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PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE
MESTRADO

MATEUS JUSTI LUVIZOTTO

ASSOCIAÇÃO ENTRE ÁCIDO ÚRICO E RIGIDEZ DE PAREDE ARTERIAL EM POPULAÇÕES APARENTEMENTE SAUDÁVEIS: REVISÃO SISTEMÁTICA

CURITIBA

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Dissertação apresentada ao programa de Pós-Graduação em Ciências da Saúde da Escola de Medicina da Pontifícia Universidade Católica do Paraná, como parte dos requisitos para obtenção do título de Mestre em Ciências da Saúde.

Orientadora: Prof.ª Drª. Cristina Pellegrino Baena.

CURITIBA

2016

ATA DA SESSÃO PÚBLICA DE EXAME DE DISSERTAÇÃO DO PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE EM NÍVEL DE MESTRADO DA PONTIFÍCIA UNIVERSIDADE CATÓLICA DO PARANÁ.

Aos doze dias do mês de dezembro de 2016 as 14h e 00min., realizou-se a sessão pública de defesa de dissertação, **"ASSOCIAÇÃO ENTRE ACIDO URICO E RIGIDEZ DE PAREDE ARTERIAL EM POPULAÇÕES APARENTEMENTE SAUDAVEIS: REVISÃO SISTEMATICA"** apresentado por **MATEUS JUSTI LUVIZOTTO** para obtenção do título de mestre; Área de Concentração: Medicina e áreas afins.

A Banca Examinadora foi composta pelos seguintes membros:

MEMBROS DA BANCA	ASSINATURA
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De acordo com as normas regimentais a Banca Examinadora deliberou sobre os conceitos a serem distribuídos e que foram os seguintes:

Profª. Drª. Cristina Pellegrino Baena — Conceito: Aprovado

Profª. Drª. Marcia Olandoski — Conceito: Aprovado

Profª. Drª. Maria Aparecida Pachaly — Conceito: APROVADO

Parecer Final: Aprovado

Observações da Banca Examinadora:

Profª. Drª. Cristina Pellegrino Baena
Presidente da Banca Examinadora

Prof. Dr. Roberto Flavio Silva Pecoits -Filho
Coordenador do PPGCS - PUCPR

NOTA BIOGRÁFICA

Mateus Justi Luvizotto, graduado em medicina pela Pontifícia Universidade Católica do Paraná em 2012. Cursa residência médica de Clínica Medica pelo Hospital Santa Casa de Misericórdia de Curitiba. Vinculado ao mestrado em Ciências da Saúde pela Pontifícia Universidade Católica do Paraná em março de 2015.

Dedico esta conquista a minha família. Nada seria possível sem a presença do meu pai Mario, minha mãe Maria Aparecida, meu irmão Luiz Guilherme e minha irmã Luiza.

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RESUMO

Objetivos: Esta revisão sistemática foi realizada com o objetivo de avaliar a relação entre ácido úrico e rigidez de parede arterial em populações saudáveis. **Métodos:** Está revisão foi realizada de acordo com o protocolo PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Foram realizadas buscas eletrônicas nas bases de dados *Embase*, *Medline*, *Pubmed*, *Web of Science* (WoS), *Cochrane Central Register of Controlled Trials* (CENTRAL) publicadas até abril de 2016. As buscas combinaram termos relacionados à exposição e ao desfecho. Resultados: A qualidade dos estudos incluídos foi avaliada com o escore de Newcastle. A direção da associação entre ácido úrico e rigidez de parede arterial e a qualidade dos estudos incluídos foi exibida em *harvest plots*. **Resultados:** De um total de 1066 referências, incluímos 22 para extração de dados. Todos os estudos foram transversais. Estes estudos únicos compreendiam 65486 indivíduos. O valor médio do ácido úrico entre a população foi de 5,25mg/dL. Notavelmente; A qualidade geral dos estudos incluídos foi baixa, com pontuações de qualidade variando de 2 a 7, sendo 9 a maior pontuação possível. Não houve diferença entre a qualidade dos estudos que relataram associação e os estudos que relataram associação positiva entre ácido úrico e rigidez de parede arterial. Conclusões: A evidência atual não apoia uma associação entre ácido úrico e rigidez arterial entre populações saudáveis.

Palavras-chave: ácido úrico, rigidez de parede arterial, hipertensão.

ABSTRACT

Aims: This systematic review performed was conducted with the objective of evaluating a relationship between uric acid and arterial wall stiffness in healthy populations. **Methods:** This review was performed according to the PRISMA protocol (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes). Electronic searches were conducted in the Embase, Medline, Pubmed, Web of Science (WoS), Cochrane Central Register of Controlled Trials (CENTRAL) published until April 2016. We combined terms related to exposure and outcome. Quality of included studies was evaluated with the Newcastle score. Direction of the association between SUA and PWV and quality of the included studies was displayed in harvest plots. **Results:** Overall, from the initial 1066 references, we included 22 for data extraction. All studies were cross sectional. These unique studies comprised 65486 individuals. The mean value of uric acid among population was 5,25 mg/dL. Notably; the overall quality of included studies was low, with quality scores ranging from 2 to 7, being 9 the highest possible score. There was a higher number of studies showing SUA positively associated with PWV in men than in women. There was no difference between quality of studies reporting no association and studies reporting positive association between SUA and PWV. **Conclusions:** Current evidence does not support an association between SUA and arterial stiffness among healthy populations.

Key-words: uric acid, arterial stiffness, hypertension.

LISTA DE ABREVIATURAS E SIGLAS

IMC	Índice de Massa Corpórea
MeSH	*Medical Subject Heading*
OR	*Odds ratio*
PRISMA	*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*
PUCPR	Pontifícia Universidade Católica do Paraná
TIAB	*Title/Abstract*
TW	*Text Words*
VOP	Velocidade de onda de pulso

LISTA DE FIGURAS

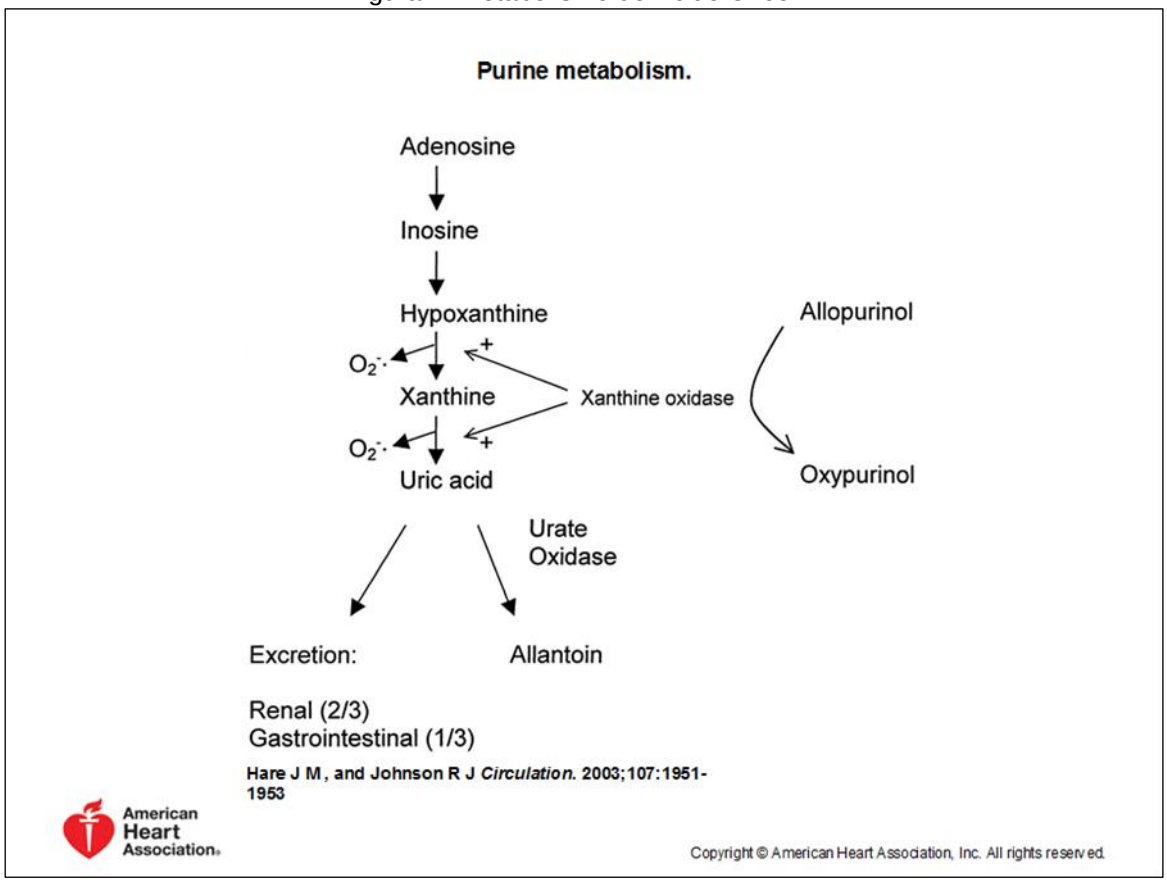
SUMÁRIO

1 INTRODUÇÃO

O ácido úrico é o produto final do metabolismo das purinas. Na maioria dos mamíferos ele é degradado pela enzima urato-oxidase (uricase), que o converte em alantoina, um produto solúvel e excretado na urina. A maioria dos humanos apresenta níveis mais elevados de ácido úrico quando comparado a outros mamíferos[1]. Durante o período evolutivo, mutações no gene da enzima uricase que se tornou inativa parecem ter se tornado fator protetor e benéfico para o ambiente da época em diversos sistemas do organismo[2]. Alguns autores propuseram que o aumento dos níveis de ácido úrico aumentaria a capacidade antioxidante e consequentemente a expectativa de vida dos hominideos, bem como uma redução nas taxas de câncer específicas para idade[3]. Além desse efeito antioxidante, vários autores encontraram uma correlação significativa entre os níveis de ácido úrico e maior inteligência em crianças e adultos jovens, assim como em pacientes portadores de Gota[4,5].

Outros autores apontaram outra vantagem evolutiva de que níveis elevados de ácido úrico poderiam ter uma atividade antioxidativa no cérebro, inclusive com efeitos protetores contra várias doenças como esclerose múltipla, doenças neurodegenerativas como doença de Parkinson, esclerose lateral amiotrófica e doença de Alzheimer[6].

Figura 1: Metabolismo do Ácido Úrico



Fonte: Reproduzido de Hare, Johnson e Johnson[7]

Todavia, na sociedade contemporânea, em que há um alto consumo de sódio, existe a hipótese de que níveis elevados de ácido úrico contribuíram para o aumento da pressão arterial e para o desenvolvimento da síndrome metabólica e todos os seus componentes, de modo a exercer um efeito deletério no sistema cardiovascular e um efeito antagonista no mundo moderno[8].

A associação entre o ácido úrico e as doenças cardiovasculares tem sido tema de interesse de estudos epidemiológicos desde a década de 60. Diversos estudos descreveram que níveis mais elevados de ácido úrico constituem um risco independente para doenças cardiovasculares e mortalidade conforme revisão realizada por Feig, Kang e Johnson[9].

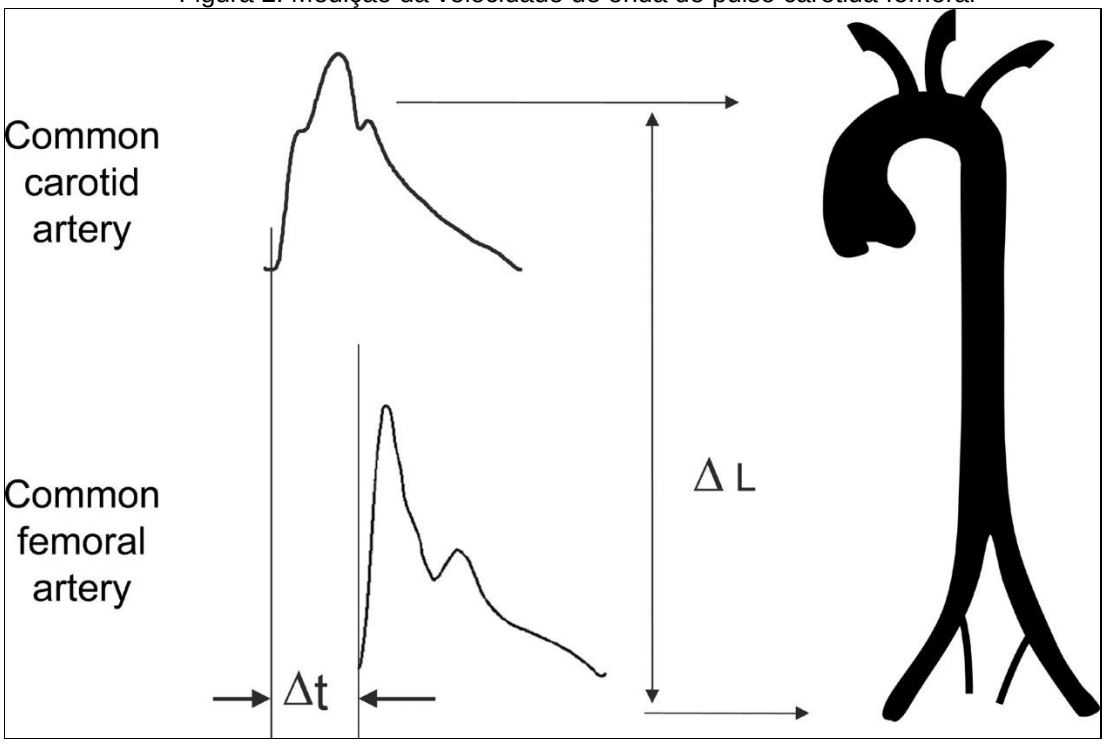
A hiperuricemia franca definida como maior que 6 miligramas por decilitro em homens e maior que 7 miligramas por decilitro em mulheres, tem sido associada a eventos cardiovasculares, doença renal, diabetes e síndrome

metabólica, com resultados contraditórios sobre o papel causal ou de biomarcador na incidência de eventos cardiovasculares[10,11].

1.1 RIGIDEZ DE PAREDE ARTERIAL

O exame clínico do pulso arterial sempre fez parte da avaliação clínica e os ancestrais já consideravam que mudanças na natureza do pulso poderiam implicar em doenças. A partir do século 19 as avaliações começaram a ser realizadas por Marey através do surgimento do esfigmômetro[12].

Figura 2: Medição da velocidade de onda de pulso carótida femoral



Fonte: Reproduzido de Laurent et al.[13]

Com o passar dos anos houve uma evolução tecnológica e entre os marcadores de doença arterial, a rigidez de parede arterial foi considerada um parâmetro importante para a avaliação do risco de doenças cardiovasculares. Entre os vários métodos disponíveis para a avaliação, a velocidade de onda de pulso (VOP) surgiu como método padrão-ouro devido à sua relativa facilidade na determinação e confiabilidade[13,14]. A VOP pode ser calculada por duas

equações. A primeira é a de Moens Korteweg que envolve as variáveis módulo de elasticidade da parede, espessura da parede, raio do vaso e a densidade do sangue. Outra equação empregada é a de Bramwell and Hill, que relaciona a VOP com a distensibilidade e é expressa da seguinte forma: PWV = (ρ × Distensibility.)[15].

Alguns estudos mostraram que a rigidez de parede arterial está associada a aumento de mortalidade cardiovascular e também em eventos isquêmicos, como acidente vascular encefálico[16,17].

1.2 RIGIDEZ DE PAREDE ARTERIAL *VERSUS* ÁCIDO ÚRICO

A associação entre ácido úrico e rigidez de parede arterial é controversa. Há uma série de estudos recentes que analisaram o ácido úrico e sua possível associação com rigidez de parede arterial, mas esta via biológica ainda não está totalmente elucidada. Embora o aumento de evidências sugira que a hiperuricemia possa ter um papel patogênico no desenvolvimento de rigidez de parede arterial, existem alguns estudos[18,19] que reportam que a elevação dos níveis de ácido úrico está associada com aumento na rigidez de parede arterial, enquanto outros estudos têm relatado ausência de associações.[20,21]

Uma explicação para esta controvérsia é que a grande maioria dos estudos sobre o ácido úrico e rigidez de parede arterial é observacional. Uma análise em um estudo na Grécia relatou que níveis séricos de ácido úrico estão associados de forma independente com a VOP carotídeo-femoral em 1225 pessoas que apresentavam pressão arterial elevada que nunca foi tratada[22]. Dois estudos independentes recrutaram participantes de exames de *check-up* periódicos no Japão (982 homens e mulheres) e na China envolvendo 620 homens e 320 mulheres, revelando uma associação significativa entre o ácido úrico e VOP[23,24]. Em outro estudo chinês, cuja população foi extraída de uma base comunitária de saúde com 1283 mulheres e 2389 homens, os resultados mostraram valores progressivamente mais elevados de ácido úrico, frequência cardíaca de repouso e pressão arterial sistólica, de acordo com os quartis, como fatores independentes entre o ácido úrico e VOP[25]. Na coorte VASORISK

(366 participantes hipertensos) a análise de regressão linear múltipla produziu uma associação positiva entre a VOP e ácido úrico em mulheres após o ajuste para fatores de risco clássicos[26].

Contrastando com esses resultados, tanto o estudo de Brisighella, com 2939 participantes livres de doenças cardiovasculares, como um estudo sul coreano de 1.276 pessoas com síndrome metabólica, não houve qualquer associação entre o ácido úrico e VOP alta do território carótida-femoral. No primeiro não havia associação após ajuste para vários parâmetros, incluindo idade, enquanto no segundo perdia-se a associação quando ajustado para circunferência abdominal.[27, 28]

Adicionalmente, existe a hipótese de diferentes efeitos do ácido úrico sobre a VOP conforme o sexo dos participantes dos estudos observacionais. No Estudo Longitudinal da Saúde do Adulto (ELSA) em uma análise envolvendo 1875 homens e 1713 mulheres, aparentemente saudáveis, foi encontrada uma associação significativa entre homens, independente da idade, frequência cardíaca, pressão arterial, índice de massa corpórea (IMC) e glicemia em jejum, porém não foi encontrada associação entre as mulheres[29].

2 JUSTIFICATIVA

É importante analisar a potencial associação entre ácido úrico e VOP em indivíduos saudáveis, uma vez que a maioria dos estudos que evidenciam o papel determinante do ácido úrico em desfechos cardiovasculares tem como limitação a causalidade reversa já que esta associação pode ser confundida por IMC, pressão arterial, triglicerídeos, colesterol, taxa de filtração glomerular, entre outros.

Embora tanto a VOP como os níveis de ácido úrico sejam considerados preditores de risco cardiovascular, os resultados divergentes entre os estudos demonstram uma notável lacuna de evidência sobre a associação independente e a direção de associação entre a rigidez de parede arterial e o ácido úrico. Deste modo, através desta revisão sistemática tem-se o objetivo de avaliar a evidência disponível sobre a associação entre ácido úrico e VOP em populações aparentemente saudáveis.

3 OBJETIVO

3.1 OBJETIVO GERAL

O objetivo do projeto é conhecer e analisar a evidência disponível sobre a relação entre o ácido úrico e a rigidez de parede arterial em populações livres de doenças cardiovasculares.

3.2 OBJETIVO ESPECÍFICO

Avaliar as possíveis diferenças na relação entre o ácido úrico e a rigidez de parede arterial entre mulheres e homens.

4 DESENVOLVIMENTO

O artigo apresentando nesta tese teve seu início ainda em Rotterdam, na Holanda, quando participei do Programa Ciências sem Fronteiras, entre os anos de 2012 e 2013. A possibilidade de realizar o intercâmbio surgiu durante a graduação em Medicina, quando o Professor Roberto Flavio Silva Pecoits que me introduziu na iniciação cientifica por meio de projetos do Programa Institucional de Bolsas de Iniciação (PIBIC) da Pontifícia Universidade Católica do Paraná. Durante a graduação me interessei pelo estudo de doenças renais e cardiovasculares e o projeto de iniciação científica se desenvolveu a partir de um estudo experimental em ratos Wistar com o objetivo de avaliar o impacto da espironolactona na miocardiopatia urêmica.

Ainda na graduação, participei de um programa de verão em Epidemiologia no Erasmus Medical Center, em Rotterdam, nos Países Baixos. Em seguida cursei as disciplinas de *Study Design*, *Biostatistics* e *Clinical Epidemiology* durante seis meses. Após esse período, iniciei a elaboração de um artigo. O meu tutor foi o professor Abbas Dehgan e tive como co-orientadora Sanaz Sedaghat, aluna de doutorado daquela instituição. O objetivo da pesquisa era avaliar a associação entre ácido úrico e rigidez de parede arterial em uma população da cidade de Rotterdam. O tema de interesse surgiu através do Professor Oscar Franco e do Professor Abbas Dehgan. Para tal, foi utilizada uma coorte de uma população residente em Rotterdam. A coorte de Rotterdam foi criada pelo professor Albert Hofman do Departamento de Epidemiologia e Bioestatística do Erasmus Medical Center. O objetivo da coorte é investigar fatores de risco para doenças cardiovasculares, oftalmológicas, neurológicas, endocrinológicas e psiquiátricas em populações mais velhas de Ommoord, subúrbio de Rotterdam[30]. Após a realização das análises estatísticas, verificou-se que não havia associação e a submissão foi desencorajada naquele momento. Como os resultados eram muito conflitantes entre os estudos usados como referência daquela análise, surgiu à ideia de realizar uma revisão sistemática. A priori, foram incluídas na revisão populações saudáveis e doentes, porém, durante a elaboração do artigo,

elegemos as populações saudáveis, para não haver uma confusão na interpretação do resultado e na relação causal. O artigo foi elaborado em duas etapas. Na primeira etapa, foi realizada uma busca nas bases eletrônicas sobre o tema, com auxílio de Wichor M. Bramer, especialista em informática com grande experiência em pesquisas para revisões sistemáticas, com intuito de abranger o maior número possível de artigos relacionados à pesquisa. No meu retorno ao Brasil, apareceu a oportunidade de trabalhar com a Professora Cristina Pellegrino Baena, da Pontifícia Universidade Católica do Paraná com quem tive contato durante o meu período de intercâmbio. Ao longo da extração de dados dos artigos incluídos na revisão, o aluno de Medicina da PUCPR, Murilo Guedes passou a colaborar na execução do artigo. A finalização do artigo deu-se durante o período de Residência em Clinica Médica na PUCPR.

O detalhamento da metodologia do artigo será apresentado nas próximas páginas.

5 MÉTODOS

5.1 ESTRATÉGIAS DE BUSCA

Esta revisão sistemática foi conduzida de acordo com o protocolo PRISMA (*Preferred Reporting Items for Systematic Reviews and Meta-Analyses*)[31]. O protocolo PRISMA consiste em uma lista de verificação de 27 itens passando pelo título, resumo, introdução, métodos e resultados até chegar à discussão. Também há um diagrama de fluxo de quatro fases que envolvem a seleção dos artigos em: identificação, triagem, elegibilidade e finalmente a inclusão dos artigos. O objetivo é ajudar os autores a melhorar os relatórios de revisões sistemáticas e meta-análises.

Foi realizada busca eletrônica sobre ácido úrico e rigidez de parede arterial nas bases *Embase*, *Medline*, *Pubmed*, *Web of Science* (WoS), *Cochrane Central Register of Controlled Trials* (CENTRAL) publicadas até abril de 2016. As buscas combinaram termos relacionados à exposição e ao desfecho, sem restrição de idioma.

A estratégia de busca utilizada foi realizada da seguinte forma: (eg 'uric acid'/de OR hyperuricemia/de OR 'uric acid blood level'/de OR ((urea/de OR uremia/de) AND (blood/de OR serum/de)) OR ('uric acid' OR ((serum OR level* OR blood) NEAR/3 (urea OR uremi* OR uraemi* OR azotaemia OR azotemia OR hyperazotemi* OR hyperuremi*))) which were combined with search terms related to the outcome (eg('arterial stiffness'/de OR 'pulse pressure'/de OR 'arterial pressure'/de OR 'blood vessel compliance'/exp OR 'blood vessel calcification'/exp OR 'augmentation index'/de OR 'Young modulus'/de OR 'pulse wave'/de OR 'pulsatile flow'/de OR (((aort* OR arter* OR vascul* OR vessel*) NEAR/6 (stiff* OR complian* OR calcif*)) OR (wave NEXT/1 (velocit* OR reflection*)) OR ('internal carotid' NEAR/3 index) OR (pulse NEAR/3 (pressure* OR tension*)) OR distensibil* OR augmentation OR 'stiffness index' OR ((capacit* OR oscillat*) NEAR/3 complian*) OR ((elastic* OR young) NEXT/1 modul*) OR PWV OR CPP OR 'pulsatile flow'):ab,ti)

5.2 CRITÉRIOS DE INCLUSÃO E EXCLUSÃO

Após a realização da estratégia de busca, dois autores independentes incluíram os artigos que preenchiam os seguintes critérios: 1) Desenho de estudo definido como Ensaio Clínico Randomizado, Estudo de Coorte, Caso-Controle, Transversal, 2) exposição principal: ácido úrico 3) desfecho principal: rigidez de parede arterial. Foram excluídas cartas, revisões e relatos de caso.

5.3 EXTRAÇÃO DE DADOS

Os dados foram extraídos usando um banco de dados estruturado criado previamente à busca na literatura. Características detalhadas dos estudos foram extraídas por dois autores, incluindo desenho de estudo e de análise (tamanho da amostra, a duração do acompanhamento e os critérios de inclusão), características da população (idade, sexo, etnia), validação da exposição e do desfecho (tais como biomarcadores, avaliação de método), avaliação de resultados, análise (como método estatístico, medida de associação, análises de sensibilidade), os resultados (estimativa de efeito, o erro padrão / intervalo de confiança) e ajustes para co-variáveis como hipertensão arterial, uso de medicamentos e outros potenciais confundidores.

5.4 AVALIAÇÃO DA QUALIDADE DOS ARTIGOS

Foi utilizado um índice de qualidade pré-definido (*Quality score*) para avaliar a qualidade dos estudos incluídos. O *Quality Score* (QS) é uma versão modificada de sistemas de pontuação utilizados anteriormente (Newcastle). Uma pontuação de 0, 1 ou 2 pontos foi alocado para cada um dos seguintes sete itens: a)representatividade da população estudada (verdadeiramente representativa da comunidade, um pouco representativa da comunidade, sem descrição da derivação da coorte; b)ácido úrico como a exposição principal (sim ou não); c)avaliação da exposição de interesse(descrição de jejum); d) método validado de rigidez de parede arterial(sim ou não); e)utilização do

método padrão ouro de rigidez de parede arterial; f)desenho do estudo(longitudinal); g)exclusão de pessoas que tomam medicação anti-hipertensiva, estatina, antidiabéticos e ajuste na análise para a idade, sexo, taxa de filtração glomerular IMC, doenças cardiovasculares. Isto permitiu uma pontuação total 0 a 9 pontos.

5.5 REPRESENTAÇÃO GRÁFICA DOS ESTUDOS INCLUÍDOS NA REVISÃO SISTEMÁTICA

Para a apresentação dos resultados foram utilizados *harvest plots* para combinar os estudos e exibir a direção dos efeitos dos estudos primários sobre ácido úrico e rigidez de parede arterial.

O *harvest plot* é um gráfico de barras que mostra os estudos com associação positiva, negativa e também aqueles sem associação significativa. Cada estudo é representado por uma barra. A altura de cada barra representa a qualidade dos estudos[32].

6 RESULTADOS

The association between uric acid and arterial stiffness in apparently healthy populations: systematic review

Luvizotto MJ[1*], Guedes MH[1*], Bramer WM[2], Pecoits-Filho R[1], Moraes TP[1], Faria Neto JR[1] Sedaghat S[2,] Franco OH[2] Dehghan A[2] Baena CP[1.]

1. Pontifícia Universidade Católica do Paraná, Curitiba, Paraná, Brazil.
2. Department of Epidemiology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands.
3. Medical Library, Erasmus MC, University Medical Center, Rotterdam, the Netherlands.
* Authors contributed equally

Corresponding author:
Prof.ª Cristina Pellegrino Baena, Pt, MSc, PhD
School of Medicine
Pontifícia Universidade Católica do Paraná
P.O.Box 80215-901
1155, Curitiba
Brazil
Phone: 554132712285
cbaena01@gmail.com

ABSTRACT

Background: Arterial stiffness is a predictor of cardiovascular disease and several studies showed that uric acid is associated with arterial stiffness. However, other studies reported contrasting results. To clarify this is important to systematically address the question about this potential association to understanding of the development of cardiovascular diseases. *Objective and Methods:* We aimed to systematically evaluate the association of uric acid and arterial stiffness within apparently healthy populations. We conducted a systematic review of literature published in Medline, Embase, Cochrane Central, PubMed, and Web of Science until April 9, 2016. Two reviewers selected the articles that met the selection criteria. Disagreements were solved by consensus. For each study we extracted information on publication, studied population, uric acid and arterial stiffness measurements, statistical analysis, controlling of possible co-variables, crude and adjusted estimates and quality of the study, author, journal, year of publication, country, ethnicity, study design, study size, age, sex, use of medication, comorbidities , assay of measure of arterial stiffness, unit of measurement. Quality of included studies was evaluated with the Newcastle score. Direction of the association between SUA and arterial stiffness and quality of the included studies was displayed in harvest plots. *Results:* Overall, from the initial 1066 references, we included 22 for data extraction. All studies were cross sectional. These unique studies comprised 65486 individuals. The mean value of uric acid among population was 5, 25 mg/dL. Notably, the overall quality of included studies was low, with quality scores ranging from 2 to 7, being 9 the highest possible score. There was a higher number of studies showing SUA positively associated with PWV in men than in women. There was no difference between quality of studies reporting no association and studies reporting positive association between SUA and PWV. *Conclusions:* Current evidence does not support an association between SUA and arterial stiffness among healthy populations.

Key-words: 1;2;3.

INTRODUCTION

The interest in uric acid as a risk factor for cardiovascular diseases has been recorded since the late 19th century. Specifically, early investigators thought serum uric acid (SUA) was the main cause of gout and hypertension. With the development of drugs that reduce SUA levels in last decades, epidemiological research explored the importance of uric acid among populations with established cardiovascular diseases[1]. Several studies showed that hyperuricemia is associated with a wide range of disorders, such as hypertension, gout, kidney disease, cardiovascular events, metabolic syndrome and diabetes[2,3]. However, the exact role of SUA was undetermined, because the majority of these studies were observational and therefore not able to address whether uric acid was a disease marker or a definite risk factor.

In spite of these limitations, studies among populations free from cardiovascular disorders have shown that SUA predicts the risk for developing hypertension[4]. The path by which uric acid exerts its effects, however, is under investigation. One of the main hypotheses is that SUA levels act in the renin-angiotensin system resulting in inhibition of endothelial nitric oxide, and proliferative effects on vascular smooth muscle. This could reduce elasticity and promote atherosclerosis[5]. On the other hand, arterial stiffness, a measure of arterial disease, is consistently associated with atherosclerosis and cardiovascular mortality[6,7]. Among the various methods available, pulse wave velocity (PWV) has emerged as the gold standard method due to its relative ease in the determination and reliability[8].

Several recently published studies that aimed to investigate the association between arterial stiffness assessed by PWV and SUA resulted in conflicting conclusions. Mostly, studies evaluating the association between SUA and arterial stiffness are observational. Moreover studies analyzing these potential associations in apparently healthy participants are scarce. A Greek study, involving 1225 participants, reported that SUA are independently associated with Carotid-femoral PWV who had high blood pressure that has never been treated[9]. Two independent studies enrolled apparently healthy

individuals from check-up programs in Japan (982 men and women) and China (940 men and women). After adjustment for confounding variables, both studies reported a significant association between SUA and PWV in multivariate analysis[10,11]. In another Chinese study, composed by 1283 women and 2389 men, both healthy and drawn by community database, showed that progressive higher levels of SUA, cardiac rate and systolic blood pressure, according to quartiles, were independently associated with PWV[12] The VASORISK cohort study with 366 hypertensive patients described a positive linear association between SUA and PWV after adjustment for classic risk factors[13]. Contrarily, both Brisighella study, with 2939 healthy individuals, and a South-Korean study, composed by 1276 patients with metabolic syndrome, did not find any significant association between SUA and PWV assessed by carotid-femoral method[14,15]. The Brazilian cohort study ELSA analyzed 1875 men and 1713 women, apparently healthy, and found significant association among men, regardless of age, heart rate, blood pressure, body mass index (BMI) and fasting glucose, but no association among women[16].

The contrasting results reported by these studies might be accounted for differences in data regarding population, methods of assessment or analysis. However, provided that the relation between SUA and arterial stiffness may yield new insights into the understanding of the development of cardiovascular diseases, it is important to systematically address the question about this potential association. Therefore, our study was designed to analyze and clarify the available evidence concerning the association between SUA levels and arterial stiffness among apparently healthy individuals.

METHODS

Search strategy

We conducted electronic searches through Embase, Medline, Pubmed, Web of Science (WoS), The Cochrane Central Register of Controlled Trials (CENTRAL) of the literature published up until April 9, 2016, together with a professional librarian. We used combinations of Medical Subject Headings (MeSH) and free text words that included search terms related to the (eg 'uric acid'/de OR hyperuricemia/de OR 'uric acid blood level'/de OR ((urea/de OR uremia/de) AND (blood/de OR serum/de)) OR ('uric acid' OR ((serum OR level* OR blood) NEAR/3 (urea OR uremi* OR uraemi* OR azotaemia OR azotemia OR hyperazotemi* OR hyperuremi*))) which were combined with search terms related to the outcome (eg('arterial stiffness'/de OR 'pulse pressure'/de OR 'arterial pressure'/de OR 'blood vessel compliance'/exp OR 'blood vessel calcification'/exp OR 'augmentation index'/de OR 'Young modulus'/de OR 'pulse wave'/de OR 'pulsatile flow'/de OR (((aort* OR arter* OR vascul* OR vessel*) NEAR/6 (stiff* OR complian* OR calcif*)) OR (wave NEXT/1 (velocit* OR reflection*)) OR ('internal carotid' NEAR/3 index) OR (pulse NEAR/3 (pressure* OR tension*)) OR distensibil* OR augmentation OR 'stiffness index' OR ((capacit* OR oscillat*) NEAR/3 complian*) OR ((elastic* OR young) NEXT/1 modul*) OR PWV OR CPP OR 'pulsatile flow'):ab,ti) No language restriction was applied and studies were translated by native speakers experienced in the health field. In the case of multiple publications, the most recent and complete report was included.

Study Selection

We included articles according following criteria: a) Study design: Randomised controlled trials, cohort studies (prospective and retrospective), case-control studies and cross sectional studies; b) studies reporting association between SUA and arterial stiffness; c) studies reporting exposure

was uric acid as a main exposure; d) studies reporting arterial stiffness as a main outcome.

We excluded articles if they were letters, reviews, conference proceedings and case reports, recruiting pregnant women or children. Studies where serum uric acid was not reported as the main explanatory variable were excluded. Additionally, studies reporting association between SUA and PWV in unhealthy population (e.g. hypertensive, diabetic, stroke, lupus, chronic kidney disease) were excluded.

Data extraction and analyses

Data were extracted by two reviewers independently. For each study we extracted information on publication, studied population, SUA and arterial stiffness measurements, statistical analysis, controlling of possible co-variables, crude and adjusted estimates and quality of the study, author, journal, year of publication, country, ethnicity, study design, study size, age, sex, use of medication, comorbidities , assay of measure of arterial stiffness, unit of measurement. When studies reported population in quartiles, we chose the higher quartiles for age and the healthier for comorbidities - e.g., the quartile with fewer numbers of criteria for metabolic syndrome. To make studies comparable and allow for a synthesis of the reported results, we recorded the direction of the association between SUA and PWV even when primary studies used different distributions in their analysis (e.g. quartiles, tertiles). Additionally, we used a weighted (for sample size) to determine the mean age and mean SUA across studies.

Quality assessment

We used a predefined quality score (QS) to evaluate the quality of included studies. The QS is a modified version of previously used scoring systems (NEWCASTLE) [17]. A score of 0, 1 or 2 points was allocated to each of the following seven items: a) representativeness of the studied (truly

representative of the community), somewhat representative of the average in the community and no description of the derivation of the cohort); b) uric acid as main exposure (yes or no); c)Ascertainment of exposure of interest (fast or no description); d)validated method for arterial stiffness (yes or no); e) Assessment of outcome - Gold standard (yes or no); f)outcome of interest was not present at start of study (yes or no); g) exclusion of potential confounders from the analysis (people taking antihypertensive medication, statin, antidiabetic and not excluded but adjusted in the analysis; for age, sex, estimated glomerular filtration rate, hypertension , body mass index, medication, diabetes, prevalence of myocardial infarction). This allowed a total score between 0 and 9 points, with 9 representing the highest quality across included studies.

Studies effect estimates

We first tried to run formal meta-analysis using random effects however since primary studies presented their estimates as linear coefficients and OR (95%) using heterogeneous categories as reference (e.g. men comparing to women, SUA quartiles, SUA quintiles, age quartiles, components of Metabolic syndrome) we ended up with only 2 comparable studies[16,18] in the forest plot. Therefore we used harvest plots to combine evidence for the association between uric acid and arterial stiffness. The harvest plots show the studies which reported significant positive associations, inverse associations, or no significant associations[19]. The height of the bar represents the quality score, while the filling of the bar represents the exposure assessment. PWV methods displayed in the plots were carotid-femoral (cf), brachial-ankle (ba) and others (which included less commonly reported methods, namely brachial-radial, *aortic distensibility*, carotid, and pulse pressure).

RESULTS

Overall, 1066 references were identified from the search strategy (Figure 1), of which 837 were excluded based either on title or abstract. The remaining papers (229) were included for full review by two independent authors, resulting in 207 additional exclusions based on population criteria. Therefore, 22 studies were included for data extraction.

Characteristics of studies included

Table 1 summarizes the main characteristics of the 22 studies included for systematic review. The studies were published between 2003 and 2015. These studies comprised 65486 individuals range 124 to 13899. According to study design, all the studies were cross-sectional. Seventeen studies enrolled individuals in Asia[10,11,15,18,20-32], two in Europe[33,34], and two in America[16,35]and one in Africa[36].

Serum uric acid measurement

SUA levels were differently reported among studies, with seven[15,18,2,24,28,31,32] reporting as means (sd) of the population, ten[10,11,16,22,23,25,26,29,34,36]by genders and five[21,27,30,33,35,]in SUA tertiles, quartiles or by subgroups of the main population. Some studies reported mean values of uric acid in general population and other studies divided into quartiles. We had to get the weighted average according to tertiles or quartiles. The conversion of SUA levels measured in mmol/L to mg/dL was carried out by dividing the value in mmol/L by a conversion factor of 59.48 [37] .

The mean value of uric acid among population was 5,25 mg/dL

Association between SUA and arterial stiffness

Figures 1 and 2 depict Harvest Plots of the association between SUA and arterial stiffness separated by genders. Notably, the overall quality of

included studies was low, with quality scores ranging from 2 to 7, being 9 the highest possible score. Among men, from six[11, 16, 18, 22, 32, 36] studies assessing PWV by carotid-femoral, four[11, 16, 18, 36] found a positive association between SUA and arterial stiffness. Among studies ascribed the higher quality using cf method, one[16] reported a positive association and another one[22] found no association. Out of nine studies[10, 15, 21, 23-26, 29, 30]measuring PWV by brachial-ankle method in males, six[10, 21, 23-25, 29] reported a positive association and three[15, 26, 30]found no association. Regarding the best quality available, two[29, 30]studies found a positive association and one[15] reported no association. Three studies[27, 28, 34] evaluating PWV by other methods in male population reported positive association between SUA and arterial stiffness and three[(31, 33, 35)]did not find any association. Just one study[35] assessing PWV by methods different than cf and ba scored 7 in QS, whose main finding was no association between uric acid and arterial stiffness among men.

Among women, a positive association between serum uric acid and arterial stiffness was found in 13 studies[10, 11, 18, 20, 23-26, 28-30, 34, 36] included in this systematic review. From seven studies measuring PWV by carotid-femoral method[11, 16, 18, 20, 22, 32, 36], four [11, 18, 20, 36] found SUA positively associated with PWV. Considering studies with the higher quality that reported PWV assessed by carotid-femoral method, two[18, 20] reported that SUA was associated with PWV, while another two[16, 22] did not find significant association. In studies evaluating arterial stiffness by brachial-ankle method, seven[10, 23-26, 29, 30] out of nine reported higher SUA levels to be associated with higher PWV measurements. Regarding studies ascribed the higher quality in brachial-ankle subgroup, two studies[29, 30] described the association of SUA and PWV as positive, whereas one[15] found no association. Finally, from seven studies approaching PWV by different methods [27, 28, 31, 33-35], four[27, 31, 33, 35] reported no association. In this subgroup, just one study[35] reached seven points (the higher quality score among included studies) in quality assessment, which reported no significant association between SUA and PWV.

DISCUSSION

Our systematic review addressed the association between uric acid and arterial stiffness. Available evidence does not support that SUA was directly associated with arterial stiffness among healthy populations. Additionally, when specific PWV measurements were considered separately (e.g. carotid-femoral, brachial or others) studies followed the same pattern in terms of direction of association and quality.

Considering previous studies[56], SUA was hypothesized to be an important factor not only in established cardiovascular disorders, but also in the development of such conditions. Recent studies proposed that SUA exerts a state of pro-oxidant environment in humans. The activity of xanthine oxidoreductase enzimes was implicated in the production of reactive oxygen species, which play a major role in the pathogenesis of cardiovascular disorders. Under an unbalanced production of oxygen reactive species, endothelial dysfunction is carried out by impairment of nitric oxide production, resulting in accelerated atherosclerosis which could reduce arterial elasticity. Hence, arterial stiffness could be the result of uric acid exposure and would be expected to be a path leading high serum uric acid levels to hypertension and cardiovascular disorders.[38] However our findings don't support this conclusion given the lack of standardization in reports preventing us from perform a meta-analysis

Some explanations for these could be that hypertension could precede arterial stiffness. In a Longitudinal community-based cohort study conducted in Framingham, the author found that PWV was associated with increased risk of hypertension[39]. However, a study among 2,512 normotensive US adults free of cardiovascular disease found that participants with the lowest, compared with the highest, aortic distensibility had an increased risk of hypertension cardiovascular disease. [40]

There were a higher number of studies showing positive association between SUA and arterial stiffness in male population than women.

Specifically, three studies[21, 41, 42] evaluating the relation between SUA and arterial stiffness in both genders found a positive association only among men. The studies enrolled relatively young individuals and reported lower levels of serum uric acid in women compared to men. [16, 21, 42]. Given the preponderance of pre-menopausal women, the exposure to estrogen could be an important factor underlying the lack of association between SUA and arterial stiffness. Another possible explanation is the known uricosuric effect of estrogen. Uric acid levels are inversely associated with serum estrogen[43]. Which, among healthy women, is expected to reduce the overall SUA exposure. Hence, the potential pro-inflammatory and pro-atherosclerotic effects of SUA could be reduced in women, supporting the differences among genders. However, whether estrogen has, in fact, an interaction with uric acid in terms of its effects on arterial vessels is not yet supported by well-designed studies. Nevertheless, publication bias could also explain the higher number of studies reporting positive associations in men.

Additionally, post-menopausal women most often present generally with hypertension, diabetes and cardiovascular risk factors which could have led those studies to be excluded from our systematic review.

Our study has some limitations that should be considered. This impact would increase or decrease the magnitude or direction of the associations reported here. The methods of PWV assessment also differed significantly between studies, which contributed to the general heterogeneity. Importantly, not all studies assessed PWV by validated methods.

As strengths our systematic review, to the best of our knowledge, it is the first to gather the evidence of the association between SUA and arterial stiffness. We used comprehensive search strategy built by a professional librarian and established well defined criteria for PWV assessment and quality assessment which validates our results. We were careful to include only studies recruiting apparently healthy populations as an attempt to rule out reversal causality between SUA and PWV.

Our findings have implications for future research and clinical practice. Firstly, it is possible that SUA is not directly associated with major vessels

atherosclerotic disease. As uric acid seems to be implicated in the development of cardiovascular diseases, different perspectives regarding pathogenesis should be explored, such as effects of SUA on small vessels. With the development of biomarkers and new measurements for microvascular diseases, the role of uric acid could be broadly approached to frame a reasonable model that would take into account the molecular evidence of SUA impact on endothelial cells function. There are several studies showing that uric acid was detected in microvascular endothelial from different organs[44-46].

Considering that the population included in our study was constituted by relatively young individuals without cardiovascular comorbidities, the lack of association between SUA and PWV could be considered to be in consonance with the hypothesis that the development of cardiovascular diseases, especially hypertension, is led by different steps in terms of pathogenesis compared to older individuals, in whom arterial stiffness might play a more important role. Among young patients, allopurinol was found to reduce blood pressure[47]. The effects of allopurinol were also tested in arterial stiffness. A meta-analysis that evaluated the effects of this drug on the pulse wave velocity and augmentation index (AIx) did not find significant difference in PWV, but showed significantly reduction in Aix [48] .

One of the main explanations is that SUA reduces renal arterial flow by lowering nitric oxide levels on account of an inhibitory action over nitric oxide sintetase enzyme, leading to high levels of angiotensin and aldosterone and, then, causing reversible hypertension. Over time, SUA tends to change renal vascular cells architecture by inducing alterations in the patterns of genetic expression in the microvascular environment, chiefly by activation of kinases, induction of nuclear factors and expression of inflammatory proteins and growth factors, such as platelet derived growth factor (PDGF) [49] . Notably, in addition to these directly induced genetic alterations led by SUA, uric acid synthesis by the enzyme xanthine oxidoreductase was found to indirectly contribute to endothelial dysfunction, as this synthetic process produces reactive oxygen species, which can magnify and maintain a pro-inflammatory state on vascular cells, given the widespread xanthine oxidoreductase activity in such tissue [50] .

Therefore, in this model, SUA effects are thought to initiate microvascular damage, then leading to hypertension and, after which, arterial stiffness. The exclusion of diseased patients in this systematic review could blunt the association between SUA and PWV if this model were to be assumed. Supporting this perspective, a recent published study showed that hypertension precedes the development of arterial stiffness assessed by PWV among young individuals. Moreover, the results of the two previously mentioned systematic reviews of allopurinol on hypertension and arterial stiffness suggest such assumption.

Clinical implication of our findings should also be considered. The lack of evidence supporting the association between SUA and PWV in healthy individuals seems to reinforce the theory that the effect of SUA is probably in an endothelium level and PWV is a measurement of outer compounds of the arteries.

Finally, available evidence on the association between SUA and PWV are not supportive of this connection among apparently healthy populations. Future studies with prospective design should focus on the temporality of these two important risk factors

Table 1 – Characteristics of included studies

First Author (year)	Country	Study design	Total (n)	Mean age (SD)	Mean SUA (SD)	Arterial Stiffness measure	Measure of association	Quality Score
Park, SJ.[20]	South Korea	Cross-Sectional	841	60.63	4.55	cf(PWV)	B=0.129	7
Shin, J. Y.[21]	South Korea	Cross-Sectional	627	48.0(6.7) 49.2(10.5) 54.5(9.0) 56.8(8.5)	3.95(0.25) 4.80(0.20) 5.51(0.23) 6.74(0.59)	ba(PWV)	OR=2.91 (1.39–6.11)	6
Hsu, P.[22]	Taiwan	Cross-Sectional	656	48.4(12.4) women 50.8(13.3) men	6.5(1.5) men 5.0(1.2) women	cf-PWV, Pb, Ai, Pa, TPR	Total population B=-0.051	7
Bian, S.[18]	Iran	Cross-Sectional	2374	58.24	4.94	PWVc-f (m/s) PWVc-r (m/s) PWVc-a (m/s), AIX	women B=0.004	5
Saijo, Y.[23]	Japan	Cross-Sectional	4266	48.4(6.8) Men 46.8(7.2) Women	5.9 (4.2) Men 4.5 (1.0) Women	ba(PWV)	men B=0.043 (0.020 - 0.067) women B=0.057 (0.009 - 0.015)	6
Ishisaka,N.[10]	Japan	Cross-Sectional	982	59.2	6.1(1.2) Men 4.7(0.9) Women	ba(PWV)	Total population OR=2.40 (1.36, 4.26) men OR=2.24 (1.10, 4.56) women OR= 2.76 (1.01, 7.55)	2
Lim, J. H.[15]	South Korea	Cross-Sectional	1276	48.3(10.1)	5.2(1.4)	Hf (heart femoral)PVW and βaPWV	men r=0.054 r=0.015 Mulheres r=0.036, r=-0.015	7
Xie, X.[24]	China	Cross-Sectional	13899	50.84	4.62	ba(PWV)	B=0,039	4

Table 1 - continued

First Author (year)	Country	Study design	Total (n)	Mean age (SD)	Mean SUA (SD)	Arterial Stiffness measure	Measure of association	Quality Score
Chen, X.[11]	China	Cross-Sectional	940	42.4	6.10 Men 4.56 Women	cf(pwv)	Total Population Beta= 0.16 Men Beta=0.15 (0.12 - .026) Women Beta= 0.04 (-0.04 - 0.18)	5
Kuo, C. F.[25]	Taiwan	Cross-Sectional	9375	55.6(12.4)	Men 6.8 (1.9) Women 5.5 (1.7)	ba(PWV)	Odds=1.33	3
Oikonen, M.[34]	Finland	Cross-Sectional	1985	37.9(4.9) Men 37.6(5.0) Women	Men 5.55(1.13) Women 4.05(0.88)	distensibility (Cdist)	Men B=-0.0005 Women B=-0.0005	4
Zi-Sheng Ai[26]	China	Cross-Sectional	2095	Men 58.12(10) Women 57.14(9.2	Men 6.16(1.31) Women 4.88(1.14)	ba(PWV)	Women B=0.083 (p = 0.015)	2
Erdogan, D[28]	Turkey	Cross-Sectional	124	42.1(7.7)	4.39(1.28)	BD, FMD, carotid IMT,AoD, AoSI and AoEM	Total Population B=0.295(p < 0.001)	3
Inoue, T.[27]	Japan	Cross-Sectional	8508	Men 47 Women 49	6.3 (1.3) 6.5 (1.3) 6.5 (1.3) 6.5 (1.3) 4.6 (1.0) 4.6 (1.0) 4.6 (1.1) 4.8 (1.1)	pulse pressure	Men B=0.33 (p = 0.0014) Women B=-0.06 (p = 0.74)	5
Magalhaes, P[36]	Angola	Cross-Sectional	301	36	Men 6.0 Women 4.2	cf(PWV)	0.109	3

Table 1 – continued

First Author (year)	Country	Study design	Total (n)	Mean age (SD)	Mean SUA (SD)	Arterial Stiffness measure	Measure of association	Quality Score
Baena CP[16]	Brazil	Cross-Sectional	3588	Men 48.9 Women 50.2	Men 6.2 Women 4.53	cf(PWV)	Men 0.06 (0.015 - 0.112) Women 0.04 (-0.01 - 0.12)	7
Bae, J. S[29]	South Korea	Cross-Sectional	5568	Men 61.5 Women 59.5	Men 5.7 Women 4.2	ba(PWV)	Men 0.0006 (p < 0.0001) Women (p = 0.04) 0.0001	7
Fang, J. I.(30)	China	Cross-Sectional	7509			ba(PWV)	-	7
Li, Y[31]	China	Cross-Sectional	1243	Men 70.6 Women 68.1	5.64	ba(PWV)	-	7
Fu, S. H[32]	China	Cross-Sectional	1540	62	4.77	cf(PWV)	-	4
Mallamaci, F[33]	Italy	Cross-Sectional	449	Group 1 45 Group 2 39 Group 3 44	Group 1 4.2 Group 2 4.7 Group 3 5.2	cr(PWV)	-	5
Mehta, T(35)	USA	Cross-Sectional	4109	Quartile 1 39.8 Quartile 2 39.6 Quartile 3 40.0 Quartile 4 40.5	Quartile 1 3.5 Quartile 2 4.7 Quartile 3 5.7 Quartile 4 7.3	cf(PWV) cr(PWV) augmentation index	Men 0.07 Women 0.04	7

Figure 1. Flow chart of study selection for articles reporting on uric acid and arterial stiffness

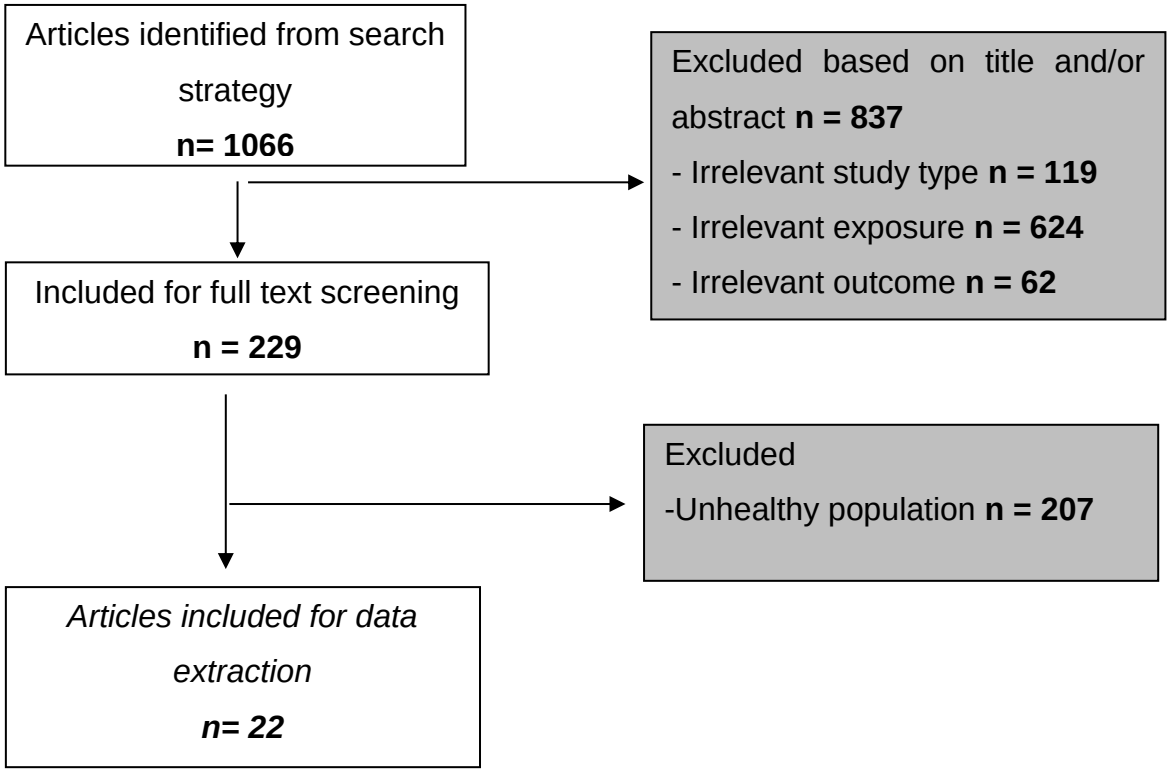


Figure 2. Harvest plot of evidence of association between uric acid and arterial stiffness in men

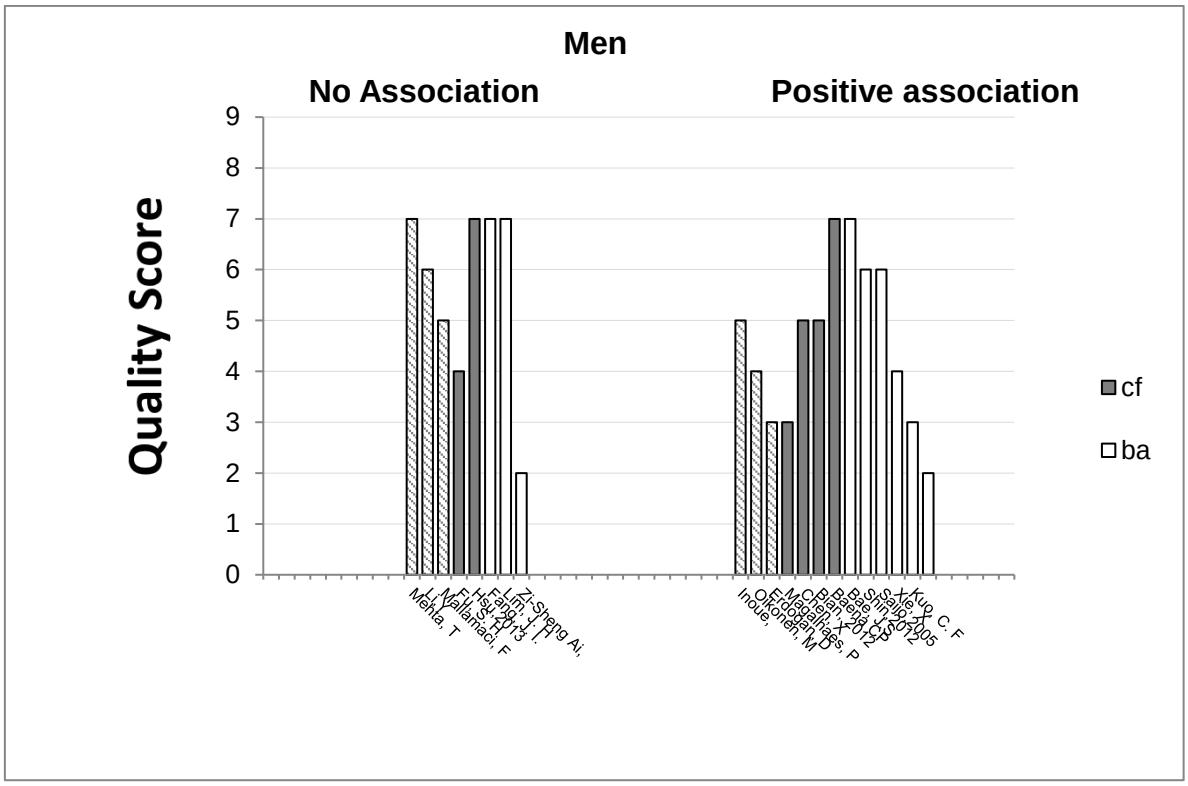
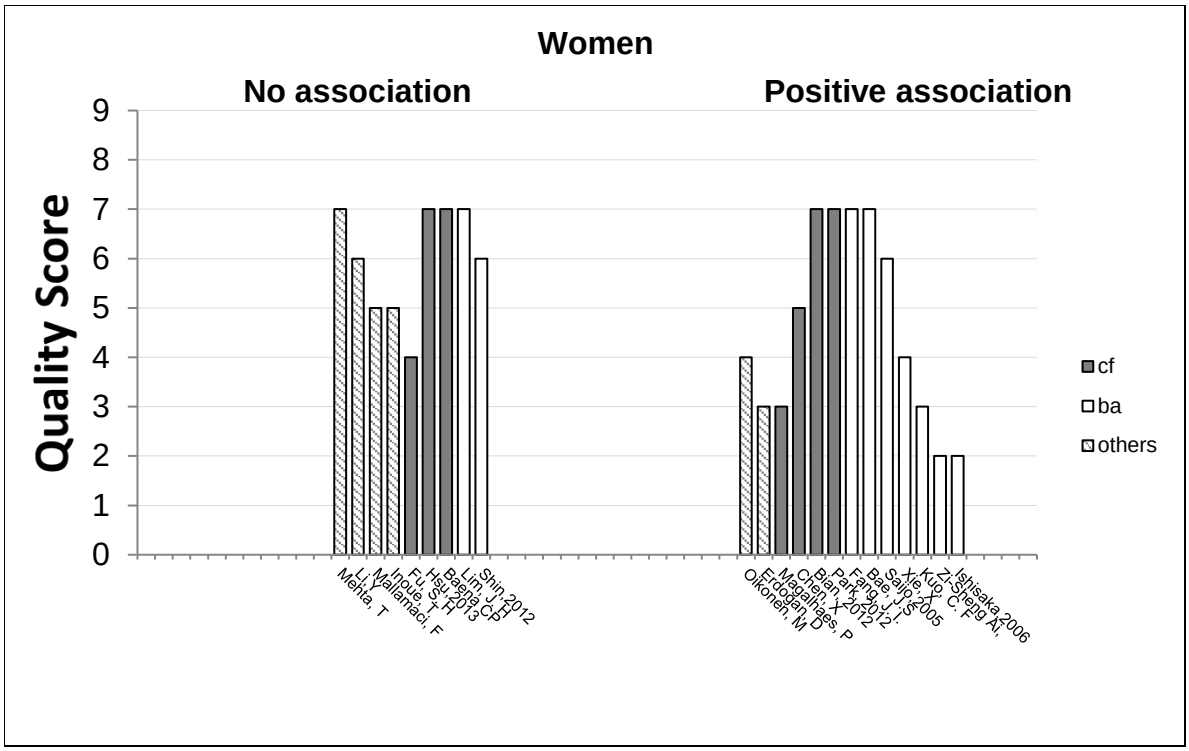


Figure 3. Harvest plot of evidence of association between uric acid and arterial wall stiffness in women



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MJL, SS and WMB searched the literature
MJL and MG structured the data
MJL, CPB and MG wrote the manuscript
RPF, TPM and JRFN contributed to the critical revision of the manuscript before publication.

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7 CONSIDERAÇÕES FINAIS

Atualmente é bem estabelecido que níveis elevados de ácido úrico estejam associados com doenças cardiovasculares. Também é definido que rigidez de parede arterial é um marcador de doença cardiovascular. A relação entre ácido úrico e rigidez de parede arterial tem resultados controversos e isso é visto principalmente em populações doentes. A utilização de populações saudáveis no nosso estudo foi motivada para tentar eliminar qualquer fator de confusão em relação à fisiopatologia do ácido úrico e da rigidez de parede arterial. A maioria dos estudos encontrados em nossa busca foi em populações com algum tipo de doença conhecida, como hipertensão arterial, *diabetes mellitus*, doença renal crônica, doenças reumatológicas, entre outras. Restaram 22 estudos em populações aparentemente livres de doenças. Encontramos em nosso estudo que não houve associação entre ácido úrico e rigidez de parede arterial. É importante ressaltar um possível viés de publicação em relação a esses achados, uma vez que estudos que não encontraram associação podem não ter sido encorajados a serem publicados. Como implicação na prática clínica, avalia-se a possibilidade de tratar um paciente hiperuricêmico a fim de evitar o desenvolvimento de hipertensão arterial e também para diminuir incidência de rigidez de parede arterial, que é um preditor de doença cardiovascular. Recentemente estudos em relação à lesão microvascular causada pelo ácido úrico têm mostrado efeitos importantes e isso nos fará entender melhor esses mecanismos. A partir de nossos resultados, fica claro o questionamento sobre qual evento ocorre inicialmente, ou seja, a hipertensão antecede a velocidade de onda de pulso ou o inverso. Futuros estudos são necessários para compreender essa complexa interação esse ácido úrico e lesão endotelial.

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ANEXO A – PRISMA *Checklist*

Supplemental Table 2. PRISMA 2009 checklist for reporting of systematic reviews and meta-analyses.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	See title, page 1.
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	See abstract, page 2.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	See introduction, page 3.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	See introduction, page 3.
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	See methods, page 4.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	See methods, page 3.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	See methods, page 4.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	See methods, page 3.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	See methods, page 4.
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	See methods, page 4.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	See methods, page 4.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	See supplemental table 1.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	See methods, page 4.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	See supplemental table 1.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	See methods, page 4.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	See figure 1.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	See table 1 and 2.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	See supplemental table 1.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	See table 1 and 2.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	See table 1 and 2.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	See results, page 8.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	See results, pages 8-9.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	See discussion, pages 9-10.
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	See discussion, pages 10-11.
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	See discussion, page 11.
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	See discussion, page 11.

ANEXO B- Fluxo de informações através das diferentes fases de uma revisão sistemática

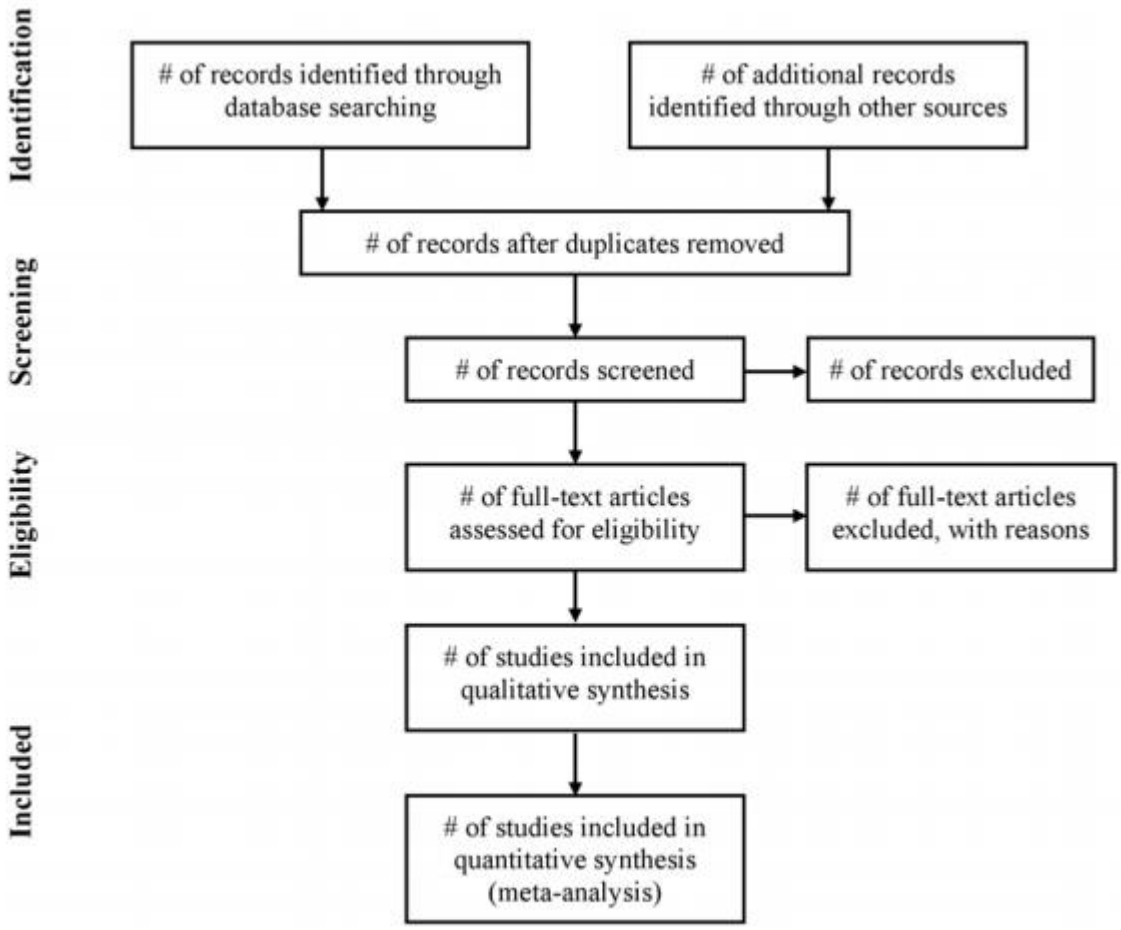

Figure 1. Flow of information through the different phases of a systematic review.
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