± 0.6	57.5 ± 0.6	60.1 ± 0.6	59.2 ± 0.6	**<0.001**
Appendicular muscle mass index, kg/m²	8.3 ± 0.04	8.1 ± 0.09	8.1 ± 0.08	8.2 ± 0.09	8.5 ± 0.08	8.5 ± 0.08	**<0.001**
Adequate appendicular muscle mass index, %	88.4 (86.1 ; 90.3)	86.2 (80.2 ; 90.6)	84.6 (78.5 ; 89.2)	86.1 (79.6 ; 90.8)	92.3 (88.2 ; 95.1)	93.2 (89.2 ; 95.8)	**0.001**
Appendicular lean mass, kg	25.4 ± 0.1	24.7 ± 0.4	25.1 ± 0.3	25.1 ± 0.3	26.4 ± 0.3	25.9 ± 0.3	**<0.001**
Total fat mass, kg	26.7 ± 0.3	24.6 ± 0.7	25.2 ± 0.5	26.8 ± 0.6	28.8 ± 0.7	28.5 ± 0.6	**<0.001**
Total fat mass, %	30.0 ± 0.2	28.7 ± 0.4	29.2 ± 0.4	30.3 ± 0.4	30.8 ± 0.4	31.1 ± 0.3	**<0.001**
Strength							
Peak force, Newtons	454.1 ± 4.0	439.1 ± 9.2	452.4 ± 9.2	442.4 ± 8.8	472.2 ± 8.4	463.9 ± 8.9	**0.014**

Time to peak force, seconds	1.1 ± 0.02	1.1 ± 0.03	1.1 ± 0.03	1.0 ± 0.03	1.1 ± 0.05	1.0 ± 0.05	0.759
Peak force velocity, degree/second	60.7 ± 0.02	60.7 ± 0.05	60.7 ± 0.04	60.8 ± 0.04	60.6 ± 0.06	60.8 ± 0.05	0.402
Biochemical parameters							
Creatinine, mg/dl	0.98 ± 0.01	0.92 ± 0.03	0.95 ± 0.02	0.99 ± 0.02	0.97 ± 0.02	1.1 ± 0.02	**<0.001**
Estimated Glomerular Filtration Rate (eGFR), ml/min/1.73m²	87.1 ± 0.6	94.3 ± 1.2	87.7 ± 1.2	84.9 ± 1.4	87.2 ± 1.3	80.7 ± 1.5	**<0.001**
C-reactive protein, mg/dl	0.40 ± 0.02	0.40 ± 0.07	0.33 ± 0.04	0.31 ± 0.03	0.39 ± 0.04	0.45 ± 0.05	0.407
Triglycerides, mg/dl	170.9 ± 8.2	140.9 ± 7.0	156.1 ± 7.4	152.7 ± 6.8	191.4 ± 25.3	216.8 ± 31.3	**0.007**
Dietary Intake							
Energy, kcal/day	2318 ± 35.8	2312 ± 83.6	2419 ± 83.1	2365 ± 90.9	2337 ± 71.9	2128 ± 62.7	0.059
Carbohydrate, g/day	278.2 ± 4.9	282.0 ± 10.2	308.2 ± 12.9	274.7 ± 11.2	271.3 ± 9.6	248.5 ± 8.1	**<0.001**
Protein, g/day	88.4 ± 1.5	90.4 ± 3.6	88.6 ± 2.8	92.2 ± 4.4	91.1 ± 3.3	79.3 ± 2.6	0.124
Protein, g/kg	1.04 ± 0.02	1.13 ± 0.05	1.08 ± 0.04	1.07 ± 0.04	1.02 ± 0.04	0.89 ± 0.03	**<0.001**
Lipids, g/day	88.7 ± 1.8	89.3 ± 4.7	90.6 ± 4.0	94.9 ± 4.7	87.5 ± 3.3	80.5 ± 3.0	0.159
Alcohol, g/day	13.9 ± 1.2	9.0 ± 1.8	9.6 ± 2.0	13.0 ± 2.3	20.1 ± 3.4	18.2 ± 3.7	**<0.001**
Caffeine, mg/day	253.7 ± 10.2	251.9 ± 24.1	244.9 ± 21.5	302.7 ± 28.6	246.8 ± 17.0	233.6 ± 21.5	0.747
Total omega-3, g/day	1.97 ± 0.06	1.91 ± 0.11	1.97 ± 0.12	2.13 ± 0.16	2.01 ± 0.12	1.81 ± 0.14	0.965

Data described as mean ± standard error or percentage (confidence interval).
Quintiles UA for older men: quintile 1: 2.3 – 4.9 mg/dL; quintile 2: 5.0 – 5.7 mg/dL; quintile 3: 5.8 – 6.3 mg/dL; quintile 4: 6.4 – 7.3 mg/dL and quintile 5: 7.4 – 13.4 mg/dL.

Table 2. Sociodemographic, health conditions and behavior, anthropometric and body composition, strength, biochemical parameters and dietary intake of older women by quintile of serum uric acid. NHANES, 1999-2002.

	Total	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p-value
Uric acid, mg/dl	5.0 ± 0.05	3.4 ± 0.03	4.3 ± 0.01	4.9 ± 0.01	5.6 ± 0.02	7.1 ± 0.07	**<0.001**
Adequate uric acid, %	80.8 (77.8 ; 83.5)	100	100	100	100	0	-
Demographic							
Age, y	62.5 ± 9.7	60.5 ± 0.7	62.1 ± 0.7	61.7 ± 0.7	62.9 ± 0.8	65.9 ± 0.9	**<0.001**
Race/ethnicity, %							**0.012**
Non-Hispanic white	79.6 (77.0 ; 82.0)	85.1 (80.2 ; 88.9)	81.3 (75.9 ; 85.7)	76.3 (69.5 ; 81.9)	78.7 (72.0 ; 84.2)	75.8 (69.2 ; 81.4)	
Marital status, %							0.432
Single/Divorced/Widowed/Never Married	36.9 (33.6 ; 40.4)	35.9 (28.8 ; 43.7)	34.9 (28.3 ; 42.1)	33.5 (26.4 ; 41.4)	38.3 (30.4 ; 46.8)	42.7 (35.0 ; 50.8)	
Married/Living with partner	57.9 (54.3 ; 61.4)	58.3 (50.4 ; 65.8)	57.5 (50.1 ; 64.7)	62.5 (54.5 ; 69.8)	58.4 (49.9 ; 66.5)	52.6 (44.5 ; 60.6)	
Missing	5.2 (3.8 ; 7.0)	5.8 (3.0 ; 10.9)	7.5 (4.3 ; 12.9)	4.0 (1.9 ; 8.2)	3.2 (1.3 ; 7.5)	4.6 (2.1 ; 9.9)	
Annual Family Income, %							**0.001**
$0-19,999	25.9 (23.0 ; 29.1)	25.0 (18.9 ; 32.2)	25.1 (19.4 ; 31.9)	22.1 (16.3 ; 29.2)	24.2 (18.1 ; 31.7)	33.4 (26.2 ; 41.4)	
$20,000-54,999	36.8 (33.4 ; 40.3)	32.3 (25.6 ; 39.0)	33.7 (27.1 ; 40.9)	34.7 (27.6 ; 42.6)	43.7 (35.3 ; 52.5)	41.3 (33.6 ; 49.6)	
Over $55,000	35.0 (31.5 ; 38.6)	40.0 (32.3 ; 48.0)	38.3 (31.1 ; 46.0)	41.8 (34.1 ; 49.9)	31.5 (23.8 ; 40.4)	21.6 (15.4 ; 29.3)	
Missing	2.3 (1.5 ; 3.4)	2.8 (1.2 ; 6.1)	2.9 (1.9 ; 6.4)	1.3 (0.6 ; 3.0)	0.5 (0.1 ; 1.4)	3.7 (1.7 ; 7.8)	
Education level, %							**0.001**
Under high school graduate	51.0 (47.4 ; 54.6)	40.5 (33.1 ; 48.2)	49.8 (42.4 ; 57.2)	51.4 (43.4 ; 59.3)	53.9 (45.1 ; 62.4)	61.0 (52.8 ; 68.6)	
Some college or over	48.9 (45.3 ; 52.5)	59.5 (51.7 ; 66.9)	49.8 (42.4 ; 57.2)	48.6 (40.7 ; 56.6)	46.1 (37.6 ; 54.9)	39.0 (31.5 ; 47.2)	
Missing	0.08 (0.01 ; 0.60)	-	0.36 (0.05 ; 2.5)	-	-	-	
Health Conditions and Behavior							
Diabetes, %							**<0.001**
Yes	7.9 (6.3 ; 9.8)	5.5 (3.2 ; 9.1)	5.9 (3.4 ; 10.0)	5.4 (3.0 ; 9.7)	8.3 (4.8 ; 14.0)	15.1 (10.3 ; 21.5)	
No	90.0 (87.8 ; 91.8)	93.4 (89.4 ; 96.0)	93.3 (89.2 ; 96.0)	93.6 (88.39 ; 96.4)	87.2 (80.2 ; 91.9)	80.9 (73.9 ; 86.4)	
Pre-diabetes	2.1 (1.2 ; 3.5)	1.1 (0.29 ; 4.0)	0.7 (0.2 ; 6.2)	0.9 (0.1 ; 6.1)	4.5 (1.8 ; 10.6)	4.0 (1.7 ; 9.0)	

Hypertension, %							**<0.001**
Yes	44.1 (40.6 ; 47.7)	29.3 (22.7 ; 36.9)	34.85 (28.0 ; 41.7)	39.2 (31.8 ; 47.2)	49.8 (41.2 ; 58.4)	71.9 (64.1 ; 78.6)	
No	55.9 (52.3 ; 59.4)	70.7 (63.1 ; 77.3)	65.4 (58.3 ; 72.0)	60.7 (52.7 ; 68.2)	50.2 (41.5 ; 58.8)	28.1 (21.4 ; 35.9)	
Arthritis, %							**0.003**
Yes	43.1 (39.6 ; 46.7)	38.2 (31.0 ; 46.0)	39.2 (32.3 ; 46.6)	42.4 (37.8 ; 50.5)	41.9 (33.8 ; 50.5)	55.0 (46.9 ; 63.0)	
No	56.9 (53.3 ; 60.4)	61.8 (54.0 ; 69.0)	60.8 (53.4 ; 67.7)	57.6 (49.5 ; 65.2)	58.1 (49.5 ; 66.2)	44.9 (37.0 ; 53.1)	
Menopause status, %							**0.002**
Yes	87.3 (84.4 ; 89.6)	80.1 (72.5 ; 86.0)	88.2 (81.7 ; 92.6)	82.4 (74.8 ; 88.1)	91.6 (84.2 ; 95.7)	95.1 (90.1 ; 97.7)	
No	11.9 (9.5 ; 14.7)	19.5 (13.7 ; 227.1)	11.4 (7.0 ; 17.9)	15.7 (10.3 ; 23.2)	6.9 (3.2 ; 14.4)	4.4 (2.0 ; 9.5)	
Missing	0.9 (0.4 ; 1.7)	0.3 (0.06 ; 2.1)	0.4 (0.05 ; 2.6)	1.9 (0.6 ; 5.5)	1.5 (0.4 ; 5.1)	0.4 (0.08 ; 2.3)	
Physical activity, %							**0.001**
Yes	6.5 (4.9 ; 8.6)	8.2 (4.7 ; 13.9)	7.8 (4.4 ; 13.2)	10.7 (6.7 ; 16.8)	4.0 (1.6 ; 9.6)	0.8 (0.1 ; 5.2)	
No	93.5 (91.4 ; 95.1)	91.7 (86.4 ; 95.2)	92.2 (86.8 ; 95.5)	89.2 (83.1 ; 93.3)	96.0 (90.4 ; 98.4)	99.2 (94.8 ; 100.0)	
Smoking status, %							0.298
Yes	44.7 (41.1 ; 48.3)	51.9 (44.1 ; 59.7)	42.5 (35.3 ; 50.0)	39.3 (31.7 ; 47.4)	46.8 (38.3 ; 55.6)	43.3 (35.5 ; 51.5)	
No	55.2 (51.7 ; 58.8)	48.1 (40.3 ; 55.9)	57.5 (49.9 ; 64.7)	60.7 (52.6 ; 68.3)	53.1 (44.4 ; 61.7)	56.7 (48.5 ; 64.5)	
Anthropometric and Body Composition							
Weight, kg	73.6 ± 0.6	66.5 ± 1.0	69.0 ± 1.1	74.8 ± 1.3	77.7 ± 1.5	82.1 ± 1.7	**<0.001**
Height, m	1.61 ± 0.00	1.61 ± 0.00	1.60 ± 0.00	1.62 ± 0.00	1.61 ± 0.00	1.60 ± 0.00	0.325
Body mass index, kg/m²	28.4 ± 0.2	25.5 ± 0.4	26.8 ± 0.4	28.6 ± 0.5	29.8 ± 0.6	31.9 ± 0.6	**<0.001**
Total lean mass, kg	40.7 ± 0.2	38.7 ± 0.5	39.1 ± 0.4	41.1 ± 0.5	42.2 ± 0.6	43.3 ± 0.7	**<0.001**
Appendicular muscle mass index, kg/m²	6.5 ± 0.04	6.1 ± 0.08	6.3 ± 0.08	6.6 ± 0.08	6.8 ± 0.11	7.0 ± 0.11	**<0.001**
Adequate appendicular muscle mass index, %	81.9 (79.0 ; 84.5)	74.1 (66.9 ; 80.2)	75.5 (68.4 ; 81.4)	84.9 (78.6 ; 89.7)	88.6 (82.1 ; 92.9)	82.2 (82.6 ; 93.6)	**<0.001**
Appendicular lean mass, kg	17.0 ± 0.1	16.1 ± 0.2	16.1 ± 0.2	17.2 ± 0.2	17.7 ± 0.3	18.1 ± 0.3	**<0.001**
Total fat mass, kg	31.5 ± 0.4	26.5 ± 0.6	28.6 ± 0.7	32.4 ± 0.8	34.0 ± 1.0	37.3 ± 1.1	**<0.001**
Total fat mass, %	41.5 ± 0.2	38.8 ± 0.4	40.4 ± 0.4	42.1 ± 0.4	42.7 ± 0.5	44.3 ± 0.4	**<0.001**
Strength							
Peak force, Newtons	305.4 ± 3.0	299.5 ± 6.7	296.9 ± 5.8	315.4 ± 6.9	308.9 ± 7.1	309.1 ± 7.8	0.149

Time to peak force, seconds	1.1 ± 0.02	1.1 ± 0.04	1.1 ± 0.06	1.0 ± 0.03	1.1 ± 0.04	1.1 ± 0.06	0.975
Peak force velocity, degree/second	60.6 ± 0.02	60.6 ± 0.04	60.7 ± 0.04	60.6 ± 0.06	60.7 ± 0.05	60.6 ± 0.05	0.823
Biochemical parameters							
Creatinine, mg/dl	0.75 ± 0.01	0.66 ± 0.01	0.71 ± 0.02	0.74 ± 0.02	0.78 ± 0.01	0.88 ± 0.02	**<0.001**
Estimated Glomerular Filtration Rate (eGFR), ml/min/1.73m²	86.6 ± 0.7	93.8 ± 1.1	90.7 ± 1.2	88.2 ± 1.4	83.2 ± 1.6	75.3 ± 1.9	**<0.001**
C-reactive protein, mg/dl	0.51 ± 0.03	0.35 ± 0.04	0.42 ± 0.04	0.55 ± 0.05	0.60 ± 1.1	0.68 ± 0.05	**<0.001**
Triglycerides, mg/dl	150.3 ± 4.0	120.0 ± 5.6	139.6 ± 9.2	152.3 ± 7.2	151.8 ± 10.2	193.0 ± 10.9	**<0.001**
Dietary Intake							
Energy, kcal/day	1680.0 ± 24.7	1733.0 ± 57.3	1751.0 ± 56.6	1585.0 ± 45.4	1722.0 ± 52.2	1596.0 ± 58.7	0.191
Carbohydrate, g/day	212.9 ± 3.2	221.4 ± 7.1	215.6 ± 7.0	206.1 ± 6.7	225.1 ± 7.9	196.6 ± 6.8	0.058
Protein, g/day	64.2 ± 1.1	66.5 ± 2.5	65.8 ± 2.3	62.3 ± 2.3	63.8 ± 2.1	62.2 ± 2.6	0.542
Protein, g/kg	0.91 ± 0.02	1.02 ± 0.04	0.99 ± 0.04	0.86 ± 0.03	0.85 ± 0.03	0.79 ± 0.03	**<0.001**
Lipids, g/day	63.8 ± 1.3	66.8 ± 3.0	67.7 ± 3.1	58.7 ± 2.1	64.4 ± 2.9	60.8 ± 2.6	0.253
Alcohol, g/day	4.75 ± 0.70	2.25 ± 0.63	7.94 ± 2.25	2.36 ± 0.56	4.15 ± 1.16	6.62 ± 1.98	0.619
Caffeine, mg/day	192.7 ± 9.1	201.7 ± 23.8	204.6 ± 22.8	171.3 ± 13.2	225.4 ± 19.9	160.6 ± 16.9	0.262
Total omega-3, g/day	1.53 ± 0.04	1.52 ± 0.08	1.69 ± 0.10	1.41 ± 0.07	1.55 ± 0.15	1.46 ± 0.08	0.307

Data described as mean ± standard error or percentage (confidence interval).
Quintiles UA for older women: quintile 1: 0.4 – 4.0 mg/dL; quintile 2: 4.1 – 4.6 mg/dL; quintile 3: 4.7 – 5.2 mg/dL; quintile 4: 5.3 – 6.0 mg/dL and quintile 5: 6.1 – 11.0 mg/dL.

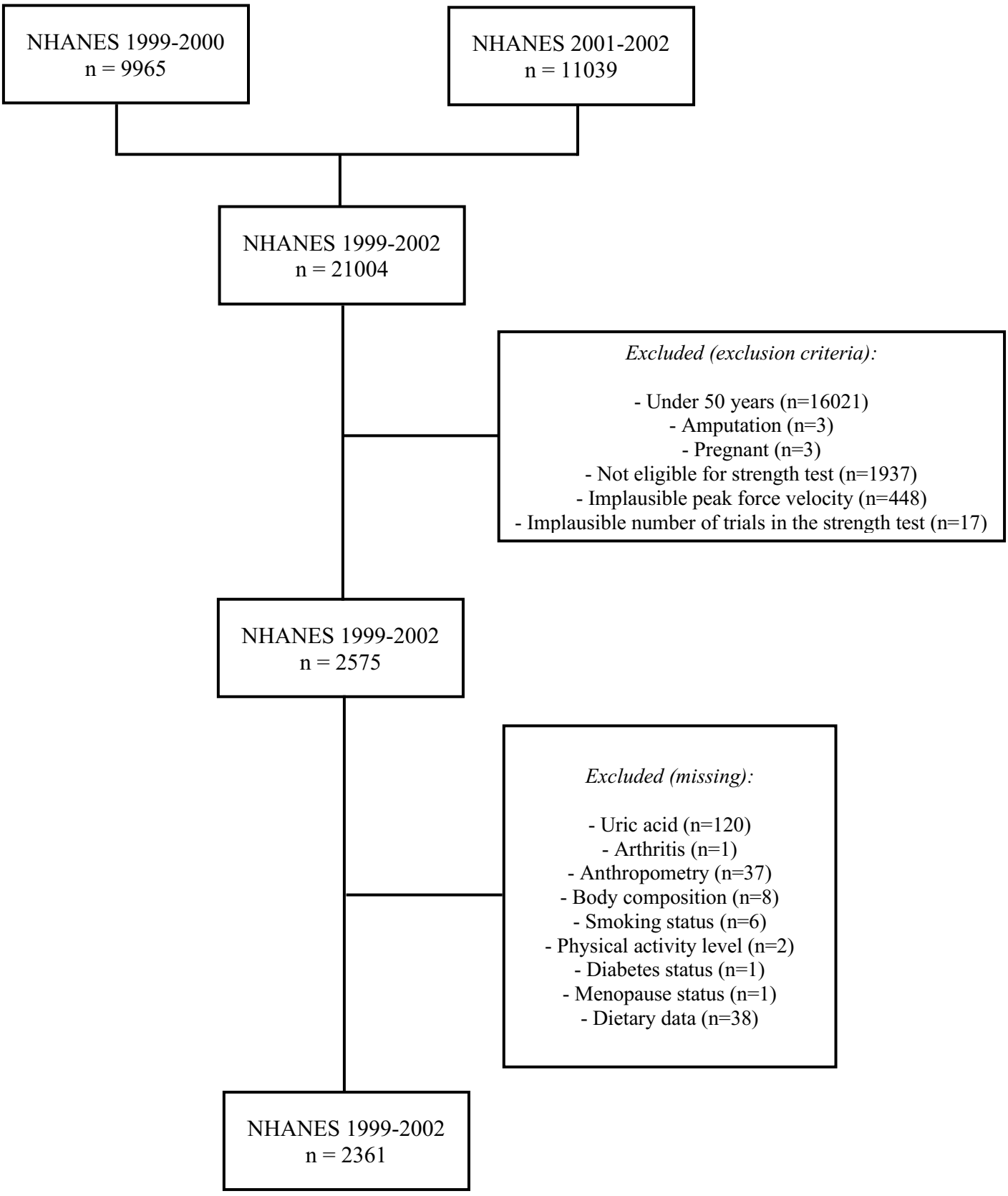

Figure 1. Flowchart of the sample selection from NHANES 1999-2002.

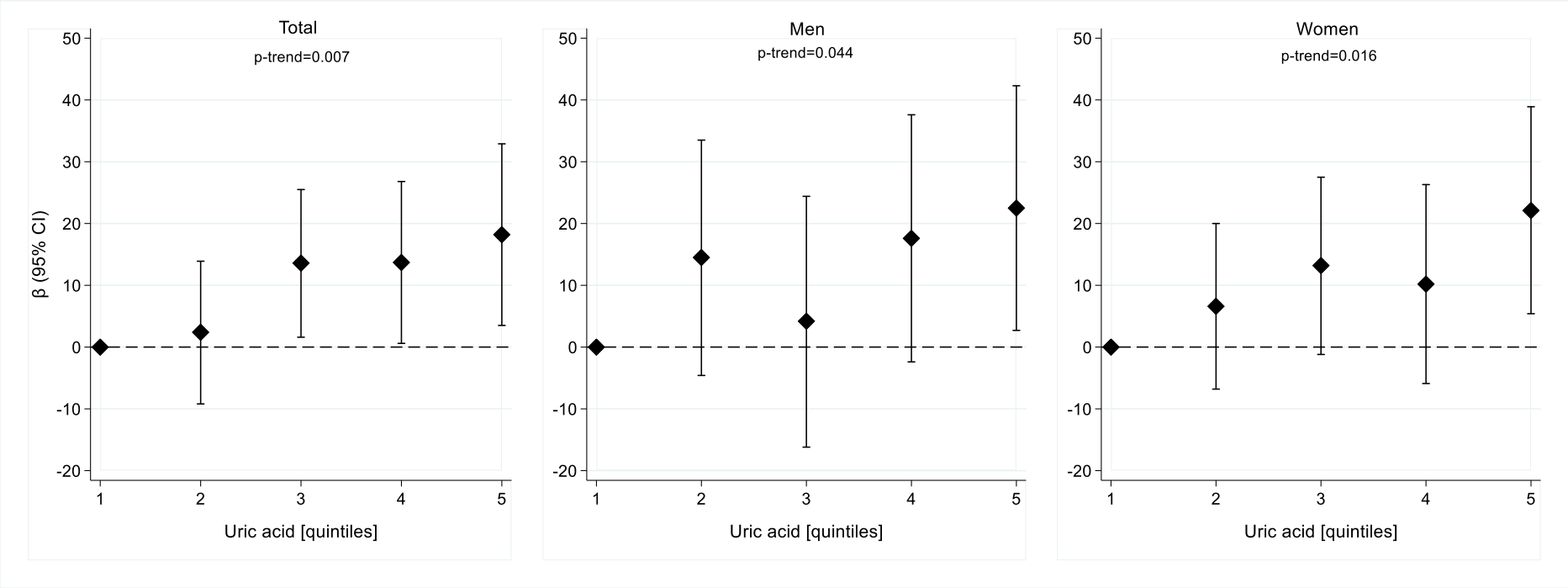

Figure 2. Linear regression between quintiles of serum uric acid and peak force (Newtons). NHANES, 1999-2002.

Adjusted for age (years), race/ethnicity, education level, marital status, annual family income, diabetes, hypertension, arthritis, allopurinol use, physical activity, smoking status, total lean mass (kg), total fat mass (kg), Estimated Glomerular Filtration Rate (eGFR; ml/min/1.73m²), C-reactive protein (mg/dl), triglycerides (mg/dl), energy intake (kcal/day), protein intake (g/day),alcohol (g/day), caffeine (mg/day) and total omega-3 intake (g/day). For women, the analyses were additionally adjusted for menopausal status. The analyses for total sample were also adjusted for sex.

UA quintiles for older men: quintile 1: 2.3 – 4.9; quintile 2: 5.0 – 5.7; quintile 3: 5.8 – 6.3; quintile 4: 6.4 – 7.3 and quintile 5: 7.4 – 13.4 mg/dL.
UA quintiles for older women: quintile 1: 0.4 – 4.0; quintile 2: 4.1 – 4.6; quintile 3: 4.7 – 5.2; quintile 4: 5.3 – 6.0 and quintile 5: 6.1 – 11.0 mg/dL.
UA quintiles for older adults: quintile 1: 0.4 – 4.4; quintile 2: 4.5 – 5.1; quintile 3: 5.2 – 5.8; quintile 4: 5.9 – 6.8 and quintile 5: 6.9 – 13.4 mg/dL.

Supplementary Tables

Supplementary Table 1. Sociodemographic, health conditions and behavior, anthropometric and body composition, strength, biochemical parameters and dietary intake of older adults by quintile of serum uric acid. NHANES, 1999-2002.

	Total	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	p-value
Uric acid, mg/dl	5.5 ± 0.04	3.8 ± 0.03	4.8 ± 0.01	5.5 ± 0.01	6.3 ± 0.02	7.8 ± 0.04	**<0.001**
Adequate uric acid, %	78.9 (76.8 ; 80.8)	100	100	100	75.1 (70.0 ; 79.5)	12.2 (9.05 ; 16.3)	**<0.001**
Demographic							
Age, y	61.7 ± 9.3	60.8 ± 8.7	61.0 ± 9.3	61.3 ± 9.3	62.4 ± 9.2	62.6 ± 9.8	**0.002**
Sex, %							**<0.001**
Male	49.6 (47.1 ; 52.1)	21.8 (17.8 ; 26.3)	37.7 (32.4 ; 43.4)	52.2 (46.6 ; 57.8)	67.8 (62.4 ; 72.7)	74.8 (69.3 ; 79.6)	
Female	50.4 (47.9 ; 52.8)	78.2 (73.7 ; 82.1)	62.2 (56.5 ; 67.6)	47.8 (42.2 ; 53.4)	32.2 (27.2 ; 37.5)	25.2 (20.4 ; 30.6)	
Race/ethnicity, %							0.711
Non-Hispanic white	81.6 (79.9 ; 83.1)	84.0 (80.8 ; 86.8)	78.2 (73.6 ; 82.2)	80.5 (76.4 ; 84.1)	83.4 (80.0 ; 86.4)	80.8 (76.8 ; 84.3)	
Marital status, %							**<0.001**
Single/Divorced/Widowed/Never Married	25.5 (23.5 ; 27.7)	30.3 (25.8 ; 35.3)	28.3 (23.5 ; 33.7)	26.9 (22.3 ; 32.1)	18.4 (14.8 ; 22.6)	23.0 (18.7 ; 28.0)	
Married/Living with partner	69.2 (66.9 ; 71.4)	63.6 (58.5 ; 68.5)	65.7 (60.1 ; 70.9)	69.0 (66.7 ; 73.9)	76.2 (71.4 ; 80.4)	72.6 (67.3 ; 77.3)	
Missing	5.2 (4.1 ; 6.5)	6.0 (3.8 ; 9.4)	5.9 (3.8 ; 9.3)	4.1 (2.3 ; 7.1)	5.4 (3.2 ; 8.9)	43.9 (2.4 ; 7.8)	
Annual Family Income, %							0.803
$0-19,999	21.2 (19.3 ; 23.2)	22.8 (18.9 ; 27.3)	21.9 (17.7 ; 26.8)	19.5 (15.7 ; 23.9)	19.6 (15.9 ; 23.9)	22.0 (17.8 ; 26.8)	
$20,000-54,999	36.6 (34.3 ; 39.0)	35.0 (30.3 ; 40.2)	36.4 (31.1 ; 42.0)	37.5 (32.3 ; 43.0)	37.8 (32.7 ; 43.1)	36.6 (31.3 ; 42.8)	
Over $55,000	39.6 (34.3 ; 39.0)	39.9 (34.7 ; 45.2)	38.9 (33.0 ; 44.7)	40.4 (35.0 ; 46.2)	41.3 (36.0 ; 46.9)	37.4 (31.9 ; 43.1)	
Missing	2.5 (1.9 ; 3.3)	2.2 (1.2 ; 3.9)	2.8 (1.5 ; 5.1)	2.5 (1.3 ; 4.7)	1.3 (0.60 ; 2.7)	4.1 (2.4 ; 6.8)	
Education level, %							0.057
Under high school graduate	48.2 (45.7 ; 50.7)	44.6 (39.5 ; 49.9)	46.9 (41.2 ; 52.6)	49.7 (44.1 ; 55.3)	48.4 (43.1 ; 53.9)	52.4 (46.7 ; 58.4)	
Some college or over	51.7 (49.2 ; 54.2)	55.2 (49.9 ; 60.3)	53.1 (47.4 ; 58.8)	50.3 (46.1 ; 56.9)	51.5 (46.1 ; 56.9)	47.5 (41.9 ; 53.2)	

Missing	0.05 (0.01 ; 0.03)	0.18 (0.02 ; 1.3)	-	-	-	0.07 (0.01 ; 0.49)	
Health Conditions and Behavior							
Diabetes, %							0.075
Yes	9.0 (7.8 ; 10.4)	9.2 (6.8 ; 12.2)	9.1 (6.4 ; 12.9)	6.6 (4.5 ; 9.6)	7.7 (5.5 ; 10.7)	12.6 (9.4 ; 1.7)	
No	88.8 (87.2 ; 90.2)	89.2 (86.2 ; 91.8)	90.2 (86.2 ; 93.0)	90.5 (86.8 ; 93.2)	89.6 (86.3 ; 92.2)	84.1 (79.7 ; 87.8)	
Pre-diabetes	2.2 (1.7 ; 3.0)	1.5 (0.7 ; 3.3)	0.7 (0.2 ; 3.0)	2.9 (1.5 ; 5.8)	2.6 (1.4 ; 4.8)	3.2 (1.7 ; 6.1)	
Arterial hypertension, %							**<0.001**
Yes	39.2 (36.8 ; 41.6)	28.0 (23.7 ; 32.8)	34.3 (29.1 ; 39.9)	37.1 (31.9 ; 42.5)	47.3 (41.9 ; 52.8)	51.8 (46.1 ; 57.4)	
No	60.8 (58.4 ; 63.2)	72.0 (67.2 ; 76.3)	65.7 (60.1 ; 70.9)	62.9 (57.4 ; 68.1)	52.7 (47.2 ; 58.0)	48.2 (42.6 ; 53.9)	
Arthritis, %							0.580
Yes	37.1 (34.8 ; 39.5)	36.7 (31.9 ; 41.9)	35.8 (30.5 ; 41.4)	38.3 (33.1 ; 43.8)	35.9 (30.9 ; 41.2)	39.2 (33.8 ; 44.9)	
No	62.8 (60.5 ; 65.2)	63.2 (58.1 ; 68.1)	64.2 (58.5 ; 69.5)	61.7 (56.2 ; 66.9)	64.1 (58.8 ; 69.0)	60.7 (55.1 ; 66.1)	
Allopurinol use, %							0.433
Yes	1.4 (1.0 ; 2.1)	1.1 (0.4 ; 2.8)	1.6 (0.7 ; 3.4)	1.4 (0.6 ; 3.3)	0.9 (0.3 ; 2.8)	2.3 (1.1 ; 4.8)	
No	98.6 (97.9 ; 99.0)	98.9 (97.1 ; 99.6)	98.4 (96.5 ; 99.3)	98.5 (96.7 ; 99.3)	99.1 (97.2 ; 99.7)	97.7 (95.2 ; 98.9)	
Physical activity, %							0.071
Yes	7.1 (5.9 ; 8.6)	7.1 (4.8 ; 10.5)	11.1 (7.8 ; 15.6)	6.5 (4.2 ; 9.9)	5.3 (3.3 ; 8.5)	5.6 (3.4 ; 9.0)	
No	92.9 (91.4 ; 94.1)	92.8 (89.4 ; 95.2)	88.9 (84.4 ; 92.2)	93.5 (90.0 ; 95.7)	94.7 (91.5 ; 96.7)	94.4 (91.0 ; 96.6)	
Smoking status, %							**<0.001**
Yes	56.2 (53.7 ; 58.7)	51.5 (46.3 ; 56.7)	49.8 (44.1 ; 55.6)	58.5 (52.9 ; 63.9)	58.5 (52.9 ; 62.8)	64.9 (59.2 ; 70.2)	
No	43.8 (41.3 ; 46.2)	48.4 (43.2 ; 53.7)	50.1 (44.4 ; 55.9)	41.5 (36.1 ; 47.1)	42.5 (37.2 ; 47.9)	35.1 (29.8 ; 40.7)	
Anthropometric and Body Composition							
Weight, kg	80.1 ± 0.45	69.9 ± 0.8	78.1 ± 1.0	80.2 ± 0.9	86.3 ± 1.0	88.2 ± 1.0	**<0.001**
Height, m	1.68 ± 0.10	1.63 ± 0.00	1.67 ± 0.00	1.68 ± 0.00	1.70 ± 0.00	1.71 ± 0.00	**<0.001**
Body mass index, kg/m²	28.3 ± 0.1	26.1 ± 0.3	27.9 ± 0.3	28.3 ± 0.3	29.7 ± 0.3	30.0 ± 0.3	**<0.001**
Total lean mass, kg	49.9 ± 0.3	42.2 ± 0.5	47.1 ± 0.7	49.7 ± 0.6	53.6 ± 0.6	55.6 ± 0.6	**<0.001**
Appendicular muscle mass index, kg/m²	7.4 ± 0.04	6.5 ± 0.06	7.1 ± 0.08	7.5 ± 0.08	7.9 ± 0.07	8.1 ± 0.08	**<0.001**
Adequate appendicular muscle mass index, %	85.1 (83.3 ; 86.8)	75.9 (71.2 ; 80.1)	85.1 (80.7 ; 88.6)	85.6 (81.3 ; 89.1)	88.4 (84.4 ; 91.4)	92.8 (89.5 ; 95.1)	**<0.001**

Appendicular lean mass, kg	21.2 ± 0.1	17.7 ± 0.2	20.1 ± 0.3	21.4 ± 0.3	23.2 ± 0.3	24.1 ± 0.3	**<0.001**
Total fat mass, kg	29.1 ± 0.2	26.3 ± 0.5	29.6 ± 0.6	28.8 ± 0.6	30.9 ± 0.6	30.7 ± 0.6	**<0.001**
Total fat mass, %	35.8 ± 0.2	36.9 ± 0.4	37.2 ± 0.4	35.3 ± 0.5	35.1 ± 0.5	34.2 ± 0.4	**<0.001**
Strength							
Peak force, Newtons	379.2 ± 3.2	327.2 ± 5.4	359.0 ± 7.3	387.2 ± 7.3	409.8 ± 7.0	424.6 ± 7.7	**<0.001**
Time to peak force, seconds	1.1 ± 0.01	1.1 ± 0.03	1.0 ± 0.02	1.1 ± 0.02	1.1 ± 0.02	1.1 ± 0.04	0.913
Peak force velocity, degree/second	60.7 ± 0.01	60.5 ± 0.02	60.6 ± 0.04	60.7 ± 0.03	60.7 ± 0.03	60.7 ± 0.04	0.216
Biochemical parameters							
Creatinine, mg/dl	0.86 ± 0.00	0.74 ± 0.02	0.79 ± 0.01	0.87 ± 0.01	0.93 ± 0.01	1.0 ± 0.02	**<0.001**
Estimated Glomerular Filtration Rate (eGFR), ml/min/1.73m²	86.9 ± 0.46	92.7 ± 0.8	91.7 ± 0.9	86.0 ± 1.0	83.4 ± 1.0	80.2 ± 1.2	**<0.001**
C-reactive protein, mg/dl	0.44 ± 0.02	0.40 ± 0.03	0.45 ± 0.04	0.45 ± 0.05	0.45 ± 0.03	0.49 ± 0.03	0.068
Triglycerides, mg/dl	160.5 ± 4.6	132.3 ± 5.5	146.5 ± 4.8	153.2 ± 6.3	162.7 ± 5.0	216.2 ± 21.3	**<0.001**
Dietary Intake							
Energy, kcal/day	1997 ± 23.3	1878 ± 44.1	1889 ± 49.9	2069 ± 59.2	2129 ± 57.8	2036 ± 47.5	**<0.001**
Carbohydrate, g/day	245.3 ± 3.0	234.5 ± 5.5	238.2 ± 6.3	267.0 ± 8.9	251.2 ± 7.0	237.3 ± 5.6	0.221
Protein, g/day	76.2 ± 1.0	71.0 ± 1.8	74.3 ± 2.3	75.7 ± 1.9	82.5 ± 2.7	78.6 ± 2.1	**<0.001**
Protein, g/kg	0.97 ± 0.01	1.0 ± 0.02	0.99 ± 0.03	0.96 ± 0.02	0.97 ± 0.03	0.9 ± 0.02	**0.001**
Lipids, g/day	76.2 ± 1.1	72.7 ± 2.3	71.3 ± 2.5	76.8 ± 2.8	82.7 ± 2.8	77.8 ± 2.2	**0.004**
Alcohol, g/day	9.37 ± 0.7	5.7 ± 1.2	5.3 ± 0.9	7.5 ± 1.3	13.2 ± 1.9	15.3 ± 2.2	**<0.001**
Caffeine, mg/day	223.1 ± 6.9	220.1 ± 17.0	203.9 ± 12.4	222.7 ± 14.8	247.5 ± 15.8	220.1 ± 15.0	0.386
Total omega-3, g/day	1.75 ± 0.04	1.7 ± 0.06	1.6 ± 0.07	1.7 ± 1.0	1.9 ± 1.0	1.8 ± 0.09	0.053

Data described as mean ± standard error or percentage (confidence interval).
Quintiles UA for older adults: quintile 1: 0.4 – 4.4; quintile 2: 4.5 – 5.1; quintile 3: 5.2 – 5.8; quintile 4: 5.9 – 6.8 and quintile 5: 6.9 – 13.4.

Supplementary Table 2. Linear regression between quintiles of serum uric acid and peak force (Newtons). NHANES, 1999-2002.

	Model 1						Model 2					
	β (95% CI)						β (95% CI)					
	Q1	Q2	Q3	Q4	Q5	P-trend	Q1	Q2	Q3	Q4	Q5	P-trend
Total	Ref	31.7 (13.9 ; 49.5)	60.0 (42.1 ; 77.9)	82.5 (65.2 ; 99.9)	97.4 (79.0 ; 115.8)	**<0.001**	Ref	2.4 (-9.2 ; 13.9)	13.6 (1.6 ; 25.5)	13.7 (0.6 ; 26.8)	18.2 (3.5 ; 32.9)	**0.007**
Men	Ref	13.2 (-12.4 ; 38.9)	3.3 (-21.7 ; 28.4)	33.1 (8.6 ; 57.6)	24.7 (-0.4 ; 49.9)	**0.014**	Ref	14.5 (-4.6 ; 33.5)	4.2 (-16.2 ; 24.4)	17.6 (-2.4 ; 37.6)	22.5 (2.7 ; 42.3)	**0.044**
Women	Ref	-2.5 (-19.9 ; 14.8)	15.9 (-3.1 ; 34.8)	9.4 (-9.8 ; 28.6)	9.6 (-10.4 ; 29.6)	0.149	Ref	6.6 (-6.8 ; 20.0)	13.2 (-1.2 ; 27.5)	10.2 (-5.9 ; 26.3)	22.1 (5.4 ; 38.9)	**0.016**

Model 1: crude analysis.
Model 2: adjusted for age (years), race/ethnicity, education level, marital status, annual family income, diabetes, hypertension, arthritis, allopurinol use, physical activity, smoking status, total lean mass (kg), total fat mass (kg), Estimated Glomerular Filtration Rate (eGFR; ml/min/1.73m²), C-reactive protein (mg/dl), triglycerides (mg/dl), energy intake (kcal/day), protein intake (g/day), alcohol (g/day), caffeine (mg/day) and total omega-3 intake (g/day). For women, the analyses were additionally adjusted for menopausal status. The analyses for total sample were also adjusted for sex in Model 2

Quintiles UA for older men: quintile 1: 2.3 – 4.9; quintile 2: 5.0 – 5.7; quintile 3: 5.8 – 6.3; quintile 4: 6.4 – 7.3 and quintile 5: 7.4 – 13.4 mg/dL.
Quintiles UA for older women: quintile 1: 0.4 – 4.0; quintile 2: 4.1 – 4.6; quintile 3: 4.7 – 5.2; quintile 4: 5.3 – 6.0 and quintile 5: 6.1 – 11.0 mg/dL.
Quintiles UA for older adults: quintile 1: 0.4 – 4.4; quintile 2: 4.5 – 5.1; quintile 3: 5.2 – 5.8; quintile 4: 5.9 – 6.8 and quintile 5: 6.9 – 13.4 mg/dL.

Artigo 2

Original Article

Association between uric acid and appendicular muscle mass index in young, middle-aged and older adults: Findings from NHANES 1999 – 2002

Paula C. Nahas [1], Luana T. Rossato [1], Flávia M.S. de Branco [1], Catarina M. Azeredo [2], Ana Elisa M. Rinaldi [2], Erick P. de Oliveira [1*]

[1] Laboratory of Nutrition, Exercise and Health (LaNES), School of Medicine, Federal University of Uberlandia (UFU), Uberlandia, Minas Gerais, Brazil.

[2] School of Medicine, Federal University of Uberlandia (UFU), Uberlandia, Minas Gerais, Brazil.

* Corresponding author. Federal University of Uberlandia, School of Medicine, Av. Para, 1.720 Bloco 2U - Sala 20, Campus Umuarama, Umuarama, 38400902, Uberlandia, MG, Brazil. Fax: +55 34 32328620.
e-mail address: erick_po@yahoo.com.br, erickdeoliveira@ufu.br

ABSTRACT

Background: Aging leads to muscle mass loss and oxidative stress can be one of the possible causes. On the other hand, uric acid (UA), an important antioxidant, could be associated with muscle mass. However, until now this association is still controversial, and it is also not clear whether the association is age-dependent, since the causes of muscle mass loss are different in relation to age.

Aim: To investigate whether serum UA is associated with appendicular muscle mass index (AMMI) in young, middle-aged and older adults.

Methods: A cross-sectional study was performed with young, middle-aged and older adults aged from 20 to 85 years, from National Health and Nutrition Examination Survey (NHANES) 1999-2000 and 2001-2002. A total of 7149 individuals of both sexes (2923 young, 2311 middle-aged and 1915 older adults) were evaluated. Body composition was assessed by Dual Energy X-ray absorptiometry (DXA) and AMMI was calculated using the lean mass from arms plus legs, divided by the squared height; and UA levels were measured by colorimetric method. Linear regression analyses were performed to observe a possible association between AMMI and quartiles of UA levels, adjusted for potential confounders.

Results: In the unadjusted analyzes, serum UA was positively associated with AMMI in young, middle-aged and older adults, both in the total sample and according to sex. However, after adjustments for confounders, UA levels were positively associated with AMMI in older men (p-trend = 0.009), but not in young and middle-aged individuals.

Conclusion*:* Serum UA is positively associated with AMMI in older men. In this way, UA levels seems to be a protective factor for muscle mass in older men, but not in older women, young and middle-aged (men and women separately) individuals.

Keywords: Muscle mass, Uric acid, Aging, Oxidative stress.

1. Introduction

Muscle mass loss starts at approximately in middle-aged and aging intensifies this process [1], which can leads difficulties in carrying out life activities [2] and increases the risk of falls [3] and death [4]. The mechanisms that lead to age-related muscle mass reduction are not completely elucidated, but it seems to be facilitated by the combination of several factors [5], such as a sedentary lifestyle [6], an inadequate diet (mainly low energy and protein intake) [7] and increased reactive oxygen species [8, 9]. For this reason, antioxidant substances could positively affect muscle mass [10].

Uric acid (UA) is the final product of purine metabolism and a strong antioxidant, responsible for about 60% of the antioxidant activity of serum [11]. The association between UA and muscle mass has been reported in middle-aged and older individuals [12-14] and the results seem to be controversial. Two studies demonstrated a positive association; in Chinese older adults (60 years or more) [12] and in Chinese middle-aged and older adults (40 – 75 years) [14]; and one study showed negative association in United States population with 40 years or more [13]. Although the association between UA and muscle mass in young individuals seems to be unlikely, since oxidative stress has no important effect on muscle mass loss in this age [15], to date, no study evaluated this association.

Since men and women have differences in the body composition [16], the relationship between UA and muscle mass can be different according to sex. In addition, sex appears to play a role in oxidative stress levels, in which women have decreased levels of oxidative stress and increased antioxidant capacity compared to men [17]. Thus, men may be at greater risk for conditions in which oxidative stress is associated, such as muscle mass loss. In this context, only few studies performed analyzed men and women separately. Xu et al [12] showed a positive association between UA and muscle mass in older men and women; whereas Beavers et al [13] observed an association between higher UA level and less muscle mass. The results analyzed by sex are still controversial and limited, since only two studies performed this analysis. In addition, it would be important that the association between UA and muscle mass be analyzed by age, since muscle mass quantity is different throughout life [1, 18].

Therefore, further studies are needed to assess the association between UA and muscle mass evaluating according to age-range and sex. Thus, the aim of the present study was to investigate whether serum UA is associated with appendicular muscle mass index (AMMI) in young, middle-aged and older adults, men and women, from National Health

and Nutrition Examination Survey (NHANES) 1999 - 2002. We hypothesized that UA is positively associated with AMMI in older adults.

2. Methods

2.1 Survey and Participants

NHANES is a major program of the National Center for Health Statistics, which is a part of the Centers for Disease Control and Prevention, designed to assess the nutritional status and health of a nationally representative sample of the noninstitutionalized United States population, using a complex, stratified and multistage probability sampling design. The first stage consists of selecting primary sampling units (counties) by proportional probability. In stage 2, the primary sampling units are divided into segments (for example, city blocks), which are also selected by probability. Stage 3 consists of the drawing of households, and finally, in stage 4, the probabilistic selection of individuals within the previously selected house.

The present study included young, middle-aged and older adults aged from 20 to 85 years, from NHANES 1999-2000 and 2001-2002. Young individuals were considered those aged between 20 and 44 years; middle-aged individuals between 45 and 64 years and older adults aged 65 and over. A total of 7149 individuals (2923 young, 2311 middle-aged and 1915 older adults), men (n = 3448) and women (n = 3701), were evaluated and had complete serum UA and lean mass data.

Participants completed in-home interviews, physical examinations, biochemical tests, dietary interviews and other examinations [19]. Individuals over 20 years, with available demographic (age, sex, race/ethnicity, marital status, annual family income and educational level), health conditions (diabetes, arterial hypertension, arthritis, menopause, allopurinol use) and behavior (physical activity and smoking status), anthropometric, body composition, biochemical parameters and dietary data were included in the analyzes. Pregnant women, individuals with amputation and those with implausible energy intake (<800 and >400 kcal or <500 and >3500 kcal for men and women, respectively) [20] were excluded from the study (Figure 1). Self-reported history of radiographic contrast material use in past 7 days, self-reported nuclear medicine studies in the past 3 days and self-reported weight over 136 kg or height over 1.96 meters were not able to perform the lean mass assessment; therefore, they were not included in the present study. NHANES is a public data set and all participants provided a written

informed consent, consistent with approval from the National Center for Health Statistics Research Ethics Review Board (protocol #98-12 for NHANES cycle 1999-2002).

2.2 Uric acid and other biochemical parameters

Colorimetric method was used to measure UA (mg/dl), creatinine (mg/dl) and triglycerides (mg/dl) levels [21, 22]. Elevated UA levels were defined as > 7.0 and > 6.0 mg/dL for men and women, respectively [23]. Glomerular Filtration Rate (eGFR; ml/min/1.73m²) was estimated by the chronic kidney disease epidemiology collaboration (CKD-EPI) equation [24]. Serum C-reactive protein (CRP) levels were measured by high-sensitivity immuno-nephelometric [21, 22].

2.3 Anthropometrics and body composition

Body weight and height were evaluated according to the Lohman's protocol [25] and body mass index (BMI) was calculated. Whole body dual-energy x-ray absorptiometry (DXA) scans were taken with a Hologic QDR-4500A fan-beam densitometer (Hologic, Inc., Bedford, Massachusetts). The participants were positioned supine on the tabletop with their feet in a neutral position and hands flat by their side. A velcro strap was used to keep the feet stationary and together. Total lean mass, appendicular lean mass (sum of arms and legs lean mass), AMMI (appendicular muscle mass divided by height squared) [26] and fat mass (total and trunk) were evaluated. AMMI was used for the analyzes because it is recommended by the European Working Group on Sarcopenia in Older People [26], since appendicular lean mass is a compartment of the non-fat and non-bony body, which is closer to muscle mass [27], and then, the lean mass of arms and legs is basically contemplated by muscle mass. Adequate AMMI was defined as > 7.0 and > 5.5 kg/m² for men and women, respectively [28].

However, the percentages of participants with valid data decrease with increasing age, due primarily to the greater number of participants with implants, such as pacemakers, stents, and hip replacements (20-29 years: 82% of valid DXA; 30-39 years: 79% of valid DXA; 40-49 years: 78% of valid DXA; 50-59 years: 75% of valid DXA; 60-69 years: 72% of valid DXA; 70-79 years: 70% of valid DXA; over 80 years: 59% of valid DXA). The percentage of participants with valid data also decreases with increasing BMI (less than 18.5 kg/m²: 78% of valid DXA; 18.5 – 24.9 kg/m²: 82% of valid DXA; 25.0 – 29.9 kg/m²: 82% of valid DXA; 30.0 – 34.9 kg/m²: 77% of valid DXA; 35.0 – 39.9 kg/m²: 58% of valid DXA; over 40 kg/m²: 19% of valid DXA). Because DXA data lack

is related to age, BMI, weight and height (due to the weight and height exclusions mentioned above), participants with missing data cannot be treated as a random subset of the original sample, since this may be biased toward participants with the least amount of missing data.

Therefore, multiple imputation was performed for invalid and missing data, using sequential regression imputation method. SAS-callable imputation and variance estimation software developed by the Survey Methodology Program at the University of Michigan's Institute of Survey Research, IVEware, was used to impute the NHANES DXA [29]. Five completed data files containing both the non-missing and imputed DXA data values were created. For the missing data, each of the five data files contains a different set of imputed values, whereas for the non-missing data, the values are identical across the five files, since no imputation was carried out for them. The five completed data files have been concatenated into a single file, and the average of these values imputed was used for the analysis.

2.4 Dietary intake

Dietary intake data was collected by an interviewer who administered one 24h dietary recall for each volunteer. Four- step multiple pass was the method used to assess dietary intake in NHANES 1999-2000 and 2001 [22, 30], while in NHANES 2002, the dietary intake was evaluated according to the U.S. Department of Agriculture (USDA) Automated 5- steps multiple-pass method [22, 30]. The intake of total energy (kcal/day), carbohydrate (g/day), protein (g/day and g/kg), lipids (g/day), alcohol (g/day), caffeine (mg/day) and total omega 3 (g/day) [31] were evaluated. Food Intake Analysis System version 3.99 with the USDA 1994-98 Survey Nutrient Database was used to code and report the NHANES 1999-2000 dietary data. The USDA Food and Nutrient Database for Dietary Study, version 1, was used for processing the intakes for 2001-2002.

2.5 Covariates of interest

Age (years), sex (men or women), race/ethnicity (non-Hispanic white or other), marital status (single/divorced/widowed/never married or married/living as married), annual family income (0 to $19999, from $20000 to 54999 or over $55000) and educational level (under/high school graduate and some college or over) were variables evaluated as demographic characteristics. Health conditions and behavior included in the present study were self-report of diabetes (no, pre-diabetes or yes), hypertension (no or

yes), arthritis (no or yes), menopause (only for women; no or yes), allopurinol use (no or yes), and smoking status (no or yes). Physical activity level included moderate, vigorous or strength exercises (no or yes), as previously described [31]. Trunk fat mass (kg), eGFR (ml/min/1.73m²), CRP (mg/dl) and triglycerides (mg/dl) levels; the intake of energy (kcal/day), protein (g/day), alcohol (g/day), caffeine (mg/day) and total omega 3 (g/day) were also assessed. For marital status, annual family income, educational level, diabetes, arterial hypertension, arthritis, smoking status, physical activity and menopause status, a missing variable was created.

2.6 Statistical analyzes

Linear regression was used to compare demographic characteristics, health conditions and behavior, anthropometric and body composition, biochemical parameters, and dietary intake according to the quartiles of UA for men and women young, middle-aged and older adults. The age ranges were divided as previously: young = 20 to 44 years; middle-aged = 45 to 64 years; and older adults = 65 or more years. Continuous variables were described as mean and standard deviation and the categorical variables were described as percentage and confidence interval. Linear regression was used to estimate the coefficients and 95% confident intervals (95%CI) for AMMI by quartiles of UA. The analyses were performed without (Model 1) and with adjustments for confounders (Model 2). The variables included as adjustments were age, race/ethnicity, educational level, marital status, annual family income, diabetes, hypertension, arthritis (yes/no), allopurinol use (yes/no), physical activity, smoking status, trunk fat mass (kg), eGFR (ml/min/1.73m²), CRP (mg/dl), triglycerides (mg/dl); intake of energy (kcal/day), protein (g/day), alcohol (g/day), caffeine (mg/day) and total omega 3 (g/day). The analyses were also adjusted for sex in the total sample. In the analyses for subgroup of women, menopausal status was added in the adjustments. Stata 14.0 software (StataCorp, College Station, TX, USA) was used for statistical analyses and $p < 0.05$ was considered as significant. All statistical analyzes were performed considering the examination sample weight [32].

3. Results

3.1 Men's characteristics

Men' characteristics are shown in Table 1 according to the quartile of UA and age. Young, middle-aged and older men in quartile 1 to 3 had normal values of UA ($\leq$ 7 mg/dl),

while in fourth quartile, 17.3% of young men and 9.8% of middle-aged men presented adequate UA; for older men, none had adequate UA in the top quartile. Young men with higher serum UA smoked less and had less prevalence of arterial hypertension; higher prevalence of arthritis, higher body weight, height, BMI, lean mass (total, appendicular and AMMI), and total/trunk fat mass (kg and %). Regarding the biochemical parameters, young men with higher serum UA presented higher creatinine, C-reactive protein and triglycerides levels, and lower glomerular filtration rate. Individuals with higher serum UA consumed lower amounts of protein in grams per kilo and caffeine (mg); and presented higher alcohol (g) intakes.

Middle-aged men with higher serum UA had lower prevalence of diabetes and arterial hypertension, performed less physical activity, presented higher body weight, height, BMI, lean mass (total, appendicular and AMMI), and total/trunk fat mass (kg and %). For biochemical parameters, middle-aged men with higher serum UA presented higher creatinine and triglycerides levels, and lower glomerular filtration rate. Individuals with higher serum UA consumed lower amounts of carbohydrate (g) and protein in grams and grams per kilo; and presented higher alcohol (g) intake.

Older men with higher serum UA had lower prevalence of arterial hypertension, higher prevalence of arthritis, higher body weight, BMI, lean mass (total, appendicular and AMMI), and total/trunk fat mass (kg and %). For biochemical parameters, they presented higher creatinine and triglycerides levels, and lower glomerular filtration rate. Individuals with higher serum UA consumed lower amounts of protein in grams per kilo.

3.1 Women's characteristics

Women' characteristics are shown in Table 2 according to the quartile of UA and age. Young women in all quartiles had normal values of UA ($\leq$ 6 mg/dl), while middle-aged and older women had normal values in quartile 1 to 3. Young women with higher serum UA presented lower annual family income, lower prevalence of arterial hypertension, performed less physical activity, smoked more, higher prevalence of menopause status, higher body weight, BMI, lean mass (total, appendicular and AMMI), and total/trunk fat mass (kg and %). Regarding the biochemical parameters, young women with higher serum UA presented higher creatinine, C-reactive protein and triglycerides levels, and lower glomerular filtration rate. Individuals with higher serum UA consumed lower amounts of protein in grams per kilo.

Middle-aged women with higher serum UA were older, with lower proportion of non-Hispanic white and lower educational level. They had higher prevalence of diabetes, arthritis and menopause, lower prevalence of arterial hypertension, performed less physical activity, presented higher body weight, BMI, lean mass (total, appendicular and AMMI), and total/trunk fat mass (kg and %). For biochemical parameters, they presented higher creatinine, C-reactive protein and triglycerides levels, and lower glomerular filtration rate. Individuals with higher serum UA consumed lower amounts of protein in grams per kilo and caffeine (g).

Older women with higher serum UA were older, had lower prevalence of married/living with partner, presented lower annual family income and lower educational level, with higher prevalence of diabetes and arthritis, lower prevalence of arterial hypertension and performed less physical activity. They had higher body weight, BMI, lean mass (total, appendicular and AMMI), and total/trunk fat mass (kg and %). For biochemical parameters, older women with higher serum UA presented higher creatinine, C-reactive protein and triglycerides levels, and lower glomerular filtration rate. They consumed lower amounts of carbohydrate (g) and protein in grams and grams per kilo.

3.3 Uric acid and lean mass

Serum UA was positively associated with AMMI in the unadjusted analyzes for young, middle-aged and older adults for both sexes (Supplementary Table 1; Model 1). However, after the adjustments for confounders, UA levels remained positively associated with AMMI only in older men (Figure 2; Supplementary Table 1 – Model 2)

4. Discussion

The main finding of the present study was that serum UA levels were positively associated with AMMI in older men; but not in older women, young and middle-aged (men and women separately) individuals. These results suggest that UA may play an important role in the muscle mass of older men; and this association appears to be age and sex-dependent. To the best of our knowledge, the present study is the first to assess the association of UA with muscle mass in all age-range and according to sex. We observed that the older men in the top quartile of UA were associated with an increase of ~0.2 kg/m² in AMMI when compared with first quartile. This association may have clinical relevance because higher AMMI is associated with lower risk of mortality [33];

however, future studies should be performed to evaluate whether higher UA levels have direct effects on muscle mass of older men.

The findings of our study are in agreement with previous studies carried out with middle-aged and older Chinese (40 – 75 years) by Dong et al [14], as well as demonstrated by Xu et al [12] only in older adults. On the other hand, Beavers et al [13] showed an inverse association; higher UA levels were associated with lower muscle mass index from NHANES III participants (1988-1994) with 40 years or more. However, to quantify the participants' muscle mass, this study used an equation based on the resistance generated by the electrical bioimpedance, as well as sex and age. It is known that DXA is the most appropriate method for assessing body composition in studies because it is more reliable than bioimpedance [34], which is a doubly indirect method. In addition, it is not clear how the classification of the muscle mass index was used to classify sarcopenia, and this index was reported in the study as percentage, which is not common. Therefore, such limitations may explain the controversial results in relation to our study, in which the participants' body composition was assessed by DXA and used the AMMI, which is closer to muscle mass [27].

The possible mechanisms that explain the association between UA and muscle mass are not yet fully elucidated; however, oxidative stress can be one of the possible causes [9, 35]. Aging increases reactive oxygen and nitrogen species and reduces endogenous antioxidants in skeletal muscle, which can change the balance between protein synthesis and degradation, causing muscular damage [36, 37]. In addition, it is known that sex appears to play a role in oxidative stress levels, in which women have decreased levels of oxidative stress and increased antioxidant capacity than men [17]. Since UA is a powerful antioxidant [38], older men with increased UA levels may have lower oxidative stress, which seems to be beneficial for muscle mass. These explanations are confirmed with our results, once the association between UA and AMMI remained significant in older men, after adjustment. In addition, probably young and middle-aged men and women have not shown an association of UA with muscle mass because they have less effect of oxidative stress on muscle loss [39]. Such evidence is reinforced with the result of our study, which demonstrated an absence of association between UA and AMMI for young and middle-aged. Therefore, it is suggested that the association between UA and AMMI may be age and sex-specific; however, we still cannot explain in a better way about this association because the literature is still scarce for this relationship for young individuals.

Another explanation for the association remained only in older men is that, as they had higher levels of UA than women (as shown in Table 1 and Table 2), which could generate greater action of this antioxidant in muscle mass. In addition, the effect of oxidative stress seems to be more evident in older men than in women [40], possibly due to hormonal effects [41], so, men are probably more prone to antioxidant action. However, these are only hypotheses and we are unable to support them due to lack of evidence in the literature.

The present study has limitations. First, the evaluation of oxidative stress biomarkers cannot be done, which could help in understanding the relationship between UA and muscle mass. Second, the association was tested in individuals with hyperuricemia, and the results found are not applicable in individuals who have a diagnosis of gouty arthritis. Third, due to the cross-sectional design, causality cannot be stablished. Fourth, because it is an observational study, the residual effect of confounding variables may be possible. However, the analyses were adjusted by important potential confounders, which reduces this possibility. As strengths, these results can be extrapolated to the United States population since they are representative. In addition, all analyzes were adjusted for important confounders. Finally, AMMI was measured by DXA, that is a reliable method for body composition measurement [34].

In conclusion, serum UA is positively associated with AMMI in older men; but not in older women, young and middle-aged (men and women separately) individuals. These results suggest that the association between UA and muscle mass appears to be age and sex-dependent. This finding support the hypothesis that UA levels seems to exert a beneficial effect on muscle mass. Further interventional studies are needed to clarify the possible causal effect of UA on muscle mass in older men.

Funding

No sources of funding were used to assist in the article preparation.

Conflicts of Interest

The authors declare no conflicts of interest.

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Table 1. Sociodemographic, health conditions and behavior, anthropometric and body composition, biochemical parameters and dietary intake of young, middle-aged and older men by quartile of serum uric acid. NHANES, 1999-2002.

	Young					Middle-aged					Older adults				
	Q1	**Q2**	**Q3**	**Q4**	**p-value**	**Q1**	**Q2**	**Q3**	**Q4**	**p-value**	**Q1**	**Q2**	**Q3**	**Q4**	**p-value**
Uric acid, mg/dl	4.8 ± 0.5	5.7 ± 0.2	6.4 ± 0.2	7.7 ± 0.8	**<0.001**	4.4 ± 0.5	5.5 ± 0.2	6.4 ± 0.3	7.8 ± 0.7	**<0.001**	4.4 ± 0.6	5.6 ± 0.3	6.5 ± 0.3	8.1 ± 1.1	**<0.001**
Adequate uric acid, %	100	100	100	17.3 (13.1-22.4)	-	100	100	100	9.8 (6.3-15.0)	-	100	100	100	-	-
Demographic															
Age, y	33.4 ± 7.4	32.9 ± 6.6	31.9 ± 7.3	32.6 ± 7.6	0.083	52.8 ± 5.4	53.1 ± 5.7	53.2 ± 5.6	53.4 ± 5.5	0.287	73.1 ± 6.1	73.3 ± 5.7	72.8 ± 5.4	73.1 ± 6.2	0.773
Race/ethnicity, %					0.068					0.466					0.394
Non-Hispanic white	63.0 (57.7-68.0	61.9 (56.0-67.5)	68.4 (62.6-73.0)	68.4 (63.1-73.2)		73.8 (67.7-79.1)	80.2 (75.3-84.3)	82.4 (77.8-86.3)	76.1 (70.4-81.1)		85.4 (80.5-89.3)	86.2 (81.6-89.9)	88.2 (84.0-91.5)	87.3 (83.3-90.4)	
Marital status, %					0.710					0.544					0.493
Single/Divorced/Widowed/Never Married	31.8 (26.7-37.4)	35.9 (30.1-42.0)	37.1 (31.3-43.5)	40.7 (34.9-46.9)		16..1 (11.6-22.0)	16.1 (11.7-21.7)	16.7 (12.0-22.6)	18.0 (13.4-23.9)		22.1 (16.5-28.8)	17.0 (12.2-23.2)	14.9 (10.3-20.9)	22.3 (16.6-29.3)	
Married/Living with partner	57.1 (51.2-62.8)	58.7 (52.4-64.7)	57.4 (51.0-63.5)	55.7 (49.5-61.7)		78.1 (71.6-83.6)	78.9 (72.7-83.9)	74.6 (67.6-80.6)	76.8 (70.4-82.2)		71.7 (64.3-78.1)	80.3 (73.8-85.5)	83.7 (77.6-88.4)	73.8 (66.2-80.1)	
Missing	11.4 (7.6-15.8)	5.4 (3.0-9.4)	5.4 (3.-9.6)	3.5 (1.8-6.8)		5.7 (3.0-1.1)	5.0 (2.7-9.4)	8.7 (5.0-14.8)	5.1 (2.7-9.4)		6.2 (3.0-12.0)	2.6 (1.1-6.4)	1.4 (0.5-3.7)	3.9 (1.5-9.6)	
Annual Family Income, %					0.422					0.185					0.848
$0-19,999	26.7 (22.0-31.9)	21.6 (17.0-27.0)	24.6 (19.6-30.2)	18.6 (14.4-23.5)		14.2 (10.4-19.2)	13.5 (9.8-18.3)	14.9 (11.0-19.8)	11.7 (8.2-16.3)		27.3 (21.2-34.3)	27.3 (21.4-34.0)	21.5 (16.3-27.9)	27.0 (20.7-34.3)	
$20,000-54,999	35.7 (30.4-41.5)	35.1 (29.3-41.3)	38.0 (32.1-44.4)	40.0 (34.1-46.1)		36.1 (29.4-43.4)	31.0 (24.9-37.9)	30.8 (24.5-37.8)	30.5 (24.4-37.5)		44.0 (36.4-52.0)	40.1 (33.1-47.6)	41.5 (34.1-49.3)	48.7 (40.7-56.8)	
Over $55,000	35.2 (29.7-41.3)	37.2 (31.2-43.7)	32.2 (26.5-38.6)	40.5 (34.5-46.8)		47.5 (40.3-54.8)	52.4 (45.3-59.4)	53.7 (46.5-60.8)	54.4 (47.2-61.4)		23.0 (17.0-30.4)	30.7 (24.1-38.3)	34.9 (27.5-43.0)	20.2 (14.2-27.9)	
Missing	2.3 (1.1-4.7)	6.0 (3.6-9.9)	5.1 (3.0-8.4)	0.9 (0.3-2.4)		2.1 (0.9-4.7)	3.1 (1.4-6.4)	0.6 (2.3-1.5)	3.4 (1.6-7.1)		5.6 (2.9-10.5)	1.8 (0.6-4.9)	2.1 (0.7-5.7)	4.0 (2.0-8.1)	
Educational level, %					0.168					0.202					0.846
Under high school graduate	48.2 (42.3-54.0)	45.8 (39.6-52.1)	46.2 (40.0-52.5)	42.9 (37.0-49.0)		36.3 (29.8-43.3)	39.5 (32.9-46.5)	43.0 (36.0-50.3)	41.9 (35.1-49.0)		54.4 (46.5-62.0)	55.6 (48.1-62.9)	50.4 (42.6-58.1)	55.6 (47.4-63.5)	
Some college or over	50.8 (45.0-56.7)	54.0 (47.7-60.2)	53.8 (47.5-60.0)	57.1 (51.0-63.0)		63.7 (56.7-70.2)	60.4 (53.4-67.1)	57.0 (49.7-63.9)	58.1 (50.9-64.9)		45.1 (37.4-53.0)	44.4 (37.1-51.9)	49.4 (41.7-57.2)	44.4 (36.4-52.6)	
Missing	1.0 (0.2-3.9)	0.1 (0.01-0.9)	-	-		-	-	-	-		0.5 (0.1-2.2)	-	0.2 (0.03-1.4)	-	
Health Conditions and Behavior															

Diabetes, %				0.462				**<0.001**					0.476
Yes	2.5 (1.2-5.1)	2.0 (0.8-4.9)	2.7 (1.2-6.0)	3.0 (1.4-6.3)	20.0 (14.8-26.4)	6.8 (4.3-10.7)	7.3 (4.5-11.7)	6.2 (3.9-9.9)	16.8 (12.0-23.2)	9,1 (5.8-14.1)	10.6 (6.6-16.7)	19.1 (13.2-26.7)	
No	97.3 (94.7-98.6)	97.9 (95.0-99.2)	95.9 (92.2-97.8)	96.8 (93.5-98.4)	77.8 (71.3-83.2)	92.4 (88.4-95.1)	92.5 (88.2-95.4)	91.2 (86.8-94.2)	81.9 (75.4-87.0)	86.1 (80.4-90.4)	85.1 (78.6-89.9)	78.7 (71.0-84.8)	
Pre-diabetes	0.04 (0.006-0.3)	-	1.3 (0.4-3.9)	0.2 (0.03-1.4)	2.1 (0.9-5.1)	0.7 (0.1-3.2)	0.1 (0.01-0.8)	2.6 (1.0-6.2)	1.2 (0.3-5.0)	4.7 (2.4-8.8)	4.2 (2.0-8.4)	2.2 (0.8-6.0)	
Missing	0.1 (0.01-0.8)	-	0.2 (0.02-1.2)	-	-	-	-	-	-	-	-	-	
Arterial Hypertension, %				**<0.001**				**<0.001**					**<0.001**
Yes	8.4 (5.7-12.1)	9.2 (6.2-13.5)	13.0 (9.2-18.0)	20.7 (16.0-26.3)	21.9 (16.4-28.2)	25.2 (19.6-31.7)	32.2 (25.9-39.1)	40.5 (33.7-47.7)	34.1 (27.2-41.7)	44.7 (37.4-52.1)	45.6 (38.0-53.4)	59.9 (51.7-67.5)	
No	90.4 (86.6-93.1)	89.4 (85.1-92.6)	85.3 (80.2-89.2)	77.3 (71.6-82.2)	78.0 (71.6-83.2)	74.0 (67.5-79.6)	67.8 (60.9-74.0)	59.5 (52.2-66.3)	65.3 (57.7-72.2)	55.3 (47.8-62.5)	54.3 (46.5-61.9)	40.1 (32.5-48.2)	
Missing	1.2 (0.6-2.3)	1.3 (0.7-2.4)	1.7 (0.9-3.2)	1.9 (0.8-4.3)	0.1 (0.02-0.8)	0.8 (0.2-2.5)	-	-	0.6 (0.1-3.0)	-	0.05 (0.007-0.3)	-	
Arthritis, %				**0.027**				0.728					**0.037**
Yes	4.6 (2.6-8.0)	4.1 (2.1-7.6)	4.7 (2.6-8.2)	10.0 (6.7-14.9)	26.7 (20.7-33.7)	22.8 (18.5-30.1)	22.2 (17.1-28.3)	25.5 (19.8-32.2)	37.3 (30.1-45.1)	40.2 (33.1-47.7)	43.3 (35.7-51.1)	48.8 (40.8-56.9)	
No	95.4 (92.2-97.4)	95.4 (91.8-97.5)	95.3 (91.8-97.3)	90.0 (85.1-93.3)	72.6 (65.6-78.8)	76.2 (69.9-81.5)	77.8 (71.7-82.9)	74.5 (67.8-80.1)	62.7 (54.8-69.9)	59.8 (52.3-66.9)	56.2 (48.3-63.8)	50.5 (42.4-58.5)	
Missing	-	0.4 (0.06-3.2)	-	-	0.6 (0.09-4.2)	-	-	-	-	-	0.5 (0.07-3.7)	0.7 (0.09-4.7)	
Allopurinol use, %				-				0.661					0.128
Yes	-	-	-	0.6 (0.2-2.4)	2.7 (1.1-6.3)	2.9 (1.3-6.7)	2.4 (1.0-6.0)	2.1 (0.8-5.7)	6.1 (3.3-11.2)	2.1 (0.8-5.8)	2.3 (0.8-6.1)	2.6 (1.0-6.4)	
No	100	100	100	99.3 (97.5-99.8)	97.3 (93.7-98.8)	97.0 (93.3-98.7)	97.5 (94.0-99.0)	97.8 (94.3-99.2)	93.8 (88.8-96.7)	97.8 (94.2-99.2)	97.7 (93.9-99.2)	97.4 (93.6-99.0)	
Physical activity, %				0.344				**0.044**					0.638
Yes	19.7 (15.3-24.9)	21.4 (16.6-27.2)	18.5 (13.8-24.2	17.0 (12.8-22.3)	14.5 (9.7-21.1)	11.5 (7.6-17.0)	10.1 (6.3-15.6)	7.7 (4.6-12.6)	3.6 (1.6-7.8)	5.6 (2.8-10.8)	2.9 (1.2-6.8)	3.5 (1.4-8.4)	
No	80.3 (75.1-84.6)	78.6 (72.8-83.4)	81.5 (75.8-86.2)	83.0 (77.7-87.1)	85.5 (78.9-90.2)	88.5 (83.0-92.4)	89.9 (84.4-93.7)	92.3 (87.4-95.4)	96.4 (92.2-98.3)	94.4 (89.2-97.2)	97.1 (93.2-98.8)	96.5 (91.6-98.6)	
Missing	-	-	-	-	**-**	-	-	-	-	**-**	-	-	-	**-**
Smoking status, %				**0.038**				0.407					0.281
Yes	51.2 (45.4-57.1)	49.8 (43.5-56.1)	47.9 (41.6-54.2)	43.0 (37.0-49.2)	67.2 (59.9-73.7)	63.9 (56.8-70.5)	62.6 (55.2-69.4)	71.6 (64.6-77.7)	62.9 (55.1-70.1)	67.5 (60.2-73.9)	59.9 (52.0-67.3)	71.9 (64.1-78.5)	
No	48.1 (42.3-53.9)	50.2 (43.8-56.5)	52.1 (45.8-58.4)	57.0 (50.8-63.0)	32.8 (26.3-40.1)	36.0 (29.4-43.2)	37.4 (30.6-44.8)	28.2 (22.1-35.2)	37.1 (29.9-44.9)	32.2 (25.8-39.4)	40.0 (32.6-47.8)	28.1 (21.4-35.8)	
Missing	0.7 (0.1-3.4)	-	-	-	-	-	-	0.2 (0.03-1.4)	-	0.3 (0.04-2.0)	0.1 (0.02-0.9)	-	

Anthropometric and Body Composition														
Weight, kg	79.1 ± 15.6	81.9 ± 15.9	87.2 ± 20.3	95.7 ± 22.2	**<0.001**	80.8 ± 15.9	88.4 ± 16.5	90.1 ± 17.0	96.5 ± 21.7	**<0.001**	81.4 ± 16.0	80.8 ± 14.0	85.4 ± 14.7	87.5 ± 16.5	**<0.001**
Height, m	1.76 ± 0.08	1.76 ± 0.07	1.76 ± 0.08	1.78 ± 0.08	**<0.001**	1.74 ± 0.08	1.77 ± 0.07	1.76 ± 0.06	1.76 ± 0.07	**<0.001**	1.73 ± 0.07	1.73 ± 0.08	1.73 ± 0.07	1.74 ± 0.06	0.616
Body mass index, kg/m²	25.5 ± 4.4	26.3 ± 4.3	27.9 ± 5.8	30.0 ± 6.4	**<0.001**	26.7 ± 5.1	28.2 ± 4.7	29.0 ± 5.0	30.9 ± 6.6	**<0.001**	27.0 ± 4.6	26.9 ± 4.1	28.4 ± 4.5	28.9 ± 4.8	**<0.001**
Total lean mass, kg	57.2 ± 8.9	58.1 ± 8.6	60.5 ± 10.3	64.8 ± 11.2	**<0.001**	56.2 ± 8.8	60.2 ± 8.8	60.4 ± 8.3	63.5 ± 10.9	**<0.001**	53.6 ± 7.8	53.6 ± 7.7	56.0 ± 7.7	56.9 ± 8.7	**<0.001**
Appendicular lean mass, kg	26.2 ± 4.5	26.4 ± 4.5	27.6 ± 5.2	29.7 ± 5.5	**<0.001**	24.9 ± 4.3	26.7 ± 4.3	26.7 ± 4.0	28.2 ± 5.4	**<0.001**	23.0 ± 3.9	23.1 ± 3.6	24.1 ± 3.7	24.3 ± 4.1	**<0.001**
AMMI, kg/m²	8.4 ± 1.2	8.4 ± 1.1	8.8 ± 1.3	9.3 ± 1.5	**<0.001**	8.2 ± 1.1	8.5 ± 1.2	8.6 ± 1.1	9.0 ± 1.6	**<0.001**	7.6 ± 1.1	7.7 ± 0.96	8.0 ± 1.1	8.0 ± 1.1	**<0.001**
Adequate AMMI, %	90.0 (85.8-93.1)	91.6 (87.4-94.5)	95.2 (91.3-97.5)	98.5 (96.4-99.4)	**<0.001**	88.4 (82.7-92.4)	90.7 (85.6-94.1)	93.7 (89.4-96.4)	96.7 (93.3-98.4)	**0.001**	73.9 (66.8-79.9)	75.2 (68.4-80.9)	84.3 (78.3-88.9)	84.5 (77.8-89.4)	**0.004**
Total fat mass, kg	20.1 ± 8.2	21.9 ± 8.7	24.9 ± 11.3	29.1 ± 12.2	**<0.001**	22.8 ± 8.2	26.3 ± 8.8	27.8 ± 9.8	31.0 ± 11.6	**<0.001**	25.8 ± 9.5	25.2 ± 7.4	27.4 ± 8.0	28.6 ± 8.8	**0.002**
Total fat mass, %	24.3 ± 5.9	25.7 ± 5.8	27.2 ± 6.5	29.0 ± 5.8	**<0.001**	27.3 ± 5.3	28.8 ± 5.1	29.8 ± 5.4	31.1 ± 4.9	**<0.001**	30.7 ± 5.8	30.5 ± 5.0	31.3 ± 4.6	31.9 ± 4.4	**0.020**
Trunk fat mass, kg	9.7 ± 4.7	10.9 ± 5.0	12.6 ± 6.4	15.1 ± 6.8	**<0.001**	12.0 ± 5.2	14.1 ± 5.3	15.1 ± 5.8	17.2 ± 6.8	**<0.001**	13.8 ± 5.6	13.7 ± 4.7	15.1 ± 4.9	15.8 ± 5.1	**<0.001**
Biochemical parameters															
Creatinine, mg/dl	0.86 ± 0.17	0.91 ± 0.18	0.89 ± 0.16	0.99 ± 0.43	**<0.001**	0.87 ± 0.35	1.01 ± 0.98	0.95 ± 0.23	0.97 ± 0.28	**0.043**	0.98 ± 0.84	1.01 ± 0.45	1.06 ± 0.34	1.21 ± 0.39	**<0.001**
eGFR, ml/min/1.73m²	116.1 ± 19.0	111.0 ± 17.6	114.7 ± 18.6	107.9 ± 21.4	**<0.001**	100.7 ± 16.5	94.3 ± 18.1	93.4 ± 16.9	92.2 ± 17.5	**<0.001**	83.9 ± 19.0	78.1 ± 17.7	74.9 ± 18.3	65.2 ± 20.1	**<0.001**
C-reactive protein, mg/dl	0.21 ± 0.40	0.23 ± 0.45	0.25 ± 0.40	0.40 ± 0.71	**<0.001**	0.31 ± 0.96	0.33 ± 0.46	0.42 ± 0.55	0.35 ± 0.60	0.237	0.47 ± 1.04	0.46 ± 1.11	0.44 ± 0.66	0.76 ± 1.74	0.118
Triglycerides, mg/dl	120.7 ±95.3	138.6 ±104.2	152.6 ±123.8	177.5 ±143.4	**<0.001**	159.7 ±182.6	165.6 ±127.0	178.6 ±134.1	240.5 ±384.9	**0.009**	126.4 ± 68.4	140.7 ± 83.7	151.2 ± 86.8	190.7 ±246.5	**0.003**
Dietary Intake															
Energy, kcal/day	2550 ± 719.5	2429 ± 788.5	2603 ± 781.0	2477 ± 759.9	0.755	2368 ± 767.6	2410 ± 721.1	2312 ± 808.1	2287 ± 706.2	0.159	2030 ± 686.1	2065 ± 608.8	2000 ± 577.9	1997 ± 662.5	0.505
Carbohydrate, g/day	321.3 ±115.8	298.4 ±114.3	336.2 ±120.1	294.8 ±110.7	0.150	284.5 ±107.8	292.8 ±104.8	268.9 ±115.4	259.2 ± 98.7	**0.003**	252.2 ±101.3	257.7 ± 81.3	248.7 ± 83.4	238.9 ± 90.2	0.149
Protein, g/day	94.7 ± 37.3	93.8 ± 38.2	92.8 ± 41.0	93.4 ± 41.6	0.644	92.6 ± 37.9	93.7 ± 33.8	87.9 ± 33.9	86.2 ± 30.8	**0.029**	82.8 ± 33.0	79.3 ± 26.4	76.0 ± 27.1	80.6 ± 34.0	0.392
Protein, g/kg	1.22 ± 0.51	1.18 ± 0.51	1.10 ± 0.53	1.01 ± 0.50	**<0.001**	1.17 ± 0.50	1.08 ± 0.40	1.00 ± 0.40	0.92 ± 0.35	**<0.001**	1.05 ± 0.48	0.99 ± 0.34	0.91 ± 0.35	0.95 ± 0.42	**0.012**
Lipids, g/day	94.5 ± 41.3	90.7 ± 42.2	90.2 ± 39.1	90.3 ± 41.0	0.240	93.1 ± 41.8	91.0 ± 39.4	89.4 ± 44.3	87.1 ± 37.0	0.142	74.7 ± 37.5	78.0 ± 32.6	75.3 ± 28.3	75.5 ± 37.8	0.986
Alcohol, g/day	10.4 ± 22.6	10.4 ± 22.7	15.4 ± 33.3	20.3 ± 38.7	**<0.001**	9.36 ± 22.7	12.8 ± 24.5	17.1 ± 31.8	22.5 ± 40.9	**<0.001**	8.8 ± 24.7	8.7 ± 21.4	9.7 ± 20.1	11.0 ± 28.6	0.452
Caffeine, mg/day	248.5 ±364.8	187.7 ±240.2	190.1 ±216.0	192.7 ±211.4	**0.036**	352.8 ±579.0	241.0 ±242.6	284.9 ±285.8	280.7±28 3.7	0.310	200.9 ±352.8	194.3 ±208.8	193.3 ±213.7	186.1 ±176.5	0.669
Total omega-3, g/day	1.86 ± 1.13	1.89 ± 1.44	1.89 ± 1.20	1.90 ± 1.31	0.724	1.95 ± 1.20	1.92 ± 1.22	2.07 ± 1.65	1.92 ± 1.33	0.911	1.61 ± 1.00	1.65 ± 0.97	1.56 ± 0.96	1.73 ± 1.31	0.604

Notes: *Q1*, quartile 1; *Q2*, quartile 2; *Q3*, quartile 3; *Q4*, quartile 4; *AMMI,* Appendicular Muscle Mass Index; *eGFR,* Estimated Glomerular Filtration Rate.
Data described as mean ± standard error or percentage (confidence interval).
Quartiles of UA for men:

- Young (22 – 44 years) - Q1: 3.0 – 5.3 mg/dl; Q2: 5.4 – 6.0 mg/dl; Q3: 6.1 – 6.8 mg/dl; Q4: 6.9 – 12.2 mg/dl.
- Middle-aged (45 – 64 years) - Q1: 1.5 – 5.0 mg/dl; Q2: 5.1 – 5.9 mg/dl; Q3: 6.0 – 6.9 mg/dl; Q4: 7.0 – 10.8 mg/dl.
- Older adults (65 or more years) - Q1: 1.5 – 5.1 mg/dl; Q2: 5.2 – 6.0 mg/dl; Q3: 6.1 – 7.0 mg/dl; Q4: 7.1 – 13.4 mg/dl.

Table 2. Sociodemographic, health conditions and behavior, anthropometric and body composition, biochemical parameters and dietary intake of young, middle-aged and older women by quartile of serum uric acid. NHANES, 1999-2002.

	Young					Middle-aged					Older adults				
	Q1	**Q2**	**Q3**	**Q4**	**p-value**	**Q1**	**Q2**	**Q3**	**Q4**	**p-value**	**Q1**	**Q2**	**Q3**	**Q4**	**p-value**
Uric acid, mg/dl	3.1 ± 0.4	4.0 ± 0.2	4.7 ± 0.2	5.8 ± 0.7	**<0.001**	3.4 ± 0.4	4.4 ± 0.2	5.2 ± 0.2	6.6 ± 0.9	**<0.001**	3.8 ± 0.5	4.8 ± 0.2	5.7 ± 0.3	7.5 ± 1.2	**<0.001**
Adequate uric acid, %	100	100	100	66.0 (59.8-71.7)	-	100	100	100	29.9 (23.8-36.9)	-	100	100	80.7 (73.5-86.1)	-	-
Demographic															
Age, y	32.7 ± 7.1	32.9 ± 7.4	32.4 ± 7.3	32.9 ± 7.5	0.987	51.5 ± 5.3	52.9 ± 5.3	53.7 ± 5.7	54.3 ± 6.0	**<0.001**	73.1 ± 5.8	74.3 ± 6.3	73.3 ± 5.8	75.7 ± 6.5	**0.001**
Race/ethnicity, %					0.659					**0.038**					0.111
Non-Hispanic white	64.7 (59.3-69.7)	66.1 (60.9-71.0)	67.9 (63.3-73.0)	65.9 (60.2-71.2)		78.3 (73.1-82.7)	74.5 (68.9-79.5)	72.8 (67.0-77.9)	70.7 (64.7-76.1)		85.7 (81.0-89.4)	83.7 (78.2-88.0)	84.2 (79.4-88.1)	79.8 (74.0-84.6)	
Marital status, %					0.648					0.932					**0.032**
Single/Divorced/Widowed/Never Married	35.0 (29.5-41.0)	36.4 (31.0-42.2)	39.3 (33.2-45.8)	36.5 (30.7-42.7)		27.5 (22.2-33.6)	28.7 (22.9-35.2)	30.1 (24.1-36.8)	32.4 (26.3-39.1)		47.2 (40.0-54.4)	42.1 (34.5-50.0)	57.9 (50.1-65.3)	53.7 (45.7-61.5)	
Married/Living with partner	60.1 (54.1-65.9)	59.1 (53.3-64.7)	55.8 (49.3-62.1)	59.1 (52.9-65.1)		65.1 (58.6-71.1)	64.4 (57.6-70.6)	67.5 (60.7-73.7)	64.4 (57.6-70.7)		46.0 (38.8-52.3)	50.5 (42.6-58.5)	35.9 (28.8-43.6)	38.1 (30.7-46.1)	
Missing	4.8 (2.8-8.3)	4.4 (2.4-7.9)	4.9 (2.7-8.6)	4.4 (2.5-7.6)		7.3 (22.2-12.3)	6.9 (4.2-11.3)	2.3 (1.2-4.6)	3.2 (1.5-6.4)		6.8 (3.9-11.7)	7.3 (4.1-12.9)	6.2 (3.4-11.1)	8.2 (4.8-13.6)	
Annual Family Income, %					**0.016**					0.070					**0.015**
$0-19,999	26.3 (21.3-32.0)	21.8 (17.4-27.0)	26.5 (21.1-32.7)	30.9 (25.4-37.1)		18.7 (14.4-24.0)	21.4 (16.5-27.4)	19.4 (14.8-25.0)	23.1 (18.1-29.0)		38.1 (31.3-45.5)	41.7 (33.9-49.9)	43.6 (36.2-51.2)	47.6 (39.7-55.5)	
$20,000-54,999	33.9 (28.5-39.7)	40.1 (34.5-45.9)	41.0 (34.9-47.4)	38.6 (32.7-44.8)		28.2 (22.7-34.5)	31.9 (25.9-38.7)	29.9 (23.8-36.8)	35.0 (28.5-42.0)		37.9 (31.2-45.2)	33.5 (26.6-41.2)	40.6 (33.2-48.4)	35.1 (28.0-42.8)	
Over $55,000	36.8 (31.1-43.0)	36.9 (31.2-42.8)	29.3 (23.7-35.5)	28,7 (23.4-34.6)		51.3 (44.6-57.8)	44.4 (37.7-51.5)	48.0 (40.9-55.1)	40.6 (33.7-47.9)		19.0 (14.0-25.2)	22.7 (16.8-29.9)	12.4 (8.2-18.3)	12.4 (8.4-17.9)	
Missing	2.9 (1.6-5.3)	1.2 (0.6-2.4)	3.2 (1.6-6.2)	1.8 (0.8-3.8)		1.8 (0.9-3.7)	2.1 (1.0-4.4)	2.7 (1.2-6.2)	1.3 (0.6-2.7)		4.9 (2.6-8.9)	2.0 (0.8-5.0)	3.4 (1.5-7.5)	4.9 (2.5-9.5)	
Educational level, %					0.217					**0.013**					**0.004**
Under high school graduate	39,1 (33.4-45.0)	38.5 (33.1-44.2)	47.0 (10.7-53.5)	41.7 (35.8-48.0)		38.9 (32.7-45.5)	45.1 (38.4-52.0)	42.6 (35.9-49.6)	52.6 (45.5-59.6)		55.0 (47.7-62.0)	65.3 (57.5-72.4)	64.2 (56.5-71.2)	70.9 (63.6-77.2)	
Some college or over	60.9 (55.0-66.5)	61.0 (55.3-66.4)	52.9 (46.5-59.3)	57.9 (51.7-63.9)		61.1 (54.5-67.3)	54.6 (47.7-61.4)	57.0 (20.0-63.8)	47.4 (40.3-54.5)		44.8 (37.7-52.0)	34.6 (27.6-42.5)	35.5 (28.5-43.2)	28.9 (22.5-36.2)	
Missing	-	0.5 (0.07-3.3)	-	0.3 (0.04-2.3)		-	0.2 (0.03-1.8)	0.3 (0.05-2.3)	-		0.2 (0.03-1.7)	-	0.3 (0.04-2.0)	0.2 (0.03-1.6)	
Health Conditions and Behavior															

Diabetes, %				0.158				**0.018**					**0.011**
Yes	3.1 (1.6-5.9)	1.7 (0.9-3.3)	2.0 (1.0-3.8)	1.6 (0.7-3.6)		7.8 (5.2-11.5)	4.4 (2.7-7.1)	5.1 (2.9-8.8)	13.9 (9.9-19.3)		11.8 (7.9-17.2)	10.6 (6.6-16.5)	13.2 (8.8-19.4)	20.7 (15.2-27.5)	
No	96.5 (93.4-98.1)	96.6 (94.1-98.1)	98.0 (96.2-98.9)	98.0 (95.7-99.0)		91.6 (87.8-94.3)	95.0 (92.2-96.8)	92.2 (87.8-95.1)	84.9 (79.5-89.1)		87.1 (81.5-91.2)	87.8 (81.5-91.2)	83.2 (76.6-88.2)	77.7 (70.8-83.3)	
Pre-diabetes	0.4 (0.06-3.1)	1.7 (0.7-4.1)	0.04 (0.006-0.3)	0.4 (0.05-2.6)		0.6 (0.1-2.3)	0.6 (0.2-2.0)	2.6 (1.1-6.2)	1.1 (0.3-3.6)		1.1 (0.3-4.4)	0.7 (0.1-4.4)	3.5 (1.5-8.0)	1.6 (0.6-4.2)	
Missing	-	-	-	-		-	-	-	-		-	0.9 (0.1-6.0)	-	-	
Arterial Hypertension, %				**<0.001**				**<0.001**					**<0.001**
Yes	7.8 (5.2-11.3)	7.8 (5.3-11.4)	13.6 (9.6-18.8)	19.9 (15.4-25.4)		19.9 (15.3-25.5)	25.0 (19.7-31.2)	34.2 (28.0-41.0)	59.3 (52.1-66.1)		45.2 (38.1-52.4)	51.6 (43.6-59.5)	62.6 (54.8-69.7)	70.9 (63.3-77.5)	
No	91.7 (88.0-94.3)	91.8 (88.2-94.3)	86.2 (81.0-90.2)	80.1 (74.6-84.6)		80.0 (74.4-84.6)	74.3 (68.1-79.7)	65.0 (58.2-71.3)	40.5 (33.7-47.7)		54.8 (47.5-61.9)	48.1 (40.2-56.2)	37.4 (30.3-45.1)	28.3 (21.8-35.9)	
Missing	0.5 (0.1-2.9)	0.4 (0.1-1.1)	0.2 (0.04-0.7)	-		0.05 (0.007-0.4)	0.7 (0.09-4.7)	0.7 (0.1-3.8)	0.2 (0.04-0.7)		-	0.2 (0.03-1.5)	-	0.7 (0.1-5.1)	
Arthritis, %				0.465				**<0.001**					**0.008**
Yes	8.5 (5.7-12.4)	5.8 (3.7-9.0)	9.4 (6.4-13.5)	9.2 (6.1-13.6)		28.3 (22.8-34.6)	26.4 (20.9-32.8)	36.6 (30.2-43.6)	42.9 (36.1-50.0)		55.9 (48.6-62.9)	49.1 (41.2-57.1)	58.1 (50.3-65.5)	68.4 (60.7-75.2)	
No	90.9 (86.8-93.8)	94.2 (91.0-96.3)	90.5 (86.4-93.6)	90.8 (86.4-93.9)		71.6 (65.4-77.2)	73.5 (67.2-79.0)	63.3 (56.4-69.8)	56.7 (49.7-63.6)		43.6 (36.5-50.9)	50.9 (42.9-58.8)	41.9 (34.5-49.7)	31.3 (24.5-39.0)	
Missing	0.6 (0.08-4.0)	-	-	-		-	-	-	0.3 (0.04-2.0)		0.5 (0.08-3.8)	-	-	0.3 (0.04-2.0)	
Allopurinol use, %				**-**				0.621					0.053
Yes	-	-	-	-		1.2 (0.3-3.9)	-	-	0.7 (0.1-4.9)		0.2 (0.04-1.8)	-	1.4 (0.3-5.6)	1.2 (0.3-4.1)	
No	100	100	100	100		98.8 (96.1-99.6)	100	100	99.3 (95.0-99.9)		99.7 (98.2-99.9)	100	98.6 (94.4-99.7)	98.8 (95.9-99.6)	
Physical activity, %				**0.024**				**0.003**					**0.001**
Yes	18.0 (13.5-23.5)	18.7 (14.4-23.9)	16.4 (12.1-22.0)	10.9 (7.5-15.6)		9.8 (6.4-14.6)	12.9 (8.8-18.5)	12.0 (7.8-18.1)	1.5 (0.5-4.3)		2.9 (1.3-6.0)	5.7 (3.0-1.1)	1.1 (0.3-4.5)	0.3 (0.04-2.0)	
No	82.0 (76.5-86.4)	81.3 (76.1-85.6)	83.6 (77.9-87.9)	89.1 (84.4-92.4)		90.2 (85.4-93.5)	87.1 (81.4-91.2)	88.0 (81.9-92.2)	98.5 (95.7-99.5)		96.9 (93.8-98.5)	94.2 (89.4-96.9)	98.5 (95.2-99.5)	99.7 (98.0-99.9)	
Missing	-	-	-	-	**-**	-	-	-	-	**-**	0.2 (0.03-1.7)	-	0.4 (0.05-2.7)	-	
Smoking status, %				**0.004**				0.584					0.903
Yes	32.0 (26.6-38.1)	39.8 (34.1-45.7)	47.0 (40.7-53.5)	43.2 (37.1-49.4)		51.6 (44.9-58.1)	44.4 (37.6-51.4)	47.7 (40.7-54.8)	47.5 (40.6-54.6)		36.6 (29.9-43.8)	36.6 (29.2-44.7)	38.9 (31.8-46.6)	37.8 (30.5-45.7)	
No	67.6 (61.6-73.0)	60.2 (54.3-65.9)	52.9 (46.4-89.3)	56.8 (50.5-62.8)		48.4 (41.8-55.0)	55.6 (48.6-62.3)	52.5 (45.1-59.2)	51.9 (44.8-58.9)		62.2 (54.9-68.9)	63.4 (55.3-70.8)	61.1 (53.4-68.2)	62.2 (54.3-69.5)	
Missing	0.3 (0.05-2.4)	-	0.05 (0.007-0.4)	-		-	-	0.08 (0.01-0.5)	0.5 (0.07-3.5)		1.2 (0.2-5.8)	-	-	-	

Menopause, %					**<0.001**				**0.001**					0.960
Yes	7.3 (4.5-11.7)	6.4 (4.0-10.2)	8.6 (5.5-13.0)	10.4 (7.0-15.0)		62.5 (55.8-68.9)	69.6 (62.7-75.8)	71.1 (63.9-77.4)	76.0 (69.2-81.8)		88.6 (83.1-92.5)	90.5 (85.0-94.1)	92.3 (87.3-95.4)	85.3 (78.5-90.2)	
No	75.1 (69.6-80.0)	73.4 (68.0-78.2)	68.6 (62.3-74.2)	61.1 (54.8-67.0)		35.4 (29.2-42.2)	28.6 (22.6-35.5)	24.2 (18.3-31.2)	20.1 (14.8-26.8)		10.1 (6.4-15.6)	8.2 (4.8-13.6)	6.8 (4.0-11.6)	10.4 (6.2-17.0)	
Missing	17.5 (13.6-22.3)	20.1 (16.0-25.0)	22.8 (17.9-26.7)	28.5 (23.2-34.5)		2.0 (0.9-4.3)	1.7 (0.6-4.5)	4.7 (2.5-8.7)	3.8 (1.9-7.2)		1.3 (0.5-3.3)	1.3 (0.5-3.3)	0.9 (0.2-3.9)	4.2 (2.1-8.4)	
Anthropometric and Body Composition															
Weight, kg	65.3 ± 14.5	69.1 ± 15.8	73.5 ± 18.3	86.0 ± 22.2	**<0.001**	69.1 ± 16.1	72.9 ± 15.7	79.5 ± 18.8	89.7 ± 22.6	**<0.001**	64.0 ± 13.2	66.7 ± 12.5	75.7 ± 16.6	74.9 ± 17.0	**<0.001**
Height, m	1.63 ± 0.07	1.63 ± 0.06	1.63 ± 0.07	1.63 ± 0.07	0.998	1.63 ± 0.06	1.62 ± 0.06	1.63 ± 0.07	1.63 ± 0.07	0.603	1.59 ± 0.07	1.59 ± 0.06	1.59 ± 0.06	1.58 ± 0.06	0.194
Body mass index, kg/m²	24.4 ± 5.3	26.1 ± 5.8	27.7 ± 6.6	32.2 ± 7.7	**<0.001**	26.1 ± 5.8	27.9 ± 5.9	30.0 ± 6.9	33.8 ± 7.9	**<0.001**	25.3 ± 4.8	26.4 ± 4.7	29.8 ± 5.8	30.0 ± 6.4	**<0.001**
Total lean mass, kg	39.9 ± 6.3	41.2 ± 6.2	42.4 ± 7.3	47.0 ± 8.7	**<0.001**	40.2 ± 6.7	41.0 ± 5.9	43.4 ± 7.3	47.3 ± 8.7	**<0.001**	36.8 ± 5.3	37.6 ± 5.3	40.3 ± 6.6	40.5 ± 6.8	**<0.001**
Appendicular lean mass, kg	17.2 ± 3.3	17.8 ± 3.2	18.2 ± 3.8	20.5 ± 4.4	**<0.001**	16.8 ± 3.3	17.1 ± 3.0	18.4 ± 3.7	20.2 ± 4.6	**<0.001**	15.0 ± 2.6	15.4 ± 2.7	16.7 ± 3.3	16.8 ± 3.5	**<0.001**
AMMI, kg/m²	6.4 ± 1.1	6.7 ± 1.1	6.8 ± 1.3	7.7 ± 1.4	**<0.001**	6.3 ± 1.1	6.6 ± 1.0	6.9 ± 1.3	7.6 ± 1.6	**<0.001**	5.9 ± 0.9	6.1 ± 0.9	6.6 ± 1.1	6.7 ± 1.2	**<0.001**
Adequate AMMI, %	80.9 (75.4-85.4)	90.7 (86.7-93.6)	88.8 (83.8-92.4)	98.1 (95.6-99.2)	**<0.001**	78.4 (72.3-83.4)	84.8 (78.9-89.3)	89.2 (83.7-93.0)	96.1 (92.5-98.0)	**<0.001**	64.4 (57.2-71.0)	69.5 (61.7-76.3)	84.8 (79.0-89.2)	85.8 (78.5-90.9)	**<0.001**
Total fat mass, kg	23.9 ± 9.3	26.4 ± 9.3	29.6 ± 11.6	37.6 ± 14.4	**<0.001**	27.6 ± 10.2	30.6 ± 10.5	34.6 ± 12.2	40.9 ± 14.4	**<0.001**	26.0 ± 8.5	27.8 ± 7.9	34.0 ± 10.5	33.1 ± 11.0	**<0.001**
Total fat mass, %	35.2 ± 6.4	36.7 ± 6.6	38.6 ± 6.5	42.0 ± 6.4	**<0.001**	38.4 ± 5.9	40.5 ± 5.9	42.2 ± 6.0	44.2 ± 5.4	**<0.001**	39.3 ± 5.8	40.7 ± 5.3	43.8 ± 5.1	42.9 ± 5.8	**<0.001**
Trunk fat mass, kg	10.3 ± 5.1	11.7 ± 5.6	13.6 ± 6.3	18.5 ± 8.0	**<0.001**	12.8 ± 5.9	14.7 ± 5.8	16.9 ± 6.5	20.7 ± 7.7	**<0.001**	12.3 ± 4.9	13.6 ± 4.4	16.5 ± 5.6	16.3 ± 5.8	**<0.001**
Biochemical parameters															
Creatinine, mg/dl	0.65 ± 0.14	0.67 ± 0.14	0.70 ± 0.43	0.73 ± 0.48	**<0.001**	0.67 ± 0.14	0.73 ± 0.60	0.74 ± 0.41	0.77 ± 0.23	**<0.001**	0.68 ± 0.18	0.81 ± 0.60	0.86 ± 0.41	1.03 ± 0.51	**<0.001**
eGFR, ml/min/1.73m²	117.5 ± 16.6	115.3 ± 17.3	113.2 ± 18.1	111.2 ± 19.9	**<0.001**	100.0 ± 13.9	97.1 ± 16.9	93.7 ± 18.1	90.3 ± 19.4	**<0.001**	84.5 ± 13.6	77.5 ± 18.0	72.1 ± 17.7	60.8 ± 20.7	**<0.001**
C-reactive protein, mg/dl	0.28 ± 0.78	0.34 ± 0.54	0.39 ± 0.56	0.68 ± 0.93	**<0.001**	0.37 ± 0.55	0.46 ± 0.59	0.56 ± 0.60	0.83 ± 1.11	**<0.001**	0.40 ± 0.59	0.47 ± 0.84	0.55 ± 0.62	0.69 ± 0.75	**<0.001**
Triglycerides, mg/dl	94.6 ± 72.5	91.5 ± 48.6	117.6 ± 79.6	147.1 ± 105.2	**<0.001**	115.4 ± 86.0	139.8 ± 105.1	152.6 ± 116.5	168.0 ± 97.2	**<0.001**	126.8 ± 58.0	153.3 ± 85.4	152.1 ± 68.5	189.6 ± 122.3	**<0.001**
Dietary Intake															
Energy, kcal/day	1913 ± 609.9	1882 ± 662.6	1879 ± 607.5	1928 ± 703.8	0.814	1752 ± 561.0	1786 ± 603.3	1702 ± 580.6	1755 ± 632.0	0.676	1543 ± 488.7	1508 ± 555.5	1483 ± 580.6	1481 ± 467.1	0.219
Carbohydrate, g/day	254.1 ± 95.4	237.5 ± 97.5	241.3 ± 92.6	249.4 ± 108.2	0.723	219.4 ± 79.8	225.4 ± 82.8	211.8 ± 84.6	216.4 ± 89.5	0.397	203.8 ± 77.1	198.7 ± 77.6	191.2 ± 80.1	188.5 ± 71.1	**0.039**
Protein, g/day	67.6 ± 27.5	68.6 ± 28.8	67.4 ± 30.6	70.2 ± 32.2	0.401	66.2 ± 27.0	66.3 ± 27.7	67.7 ± 30.0	67.8 ± 28.0	0.473	61.5 ± 23.7	56.5 ± 25.3	56.4 ± 23.0	56.5 ± 20.4	**0.049**
Protein, g/kg	1.08 ± 0.49	1.04 ± 0.50	0.96 ± 0.47	0.86 ± 0.47	**<0.001**	0.99 ±0.44	0.94 ± 0.42	0.90 ± 0.47	0.79 ± 0.36	**<0.001**	1.00 ± 0.44	0.88 ± 0.43	0.77 ± 0.33	0.80 ± 0.36	**<0.001**

Lipids, g/day	69.8 ± 30.3	70.7 ± 33.4	69.7 ± 30.5	70.3 ± 33.8	0.956	68.4 ± 31.8	67.9 ± 32.8	65.2 ± 32.2	66.9 ± 33.0	0.445	55.6 ± 25.3	56.0 ± 28.6	56.5 ± 31.0	57.2 ± 22.9	0.547
Alcohol, g/day	4.5 ± 15.5	7.3 ± 16.9	6.3 ± 20.1	6.4 ± 21.1	0.419	4.6 ± 15.6	6.4 ± 21.2	4.2 ± 12.4	7.3 ± 20.9	0.299	2.7 ± 10.3	2.7 ± 9.7	3.0 ± 11.6	2.7 ± 9.6	0.965
Caffeine, mg/day	137.5 ± 169.9	167.4 ± 202.8	179.4 ± 222.4	163.2 ± 216.4	0.118	252.5 ± 298.4	206.5 ± 234.2	191.0 ± 186.2	204.2 ± 218.9	**0.049**	135.7 ± 163.1	149.8 ± 149.6	138.3 ± 159.3	112.3 ± 115.9	0.130
Total omega-3, g/day	1.49 ± 1.01	1.54 ± 0.99	1.51 ± 1.15	1.46 ± 1.03	0.670	1.49 ± 0.95	1.60 ± 1.14	1.59 ± 1.35	1.47 ± 1.00	0.914	1.34 ± 0.84	1.37 ± 0.98	1.36 ± 1.01	1.50 ± 0.92	0.121

Notes: *Q1*, quartile 1; *Q2*, quartile 2; *Q3*, quartile 3; *Q4*, quartile 4; *AMMI,* Appendicular Muscle Mass Index; *eGFR,* Estimated Glomerular Filtration Rate.
Data described as mean ± standard error or percentage (confidence interval).
Quartiles of UA for women:

- Young (22 – 44 years) - Q1: 1.8 – 3.6 mg/dl; Q2: 3.7 – 4.3 mg/dl; Q3: 4.4 – 5.0 mg/dl; Q4: 5.1 – 9.3 mg/dl.
- Middle-aged (45 – 64 years) - Q1: 0.4 – 4.0 mg/dl; Q2: 4.1 – 4.7 mg/dl; Q3: 4.8 – 5.6 mg/dl; Q4: 5.7 – 11.7 mg/dl.
- Older adults (65 or more years) - Q1: 2.1 – 4.4 mg/dl; Q2: 4.5 – 5.2 mg/dl; Q3: 5.3 – 6.2 mg/dl; Q4: 6.3 – 13.9 mg/dl.

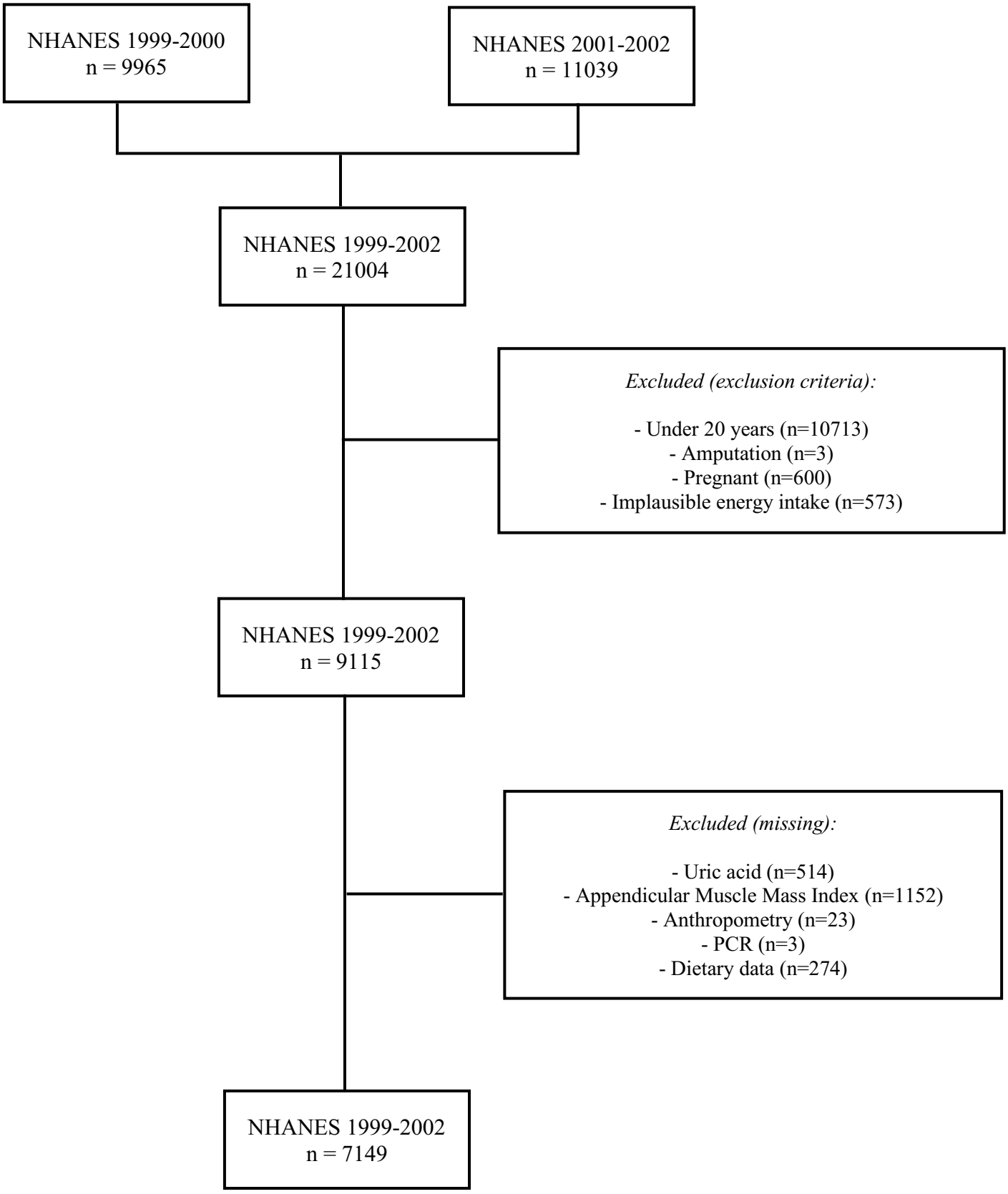

Figure 1. Flowchart of the sample selection from NHANES 1999-2002.

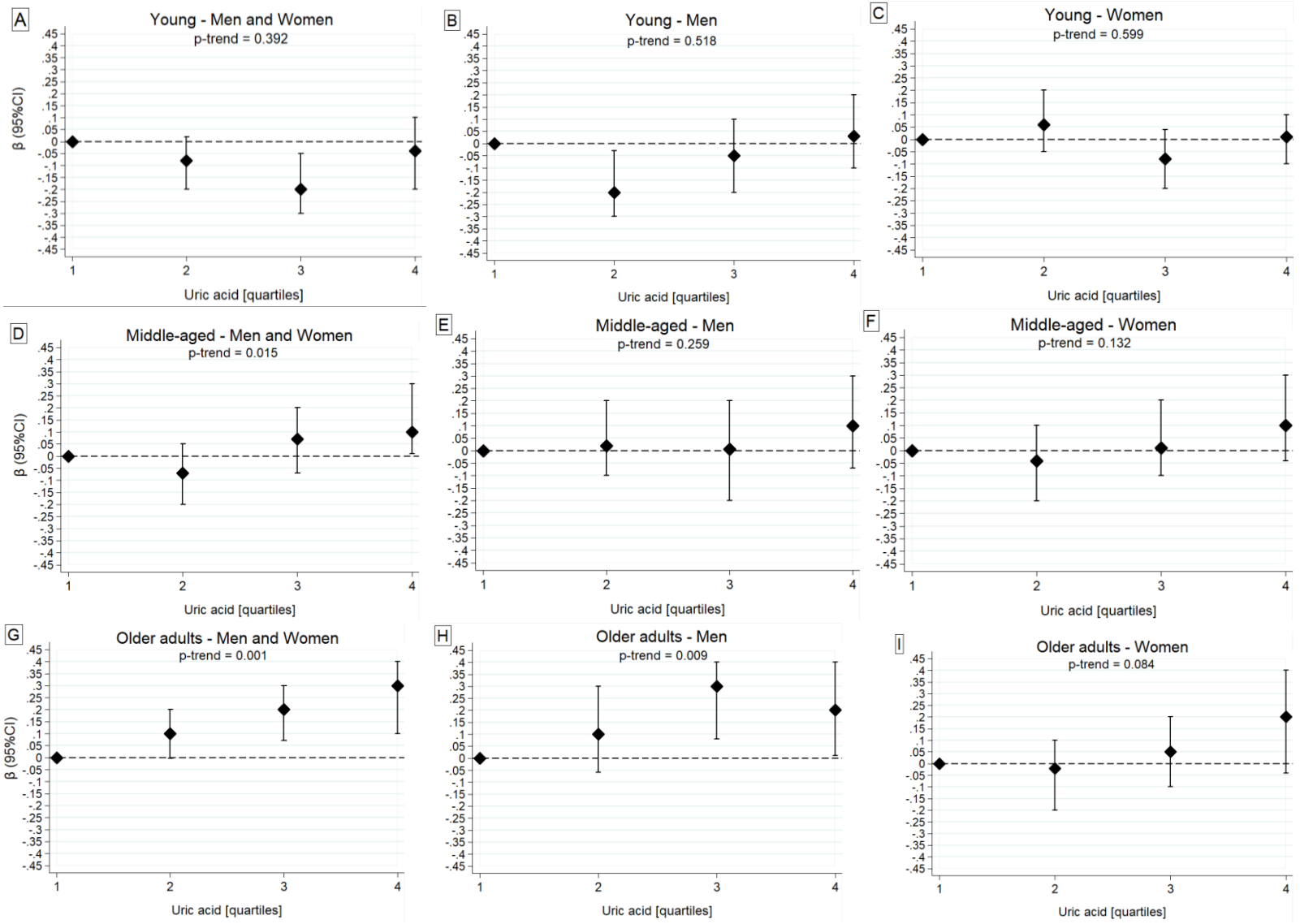
A
Young - Men and Women
p-trend = 0.392
B
Young - Men
p-trend = 0.518
C
Young - Women
p-trend = 0.599
D
Middle-aged - Men and Women
p-trend = 0.015
E
Middle-aged - Men
p-trend = 0.259
F
Middle-aged - Women
p-trend = 0.132
G
Older adults - Men and Women
p-trend = 0.001
H
Older adults - Men
p-trend = 0.009
I
Older adults - Women
p-trend = 0.084
β (95%CI)
Uric acid [quartiles]

Figure 2. Linear regression between quartiles of serum uric acid and appendicular muscle mass index in young, middle-aged and older adults. NHANES, 1999-2002.

A, young men and women; *B,* young men; *C,* young women; *D,* middle-aged men and women; *E,* middle-aged men; *F,* middle-aged women; *G,* older men and women; *H,* older men; *I,* older women.

Adjusted for age (years), race/ethnicity, education level, marital status, annual family income, diabetes, hypertension, arthritis (yes/no), allopurinol use (yes/no), physical activity, smoking status, trunk fat mass (kg), Estimated Glomerular Filtration Rate (ml/min/1.73m²), C-reactive protein (mg/dl), triglycerides (mg/dl); intake of energy (kcal/day), protein (g/day), alcohol (g/day), caffeine (mg/day) and total omega-3 (g/day). For women, the analyses were additionally adjusted for menopausal status. The analyses for total sample were also adjusted for sex.

Quartiles of UA for men:
- Young (22 – 44 years) - Q1: 3.0 – 5.3 mg/dl; Q2: 5.4 – 6.0 mg/dl; Q3: 6.1 – 6.8 mg/dl; Q4: 6.9 – 12.2 mg/dl.
- Middle-aged (45 – 64 years) - Q1: 1.5 – 5.0 mg/dl; Q2: 5.1 – 5.9 mg/dl; Q3: 6.0 – 6.9 mg/dl; Q4: 7.0 – 10.8 mg/dl.
- Older adults (65 or more years) - Q1: 1.5 – 5.1 mg/dl; Q2: 5.2 – 6.0 mg/dl; Q3: 6.1 – 7.0 mg/dl; Q4: 7.1 – 13.4 mg/dl.

Quartiles of UA for women:
- Young (22 – 44 years) - Q1: 1.8 – 3.6 mg/dl; Q2: 3.7 – 4.3 mg/dl; Q3: 4.4 – 5.0 mg/dl; Q4: 5.1 – 9.3 mg/dl.
- Middle-aged (45 – 64 years) - Q1: 0.4 – 4.0 mg/dl; Q2: 4.1 – 4.7 mg/dl; Q3: 4.8 – 5.6 mg/dl; Q4: 5.7 – 11.7 mg/dl.
- Older adults (65 or more years) - Q1: 2.1 – 4.4 mg/dl; Q2: 4.5 – 5.2 mg/dl; Q3: 5.3 – 6.2 mg/dl; Q4: 6.3 – 13.9 mg/dl.

Supplementary Table 1. Linear regression between quartiles of serum uric acid and appendicular muscle mass index in young, middle-aged and older adults. NHANES, 1999-2002.

	Model 1					**Model 2**				
	β (95% CI)					β (95% CI)				
					Young					
	Q1	Q2	Q3	Q4	P-trend	Q1	Q2	Q3	Q4	P-trend
Total	Ref	0.8 (0.7 ; 1.0)	1.6 (1.4 ; 1.7)	2.3 (2.1 ; 2.5)	**<0.001**	Ref	-0.08 (-0.2 ; 0.02)	-0.2 (-0.3 ; -0.05)	-0.04 (-0.2 ; 0.1)	0.392
Men	Ref	0.04 (-0.1 ; 0.2)	0.4 (0.2 ; 0.6)	0.9 (0.7 ; 1.1)	**<0.001**	Ref	-0.2 (-0.3 ; -0.03)	-0.05 (-0.2 ; 0.1)	0.03 (-0.1 ; 0.2)	0.518
Women	Ref	0.3 (0.1 ; 0.5)	0.4 (0.2 ; 0.6)	1.2 (1.0 ; 1.4)	**<0.001**	Ref	0.06 (-0.05 ; 0.2)	-0.08 (-0.2 ; 0.04)	0.01 (-0.1 ; 0.1)	0.599
					Middle-aged					
	Q1	Q2	Q3	Q4	P-trend	Q1	Q2	Q3	Q4	P-trend
Total	Ref	0.7 (0.5 ; 0.8)	1.3 (1.1 ; 1.5)	2.0 (1.7 ; 2.2)	**<0.001**	Ref	-0.07 (-0.2 ; 0.05)	0.07 (-0.07 ; 0.2)	0.1 (0.01 ; 0.3)	**0.015**
Men	Ref	0.3 (0.1 ; 0.6)	0.4 (0.2 ; 0.6)	0.8 (0.5 ; 1.1)	**<0.001**	Ref	0.02 (-0.1 ; 0.2)	0.007 (-0.2 ; 0.2)	0.1 (-0.07 ; 0.3)	0.259
Women	Ref	0.2 (0.02 ; 0.4)	0.6 (0.4 ; 0.8)	1.3 (1.0 ; 1.5)	**<0.001**	Ref	-0.04 (-0.2 ; 0.1)	0.01 (-0.1 ; 0.2)	0.1 (-0.04 ; 0.3)	0.132
					Older adults					
	Q1	Q2	Q3	Q4	P-trend	Q1	Q2	Q3	Q4	P-trend
Total	Ref	0.5 (0.3 ; 0.7)	1.0 (0.8 ; 0.7)	1.1 (0.9 ; 1.4)	**<0.001**	Ref	0.1 (-0.004 ; 0.2)	0.2 (0.07 ; 0.3)	0.3 (0.1 ; 0.4)	**0.001**
Men	Ref	0.03 (-0.2 ; 0.2)	0.4 (0.1 ; 0.6)	0.4 (0.2 ; 0.6)	**<0.001**	Ref	0.1 (-0.06 ; 0.3)	0.3 (0.08 ; 0.4)	0.2 (0.01 ; 0.4)	**0.009**
Women	Ref	0.1 (-0.04 ; 0.3)	.7 (0.5 ; 0.9)	0.8 (0.6 ; 1.1)	**<0.001**	Ref	-0.02 (-0.2 ; 0.1)	0.05 (-0.1 ; 0.2)	0.2 (-0.04 ; 0.4)	0.084

Model 1: crude analysis.
Model 2: adjusted for age (years), race/ethnicity, education level, marital status, annual family income, diabetes, arterial hypertension, arthritis, allopurinol use, physical activity, smoke status, trunk fat mass (kg), Estimated Glomerular Filtration Rate (eGFR; ml/min/1.73m²), C-reactive protein (mg/dl), triglycerides (mg/dl); intake of energy (kcal/day), protein (g/day), alcohol (g/day), caffeine (g/day) and total omega 3 (g/day). For women, the analyses were additionally adjusted for menopausal status. The analyses for total sample were also adjusted for sex in Model 2.

Quartiles of UA for men:
- Young (22 – 44 years) - Q1: 3.0 – 5.3 mg/dl; Q2: 5.4 – 6.0 mg/dl; Q3: 6.1 – 6.8 mg/dl; Q4: 6.9 – 12.2 mg/dl.
- Middle-aged (45 – 64 years) - Q1: 1.5 – 5.0 mg/dl; Q2: 5.1 – 5.9 mg/dl; Q3: 6.0 – 6.9 mg/dl; Q4: 7.0 – 10.8 mg/dl.
- Older adults (65 or more years) - Q1: 1.5 – 5.1 mg/dl; Q2: 5.2 – 6.0 mg/dl; Q3: 6.1 – 7.0 mg/dl; Q4: 7.1 – 13.4 mg/dl.

Quartiles of UA for women:
- Young (22 – 44 years) - Q1: 1.8 – 3.6 mg/dl; Q2: 3.7 – 4.3 mg/dl; Q3: 4.4 – 5.0 mg/dl; Q4: 5.1 – 9.3 mg/dl.
- Middle-aged (45 – 64 years) - Q1: 0.4 – 4.0 mg/dl; Q2: 4.1 – 4.7 mg/dl; Q3: 4.8 – 5.6 mg/dl; Q4: 5.7 – 11.7 mg/dl.
- Older adults (65 or more years) - Q1: 2.1 – 4.4 mg/dl; Q2: 4.5 – 5.2 mg/dl; Q3: 5.3 – 6.2 mg/dl; Q4: 6.3 – 13.9 mg/dl.

5 CONCLUSÕES E PERSPECTIVAS

A partir dos resultados transversais obtidos no presente estudo, foi possível observar associação entre os níveis séricos de AU com a força muscular de indivíduos mais velhos, tanto para homens quanto mulheres, sendo que maiores níveis de AU foram associados positivamente com maior quantidade de força nessa população (Artigo 1). Sendo assim, tal associação parece ser idade-dependente. Além disso, também foi demonstrada associação entre o AU e o IMMA apenas em homens mais velhos, mas não em indivíduos jovens ou de meia-idade, ou seja, maiores níveis séricos de AU se associaram positivamente com maiores valores de IMMA para tais indivíduos (Artigo 2). Neste sentido, a associação apresenta caráter de idade e sexo-dependente.

Desta forma, tais resultados sugerem que os níveis séricos de AU parece ser um fator de proteção para a saúde muscular nesta população. Isso para homens e mulheres mais velhos, em relação à função do músculo (força muscular), bem como para homens idosos, em relação à quantidade de massa muscular (IMMA). No entanto, sabendo que o AU pode agir como uma substância pró-oxidante e está associado à diversos desfechos negativos à saúde, é preciso cautela na extrapolação dos resultados do presente estudo.

Isso porque, devido à limitação de estudos transversais, não é possível a relação de causa e efeito entre as variáveis em questão. Sendo assim, tais resultados precisam ser confirmados em desenhos de estudo que possibilitam clarear a relação causal entre o AU com a força e com o IMMA nesta população.