Review Article/บทฟื้นฟูวิชาการ

Association Between Uric Acid and Arterial Stiffness in General Adults: A Systematic Review and Meta-analysis

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Abstract

Background: Arterial stiffness (AS) was a surrogate marker of atherosclerosis and cardiovascular disease and may associate with serum uric acid (UA) level.

Objective: To systematically review the association between serum UA and AS.

Methods: Observational studies that studied the effect of serum UA level and AS in adult population were searched from MEDLINE and Scopus databases since inception to June 30, 2016. Mean differences (MDs) of serum UA level between AS groups and odds ratios of high vs low UA on AS measurement were estimated and pooled.

Results: A total of 61 studies met inclusion criteria, and 44 studies were pooled. Pooled MDs of serum UA between AS vs non-AS measured by carotid femoral pulse wave velocity (cfPWV) and brachial ankle pulse wave velocity (baPWV) in 7 and 5 studies were 0.76 (95% CI, 0.50 - 1.03) mg/dL and 0.58 (95% CI, 0.31 - 0.85) mg/dL, respectively. Three baPWV studies with the pooled odds ratio of high vs low serum UA on AS was 1.49 (95% CI, 1.25 - 1.78). Pooled MDs of AS among high vs low serum UA groups were 62.43 (95% CI, 46.97 - 77.88), 86.20 (95% CI, 35.40 - 136.99), and 32.69 (95% CI, 13.45 - 51.94) cm/s for cfPWV (10 studies), baPWV (4 studies), and carotid radial pulse wave velocity (crPWV) (4 studies), respectively. Pooling beta correlation coefficients of serum UA for AS for cfPWV and baPWV were 2.51 (95% CI, 2.26 - 2.76) and 3.75 (95% CI, 2.24 - 5.25), respectively.

Conclusions: Serum UA was statistically associated with AS measured by cfPWV, baPWV, and crPWV but poolings had high heterogeneity.

Keywords: Uric acid, Arterial stiffness, Carotid femoral pulse wave velocity, Brachial ankle pulse wave velocity, Carotid radial pulse wave velocity

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Introduction

High serum uric acid (UA) level has shown to be associated with many non-communicable diseases including arterial stiffness (AS),[1-3] carotid atherosclerosis,[4, 5] cardiovascular disease (CVD),[6] hypertension,[7] brain ischemia[4, 5, 8] and stroke.[9] In Framingham heart study, it had been showed that high serum UA level increased the risk of AS and CVD in stroke or hypertension patients.[10] In healthy population, high serum uric acid level was also associated with AS in women.[11] Previous meta-analysis shown that carotid stiffness is a significant predictor for future CVDs and all-cause mortality, which may facilitate the identification of high risk patients for the early diagnosis and prompt treatment for CVD.[12] Early detecting changes in AS at the early stages of atherosclerosis is of great value for prevention, treatment and references for diagnosis of CVD. Association between serum UA and AS had been studied in many regions and it has been revealed that increase in serum UA was associated with AS.[1, 12-17] However, other studies did not find any significant association between serum UA level and AS.[2, 18] Therefore, we conducted a systematic review and meta-analysis. The objective of this study was to determine the association between serum UA and AS which was measured by pulse wave velocity (PWV) (ie, carotid femoral pulse wave velocity [cfPWV], brachial pulse wave velocity [baPWV], carotid-radial pulse wave velocity [crPWV], carotid-distal pulse wave velocity [cdPWV], aortic pulse wave velocity [aPWV], augmentation index (AI), and cardio-ankle vascular index (CAVI).

Methods

Search Strategy

We identified relevant studies from MEDLINE (via PubMed) and Scopus since inception to June 30, 2016. Search terms were constructed based on domains of patient (P), intervention/exposure (I), comparative (C), outcome (O). Searching strategies were constructed by combing search terms with "OR" within the same domain and "AND" for between domains (see Appendix 1).

Study Selection

After identifying articles from MEDLINE and Scopus, relevant articles were screened on abstract and title. Duplicated articles were removed. The remaining relevant articles were viewed as full articles and were assessed for eligibility. Analytical observational study which could be cross-sectional, case-control or cohort study, with participant age ≥ 18 years, measured the serum UA level, studied outcome of AS which could be measured by PWV, AI, or CAVI were included in this study. We exclude studies that are not in English language, have insufficient data for pooling after contacting authors for providing the data, studies that did not measure association between serum UA and AS, or studies with same data by same authors (multiple publications). Selection process was done by two independent reviewers and agreements of selection were done.

Data Extraction

Data were extracted by one author (Y.N.W.) and randomly checked about 20% by senior author (P.N.). A standardized data extraction form, was used to obtain data which consisted of general characteristics of journal (eg, author, journal, year of publication) and characteristics of studies and subjects including study design, type of patient, mean age, percentage of male, and type of measurement. All disagreements were solved by discussion with third author (A.T.).

Risk of Bias Assessment

Two authors independently assessed risk of bias of each study by using Newcastle and Ottawa risk of bias criteria.[20] Three domains were assessed: representativeness of studied participants, comparability between exposed and non-exposed participants for cohort study, and ascertainment of exposures and outcome. Each item was graded by giving stars if there was evidence of low risk of bias. Each study was categorized according to the total stars as low or high risk of bias, and if total stars were seven or more it was graded as low risk of bias. All the disagreements were resolved by consensus of three authors. If there was insufficient information to judge, it was classified as 'unclear'.

Statistical Analysis

For frequency data of AS occurrences in high vs low/normal uric acid groups, log odds ratios (ORs) were estimated and then combined with those studies where summary statistics (ie, ORs) were provided. For serum UA levels, unstandardized mean differences (USMDs) of serum UA levels between AS groups were estimated. For studies that categorized participants into high and low UA level and reported measured levels of AS (eg, PWVs), USMDs of the measurement between UA groups were also estimated. These parameters were then pooled across studies using random-effect model by DerSimonian and Laird[21] if heterogeneity was present, otherwise fixed-effect model was used. For pooling of regression coefficients, regression coefficients from each study were extracted and then pooled across studies. Heterogeneity of the effect sizes was assessed by using the Q statistic and the degree of heterogeneity was quantified using I^2 statistics. Heterogeneity was determined, and it was present if P value from heterogeneity test < 0.10 or $I^2 \geq 25\%$. A meta-regression was performed to explore possible sources of heterogeneity by fitting patients' characteristics (eg, age, percentage of males, type of patients), and a subgroup analysis was then performed accordingly. Publication bias was assessed by funnel plot and Egger's test. If asymmetry of a funnel was indicated, a contour-enhanced funnel plot was constructed to distinguish whether asymmetry was due to publication bias or heterogeneity. All analyses were performed using STATA software, version 14.0 (StataCorp. Version 14. College Station, TX: StataCorp LP; 2015). Apart from the heterogeneity test, a P value of < 0.05 was considered statistically significant.

Results

Study Selection

A total of 1725 articles were identified from MEDLINE and Scopus databases and 148 articles were duplicated and therefore excluded (Figure 1). Among them, 1605 articles were excluded after reviewing titles and abstracts leaving 120 articles for full article reviews. Finally, 61 out of 120 studies met with inclusion criteria and were included in pooling.

Most of the study designs were cross-sectional studies (n = 57), followed by case control (n = 2) and cohort (n = 2). Mean age of patients ranged from 38 to 69.2 years and type of patients were 32.8% of general patient and 67.2% of disease specific patient (Table 1). Percentage of male participants ranged from 0% to 100%. Among 61 studies eligible for quantitative pooling data,[3, 19, 22-33] some studies reported more than one AS measurements. It reported as 44[1, 2, 13-18, 26, 34-68] and 17[3, 18, 19, 22, 23, 25-33, 69, 70] studies had continuous and categorical data for AS respectively. Among 44 studies with continuous AS data, 18 studies categorized serum UA and 26 studies did not categorize serum UA and reported as continuous serum UA data of beta coefficient with standard error (SE) or 95% confidence interval (CI). All of the included studies had risk of bias score equal or greater than 7 (see Appendix 2).

Arterial Stiffness vs Non-Arterial Stiffness

Mean Differences of Uric Acid Levels Between Arterial Stiffness Groups

Among the 17 studies which categorized participants as having AS or not, a total of 12 studies compared mean differences of serum UA levels between groups, and 5 studies also categorized UA levels and had frequency data of low/high serum UA between groups. Out of 12 studies that reported the mean differences of serum UA between AS and non-AS studies, 7[23, 26, 29-32, 69] and 5[22, 24, 27, 70, 71] studies had AS measured by cfPWV and baPWV, respectively.

In 7 studies[23, 26, 29-32, 69] which measured AS by cfPWV, USMDs were highly varied across studies (Heterogeneity test, $P < 0.001$) with the I^2 of 97.1% (Figure 2a). A random effect model was thus applied, which yield the pooled USMDS of 0.76 cm (95% CI, 0.50 - 1.03) (Table 2). The source of heterogeneity was explored using meta-regression by fitting the age, type of patient and male percentage in the regression model but none of these could explain the source of heterogeneity (see Appendix 3). However, subgroup analysis by distribution of gender showed that studies with male proportion below 25%[23, 69] (ie, more involved females) had higher USMDs about 1.26 cm (95% CI, 0.69 - 1.84) with I^2 of 97.9%. The funnel plot suggested a deviation of the funnel for USMDs. Contrastingly, the Egger's tests yielded asymmetry of the funnels (coefficient = 4.08; SE = 2.52; P = 0.16). A contour-enhanced funnel plot was therefore performed and showed that asymmetry might be more likely caused by both heterogeneity and missing studies (see Appendix 9).

Among 5 studies[22, 24, 27, 70, 71] which measured baPWV, USMDs were estimated, which were also highly varied across the studies, (heterogeneity test, P < 0.001; I^2= 96.1%) (Figure 2b). The pooled USMDs was 0.58 (95% CI, 0.31 - 0.85) (Table 2). We could not identify any source of heterogeneity. A funnel plot was constructed and indicated symmetry of the funnel, which corresponded to the Egger's test (coefficient = 1.9; SE = 3.7; P = 0.63) (see Appendix 10).

High vs Low Uric Acid and Arterial Stiffness Groups

Five studies reported numbers of patients assessing association with high/low serum UA and AS,[3, 18, 21, 28, 33] in which 3 studies[3, 18, 33] were measured AS by baPWV, and in 2 other studies,[21, 28] the AS were measured by aPWV and CAVI respectively.

Pooling was performed only for 3 studies of AS measured by baPWV. The effects of high vs low serum UA were heterogeneous (chi-square = 3.32; degrees of freedom [*df*] = 2; P = 0.190; I^2 = 39.7%) with a pooled OR of 1.49 (95% CI, 1.24 - 1.78) (see Appendix 4), with moderate heterogeneity across the studies (Figure 2c). Source of heterogeneity was explored but none of them was identified as the source of heterogeneity (see Appendix 5). Publication bias was assessed by Egger's test (coefficient = 0.97; SE = 2.96; P = 0.798) and funnel plot which suggested that the plot was not quite symmetrical. Contour-enhanced funnel plot showed that asymmetry might be more likely caused by heterogeneity than publication bias (see Appendix 11).

Mean Arterial Stiffness Between High and Low Uric Acid Group

Forty four studies[1, 2, 10, 12-17, 25, 34, 36-40, 42-55, 57-63, 65-67, 72] dealt with AS as continuous data. Among them, 18 studies compared means of AS between high and low serum UA groups and 26 studies reported as continuous serum UA data of beta coefficient with standard error or 95% CI.

Among 18 studies, 10 studies[1, 2, 10, 13, 16, 40, 46, 49, 50, 63] measured AS by cfPWV, 4 studies[15, 25, 51, 62] by baPWV, 4 studies[1, 10, 13, 38] by crPWV, 2 studies[10, 39] by AI, 2 studies[63, 66] by CAVI and 1 study[39] by aPWV (Figure 1). We therefore could only pool data of AS measured by cfPWV, baPWV and crPWV. The pooled USMDs of 10 cfPWV studies were 62.43 cm (95%CI, 46.97 - 77.88) (Table 3), with highly heterogeneity (heterogeneity test, P < 0.001; I^2 = 99.7%) (Figure 3a). Subgroup analysis was performed by type of patients, which yielded the pooled USMDs of 117.26 cm (95% CI, 83.04 - 151.48) and 39.09 (95% CI, 46.97 - 77.88) in diseased and general patients, respectively. However, there were still highly heterogeneous, ie, I^2 = 93.4% and 99.3%, respectively. Source of heterogeneity was explored but none of them was identified as the source of heterogeneity (see Appendix 6). The Egger's test was significant (coefficient = 62.42; SE =15.20; P = 0.03). Contour-enhanced funnel plot suggested asymmetry might be more likely caused by heterogeneity than publication bias (see Appendix 12).

Four studies[15, 25, 51, 62] reported mean differences of baPWV. The pooled USMDs was 86.20 cm (95% CI, 35.40 - 136.99) (Table 3b), with high heterogeneity (chi-square = 52.70; P = 0.000; I^2 = 94.3%) (Figure 3). Meta regression was done by fitting the variables (age, percentage of male) in the model. The result showed that age was the source of heterogeneity, in which the degree of heterogeneity decreased to moderate level with I^2 of 36.91% (see Appendix 6). We did the sensitivity analysis by omitting the Chen et al[62] study where effect size was most deviated from others, the result reduced the heterogeneity I^2 from 94.3% to 56.7% with USMDs of 111.35 cm. Publication bias was assessed and the funnel plot showed asymmetry. Egger's test was non-significant (coefficient = 4.82; SE = 3.96; P = 0.34). Contour-enhanced funnel plot suggested asymmetry might be caused by missing studies or heterogeneity (see Appendix 13).

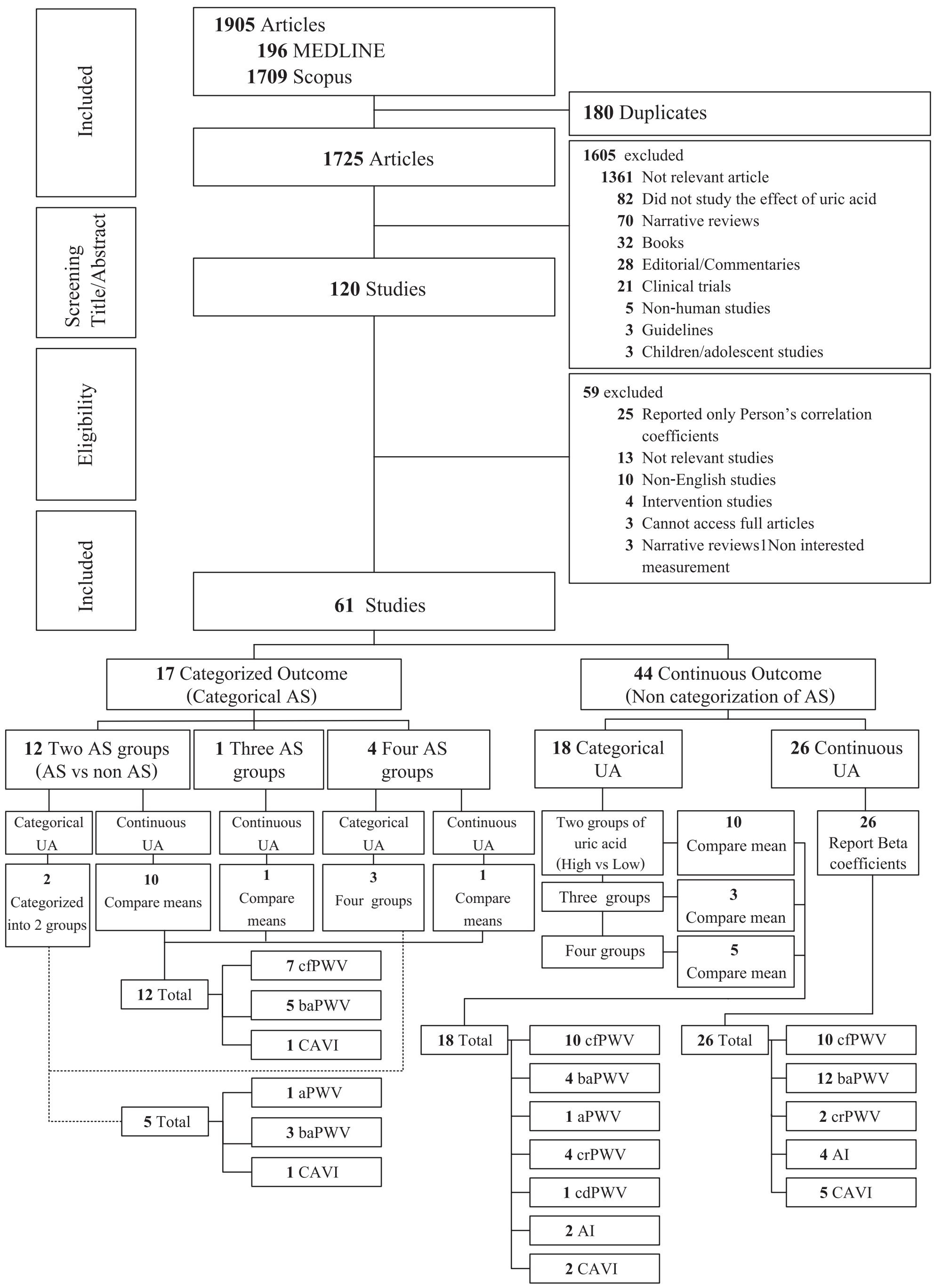

Figure 1 *PRISMA Flow Diagram of Study Selection for Meta-analysis*

AI indicates augmentation index; aPWV, aortic pulse wave velocity; As, arterial stiffness; baPWV, brachial pulse wave velocity; cfPWV, carotid femoral pulse wave velocity; CAVI, cardio-ankle vascular index; cdPWV, carotid-distal pulse wave velocity; crPWV, carotid-radial pulse wave velocity; UA, uric acid.

Table 1 Characteristic of Included Studies

Author, Year	Study Design	Type of Patient	Mean Age, y	Male Percentage, %	Type of Measurement
Saijo Y, 2005[17]	Cross-sectional	General	48.08	79.9	baPWV
Ishizaka N, 2007[3]	Cross-sectional	General	58.8	68.8	baPWV
Song SH, 2007[22]	Cross-sectional	General	51.3	53.4	baPWV
Sabio JM, 2009[23]	Cross-sectional	Systemic Lupus Erythematosus	42.6	25	cfPWV
Tsai WC, 2009[38]	Cross-sectional	Uncomplicated essential hypertension	41	68	crPWV
Chen X, 2010[16]	Cross-sectional	General	42.4	66	cfPWV
Kuo CF, 2010[15]	Cross-sectional	General	55.6	54.1	baPWV
Lim JH, 2010[18]	Cross-sectional	General	48.3	54.3	baPWV
Sabio JM, 2010[40]	Cross-sectional	Hyperuricemia / Normal	40	0	cfPWV
Vlachopoulos C, 2010[41]	Case-control	Nonalcoholic fatty liver disease vs Control	53.3	47.8	cfPWV / AI
Odaira M, 2011[70]	Cross-sectional	General	43.8	100	baPWV
Syrseloudis D, 2011[45]	Cross-sectional	Night time hypertension / Night time no hypertension	48.4	67.2	cfPWV
Tsioufis C, 2011[46]	Cross-sectional	Never treated newly diagnosed stage I-II essential hypertension	53	65.1	cfPWV / AI
Vlachopoulos C, 2011[14]	Cross-sectional	Never treated hypertension	57.8	59.4	cfPWV / crPWV
Wang F, 2011[47]	Cross-sectional	General	49.3	48.1	cfPWV / crPWV
Bian S, 2011[48]	Cross-sectional	General	58.24	47.9	cfPWV
Krishnan E, 2012[49]	Cross-sectional	General	40.3	57.6	cfPWV
Lee MJ, 2012[72]	Cross-sectional	General	45.5	63	cfPWV / crPWV / cdPWV
Liang J, 2012[13]	Cross-sectional	Postmenopausal women	60.6	0	cfPWV
Park JS, 2012[50]	Cross-sectional	Postmenopausal women	60.6	0	cfPWV
Shin JY, 2012[51]	Cross-sectional	General	55.4	62.7	baPWV
Xiong Z, 2012[24]	Cohort	Coronary artery disease	64.7	53.5	baPWV

Abbreviation: AI, augmentation index; baPWV, brachial pulse wave velocity; cdPWV, carotid-distal pulse wave velocity; cfPWV, carotid femoral pulse wave velocity; crPWV, carotid-radial pulse wave velocity.

Table 1 Characteristic of Included Studies (Continued)

Author, Year	Study Design	Type of Patient	Mean Age, y	Male Percentage, %	Type of Measurement
Zhu C, 2012[53]	Cross-sectional	Coronary artery disease	64.6	53.5	baPWV
Bae JS, 2013[25]	Cross-sectional	General	60.3	38.9	baPWV
Gomez-Marcos MA, 2013[54]	Cross-sectional	General	55.5	61.8	cfPWV / AI
Kim BJ, 2013[71]	Cross-sectional	General	54.5	67.9	baPWV
Magalhaes P, 2013[55]	Cross-sectional	Less healthy / Healthy	37.9	48.8	cfPWV
Wang X, 2013[26]	Cross-sectional	General	43.9	59.9	cfPWV
Xie X, 2013[58]	Cross-sectional	General	50.8	46.3	baPWV
Zhu C, 2013[59]	Cross-sectional	General	60.8	51.8	baPWV
Elsurer R, 2014[60]	Cross-sectional	Hypertensive chronic kidney disease	57.9	43.4	cfPWV
Fang JI, 2014[27]	Cross-sectional	General	45.3	57.6	baPWV
Mule G, 2014[29]	Cross-sectional	Hypertension	45.3	62.6	cfPWV
Valero-Gonzalez S, 2014[69]	Cross-sectional	Systemic lupus erythematosus	49.3	100	cfPWV
Zhang J, 2014[1]	Cross-sectional	Early diagnosed type-2 diabetes mellitus	49.5	52.2	cfPWV / crPWV
Baena CP, 2015[61]	Cross-sectional	General	45	0	cfPWV
Chen L, 2015[62]	Cross-sectional	General	46.2	77.4	baPWV
Elewa U, 2015[31]	Cross-sectional	Chronic kidney disease and non-chronic kidney disease	61.2	73	cfPWV
Erkmen UM, 2015[63]	Cross-sectional	Kidney transplant recipients with normal graft function	38.7	69	cfPWV
Fu S, 2015[32]	Cross-sectional	General	69.2	45.2	cfPWV / AI
Mehta T, 2015[10]	Cross-sectional	General	40.3	57.6	cfPWV / crPWV / AI
Tanindi A, 2015[30]	Cross-sectional	Coronary artery disease	60.1	53.8	cfPWV / AI
Wijnands JM, 2015[2]	Cross-sectional	General	45.3	57.6	cfPWV
Zhu WH, 2015[33]	Cross-sectional	Non-alcoholic fatty liver disease	46.3	77.4	baPWV

Abbreviation: AI, augmentation index; baPWV, brachial pulse wave velocity; cdPWV, carotid-distal pulse wave velocity; cfPWV, carotid femoral pulse wave velocity; crPWV, carotid-radial pulse wave velocity.

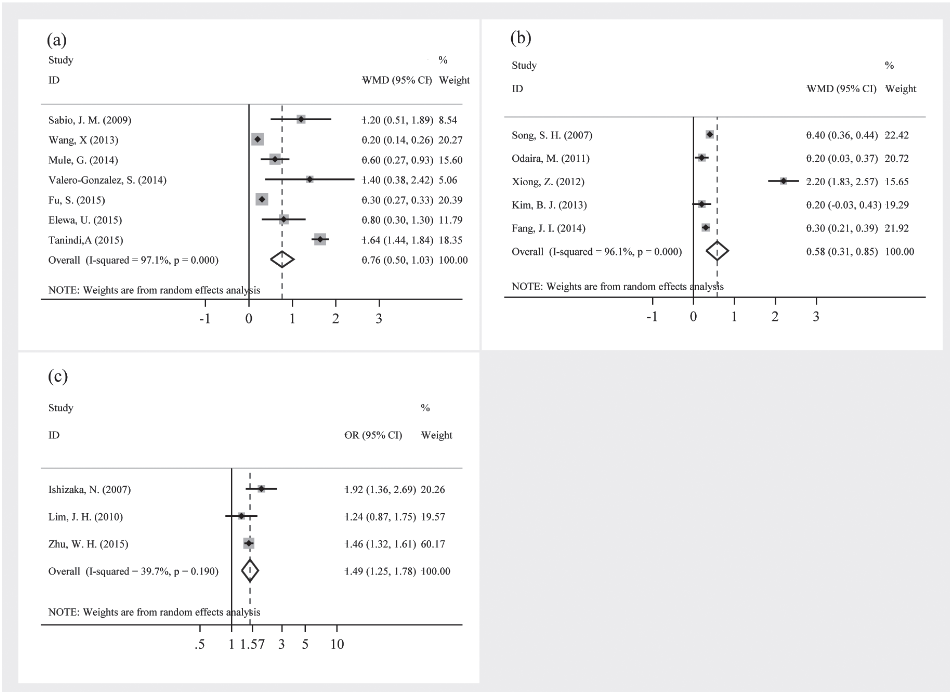

Figure 2 *Forest Plot of Pooled USMDs of AS Measured by a) cfPWV b) baPWV Between High vs Low Serum UA Groups and c) Pooled Odds Ratio (OR) of AS between High vs Low Serum UA Groups as Measured by baPWV*

Table 2 Pooled Mean Difference of Serum UA Level Between AS and Non-AS

Author, Year	AS			Non-AS			USMD (95% CI)
	No.	Mean	SD	No.	Mean	SD	
Studies that had AS measured by cfPWV							
Sabio JM, 2009[23]	32	5.5	1.9	96	4.3	1.1	1.20 (0.51 to 1.89)
Wang X, 2013[27]	3796	5.4	1.5	11513	5.2	1.5	0.20 (0.14 to 0.26)
Mule G, 2014[29]	111	5.7	1.25	111	5.1	1.24	1.4 (0.38 to 2.42)
Valero-Gonzalez S, 2014[70]	23	5.7	2.2	23	4.3	1.2	0.60 (0.27 to 0.93)
Elewa U, 2015[31]	85	6.9	1.8	92	6.1	1.6	0.30 (0.27 to 0.33)
Fu S, 2015[32]	770	4.9	0.3	770	4.6	0.3	0.80 (0.30 to 1.30)
Tanindi A, 2015[30]	47	6.31	0.59	98	4.67	0.53	1.64 (1.44 to 1.84)
Pooled USMD							0.76 (0.50 to 1.03)
Studies that had AS measured by baPWV							
Song SH, 2007[22]	347	5.6	0.3	1040	5.2	0.3	0.40 (0.36 to 0.44)
Odaira M, 2011[70]	258	6.4	1.3	2433	6.2	1.2	0.20 (0.03 to 0.37)
Xiong Z, 2012[24]	107	8	1.56	214	5.8	1.7	2.20 (1.83 to 2.57)
Kim BJ, 2013[72]	331	5.7	1.6	324	5.5	1.4	0.20 (-0.03 to 0.43)
Fang JI, 2014[27]	1137	5.9	1.4	4013	5.6	1.4	0.30 (0.21 to 0.39)
Pooled USMD							0.58 (0.31 to 0.85)

Abbreviation: AS, arterial stiffness; baPWV, brachial pulse wave velocity; cfPWV, carotid femoral pulse wave velocity; CI, confidence interval; SD, standard deviation; USMD, unstandardized mean difference.

Table 3 Mean Difference of PWVs Between High vs Low Serum UA Groups

Author, Year	High Serum UA			Low Serum UA			USMD (95% CI)
	No.	Mean	SD	No.	Mean	SD	
Studies that had PWV measured by cfPWV							
Chen X, 2010[17]	135	757	10	805	729	4	22.00 (20.29 to 23.71)
Sabio JM, 2010[40]	15	944	21.3	87	826	36.2	118.00 (104.81 to 131.19)
Tsioufis C, 2011[46]	143	870	12	149	790	12	80.00 (77.25 to 82.75)
Krishnan E, 2012[49]	41	483	129	122	477.8	104.6	5.20 (-38.43 to 41.831)
Liang J, 2012[13]	942	1072	5	2826	1054.7	8.9	17.33 (16.88 to 17.79)
Park JS, 2012[50]	280	790	11.8	561	758.4	15.2	0.80 (0.30 to 1.30)
Zhang J, 2014[1]	53	1162	96	53	1035	104	127.00 (88.90 to 165.10)
Erkmen UM, 2015[63]	27	872	264	73	627	153	245.00 (139.42 to 350.58)
Mehta T, 2015[10]	979	750	150	3130	680.4	114.5	69.60 (59.38 to 79.82)
Wijnands JM, 2015[2]	201	920	23	412	851.5	35	68.50 (63.86 to 73.14)
Pooled USMD							62.43 (46.97 to 77.88)
Studies that had PWV measured by baPWV							
Kuo CF, 2010[16]	1362	1618.9	379.5	8012	1501.7	334.9	117.20 (95.75 to 138.65)
Shin JY, 2012[51]	170	1392.8	217.8	457	1332.5	201.6	52.50 (8.63 to 96.37)
Bae JS, 2013[26]	456	1636.9	379.9	6963	1502	326.4	134.90 (97.58 to 172.22)
Chen L, 2015[62]	2118	1374.8	229	6493	1333.2	1.2	41.6 (30.26 to 52.94)
Pooled USMD							86.20 (35.40 to 136.99)
Studies that had PWV measured by crPWV							
Tsai WC, 2009[38]	50	913	127	150	851.3	132.6	61.7 (20.59 to 102.80)
Liang J, 2012[13]	942	1035	5	2840	1031.7	8.1	3.3 (2.86 to 3.74)
Zhang J, 2014[1]	53	975	9.5	53	905	9.5	70 (66.38 to 73.62)
Mehta T, 2015[10]	979	946	15	3130	933.3	27.8	12.7 (11.35 to 14.05)
Pooled USMD							32.69 (13.45 to 51.94)

Abbreviation: cfPWV, carotid femoral pulse wave velocity; CI, confidence interval; crPWV, carotid-radial pulse wave velocity; PWV, pulse wave velocity; SD, standard deviation; UA, uric acid; USMD, unstandardized mean difference.

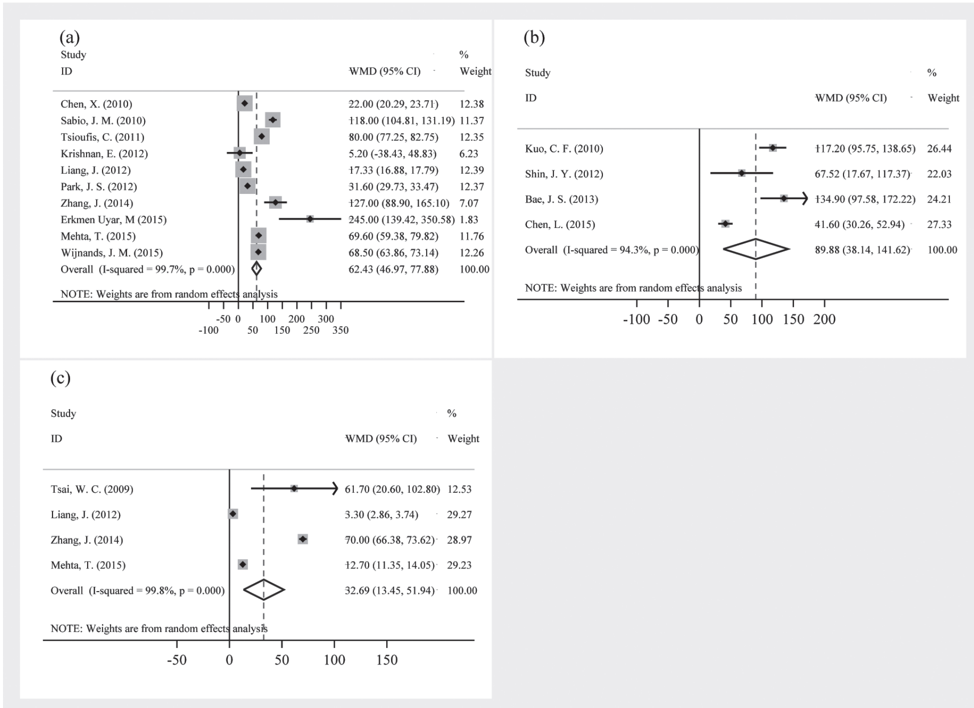

Figure 3 *Forest Plot of Pooled USMDs of AS Measured by a) cfPWV b) baPWV and c) crPWV Between High vs Low Serum UA Groups*

Four[1, 10, 13, 38] studies had data available for pooling the USMDs of crPWV. The pooled USMDs was 32.69 cm (95% CI, 13.45 - 51.94) with high heterogeneity (I^2= 99.8%) (Figure 3c). Source of heterogeneity was explored (see Appendix 6). Publication bias for studies which reported the USMDs for crPWV, was explored and funnel plots showed asymmetry. Egger's test was non-significant (coefficient = 19.48; SE = 12.20; P = 0.25). Contour-enhanced funnel plot suggested that asymmetry might be more likely caused by heterogeneity (see Appendix 14).

Pooling of Beta Coefficients of Uric Acid Levels and Arterial Stiffness

A total of 26 studies reported beta coefficient data of relationship between serum UA and AS in the regression model. Among 26 studies, 10 studies had arterials stiffness data measured by cfPWV,[12, 14, 41, 45, 47, 48, 54, 55, 60, 61] 12 studies by baPWV,[17, 34, 36, 37, 42, 43, 52, 53, 58, 59, 60, 72] 5 studies by CAVI,[43, 44, 57, 65, 67] 4 studies by AI[12, 14, 48, 54] and 2 study by crPWV.[47, 48] We therefore pooled cfPWV and baPWV studies. Among 10 studies with cfPWV, 8 studies[14, 41, 45, 47, 48, 54, 55, 61] reported enough data (coefficients and their standard errors) which could be pooled. The pooling of beta coefficient showed high heterogeneity (chi-square = 59924.61; P < 0.001; I^2 = 100%) with pooled beta coefficient of 2.51 (95% CI, 2.26 - 2.76) (see Appendix 7 and Appendix 15). We did the sensitivity analysis by excluding the Vlachopoulos et al[14] and Gomez-Marcos et al[54] which were mostly deviated studies, but heterogeneity was still high (I^2 = 100%). Meta regression was done but they could not reduce degree of heterogeneity, thus we could not explain the source of heterogeneity (see Appendix 8). Subgroup analysis was done according to the type of subject, studies with disease subjects were greater than studies in general subjects with pooled beta coefficient 3.34 (95% CI, 1.33 - 5.34) and pooled beta coefficient 1.96 (95% CI, 1.92 - 2.01), respectively. The overall pooling suggested that Egger's test was still not significant (coefficient = 53.10; SE = 37.32; P = 0.205). Contour-enhanced funnel plot was performed and suggested that it may be likely due to missing studies or heterogeneity but not publication bias (see Appendix 16).

In 12 studies with AS measured by baPWV, we can only performed overall pooling in 6[17, 53, 58-60, 72] studies that reported SE or CI of beta coefficients. Coefficients of serum UA were highly heterogeneous with overall pooled beta coefficient 3.74 (95% CI, 2.24 - 5.25; I^2 = 100%) (see Appendix 7 and Appendix 15). The source of heterogeneity was explored by meta-regression but it was still substantial heterogeneity (see Appendix 8). Subgroup analysis was done according to type of patients which showed that general subjects have higher beta coefficient than the disease subjects 4.01 (95% CI, 2.22 - 5.80) and 3.02 (95% CI, -4.38 to 10.42), respectively. Publication bias was assessed by Egger's test (coefficient = -188.39; SE = 93.31; P = 0.11). A contour-enhanced funnel plot was done which suggested that asymmetry might more likely due to heterogeneity than publication bias (see Appendix 17).

Discussion

We performed the systematic review and meta-analysis of serum UA effects on AS and non-AS. Our results indicated that serum UA were 0.58 mg/dL (95% CI, 0.31 - 0.85) and 0.76 mg/dL (95% CI, 0.50 - 1.03) significantly higher in AS subjects than non-AS subjects measured by cfPWV and baPWV, respectively. The risk of AS was approximately 49% higher in high serum UA patients than lower serum UA patients.

Previous evidences revealed that increasing serum UA was associated with AS[1, 12-17] in both male and female subjects.[16, 17] AS is a known surrogate end point of CVD as for evidences of recent systematic review and individual participant data meta-analysis, which showed that carotid stiffness was independently associated with total cardiovascular events and incidence of stroke, cardiovascular and all-cause mortality but was not associated with coronary heart disease.[73] Although the mechanism of association between UA and AS has not yet been clearly defined, it is thought to be through an increase in inflammation of arterial wall, promotion of vasculcular smooth muscle cell proliferation, and an increase in oxidative stress of renin-angiotensin system.[75]

Our pooled results were substantially heterogeneous. The sources of heterogeneity were explored, including age, male percentage, type of included subjects (disease subject and general subject), but only male percentage was identified as the source of heterogeneity. Magnitude of mean differences of serum UA were high in the group of more-female-included studies than the group of male-prominent group with pooled USMDs of 1.26.

We also found that AS measurements were different between high vs low serum UA groups, with the pooled USMDs of 62.42 cm/s (95 CI%, 46.94 - 77.88), 86.2 cm/s (95 CI%, 33.40 - 136.99), and 32.69 cm/s (95 CI%, 13.45 - 51.94) for cfPWV, baPWV and crPWV, respectively. Our subgroup analysis showed higher cfPWV in specific disease patients (eg, hypertension, diabetes, and chronic kidney disease, etc.) than general patients. This corresponded to previous evidences indicating hypertension, age, sex,[55, 60, 64] chronic kidney disease, type 2 diabetes mellitus,[1] and metabolic syndrome[62] influenced cfPWV, crPWV, baPWV, aPWV, CAVI and AI. All of the AS measurements were non-invasive which may be used as surrogate factors of CVD risk or progression in clinical practice. Clinician who encounter patient with high serum UA levels may consider measuring one of the AS measurements for a marker of CVD.

There are some strengths in our systematic review of observational studies. First, poolings were based on 44 observational studies with very large sample size of 116,898. Second, we assessed associations between serum UA and AS, which considered all types of measurements, ie, cfPWV, baPWV, and crPWV. Third, serum UA was considered as continuous and low/high levels. Fourth, subgroup analyses were performed according to general and disease specific patients. But our study has some limitations. First, we used aggregated data, in which some important covariables (status of diabetes mellitus, hypertension, smoking, chronic kidney disease, etc) were not available for data extractions. Second, our pooling results were highly heterogeneous, so there might be other sources of heterogeneity which we could not assess. Finally, cutoffs for classifying low/high serum UA and AS/non-AS varied across studies, which could result in heterogeneity of association effects. Based on aggregated data, we could not standardize or reclassify these groups. Individual patient data is required in order to standardize the cutoffs and also adjust for important covariables.

Conclusions

High serum UA level was associated with AS measured by cfPWV, baPWV, and crPWV. However, pooling results were heterogeneous. Further studies with subgroups analysis of homogenous patients are required. Other AS measurements such as aPWV, AI, CAVI are still needed to study the association of serum UA and AS.

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Appendices

Appendix 1 Search Terms Used for Medline Database

There domain were used to construct the search terms

("Uric acid") OR "Hyperuricemia") OR "Serum uric acid") OR "Uric Acid"[Mesh]) OR "Hyperuricemia"[Mesh])

("Aorta") OR "Aorta"[Mesh]) OR "Arterial") OR "Arteries"[Mesh]) OR "Carotid") OR "Carotid Arteries "[Mesh]) OR "Vessel") OR "Tunica Media"[Mesh]) OR "Vascular") OR "Vascular Resistance"[Mesh])

("Stiffness") OR "Elastic Modulus"[Mesh]) OR "Elasticity") OR "Elasticity"[Mesh]))) OR (((“Arterial stiffness”) OR "Vascular stiffness") OR "Vascular stiffness"[Mesh]))) OR ((((("Pulse wave velocity") OR "pulse wave analysis"[Mesh]) OR "Augmentation index") OR "Cardio-ankle vascular index”) OR "CAVI")

Three terms combined with AND

(((((("Uric acid") OR "Hyperuricemia") OR "Serum uric acid") OR "Uric Acid"[Mesh]) OR "Hyperuricemia"[Mesh])) AND ((((((((((((((("Aorta") OR "Aorta"[Mesh]) OR "Arterial") OR "Arteries"[Mesh]) OR "Carotid") OR "Carotid Arteries "[Mesh]) OR "Vessel") OR "Tunica Media"[Mesh]) OR "Vascular") OR "Vascular Resistance"[Mesh])) AND (((("Stiffness") OR "Elastic Modulus"[Mesh]) OR "Elasticity") OR "Elasticity"[Mesh]))) OR (((“Arterial stiffness”) OR "Vascular stiffness") OR "Vascular stiffness"[Mesh]))) OR ((((("Pulse wave velocity") OR "pulse wave analysis"[Mesh]) OR "Augmentation index") OR "Cardio-ankle vascular index”) OR "CAVI"))

Search terms used for Scopus database

We used two domain to construct the search terms

(“Uric acid”) OR (“Hyperuricemia”) OR (“Serum uric acid”)

(“Aorta”) PRE/5 ("Stiffness")) OR (("Aorta") PRE/5 ("Elasticity")) OR (("Carotid") PRE/5 ("Elasticity")) OR (("Carotid") PRE/5 ("Stiffness")) OR (("Vessel") PRE/5 ("Stif fness")) OR (("Vessel") PRE/5 ("Elasticity"))) OR ((("Vascular") PRE/5 ("Elasticity")) OR (("Vascular") PRE/5 ("Stiffness")) OR (("Arterial") PRE/5 ("Stiffness")) OR (("Arterial") PRE/5 ("Elasticity")))) O R (("Pulse wave velocity") OR ("Augmentation index") OR ("Cardio-ankle vascular index") OR ("CAVI")

We combined two domain by “AND”

(("Uric acid") OR ("Hyperuricemia") OR ("Serum uric acid")) AND

((((("Aorta") PRE/5 ("Stiffness")) OR (("Aorta") PRE/5 ("Elasticity")) OR (("Carotid") PRE/5 ("Elastic ity")) OR (("Carotid") PRE/5 ("Stiffness")) OR (("Vessel") PRE/5 ("Stiffness")) OR (("Vessel") PRE/5 ("Elasticity"))) OR ((("Vascular") PRE/5 ("Elasticity")) OR (("Vascular") PRE/5 ("Stiffness")) OR (("A rterial") PRE/5 ("Stiffness")) OR (("Arterial") PRE/5 ("Elasticity"))))) OR (("Pulse wave velocity") OR ("Augmentation index") OR ("Cardio-ankle vascular index") OR ("CAVI")))

Appendix 2 Risk of Bias Assessment for Cohort and Cross Sectional Studies of Serum UA and AS

Author	Year	Representative of the Sample	Sample Size	No-Respondents	Ascertainment of Risk Factor	Control Important Factor	Control Additional Factor	Assessment of Outcome	Statistical Test	Total Star
Sabio JM[23]	2009	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Vlachopoulos C[14]	2011	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Saijo Y[17]	2005	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Ishizaka N[3]	2007	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Song SH[22]	2007	B(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	7
Tsai WC[38]	2009	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	7
Chen X[16]	2010	B(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(0)	A(1*)	A(1*)	8
Kuo CF[15]	2010	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Lim JH[18]	2010	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Sabio JM[40]	2010	B(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Odaira M[70]	2011	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Syrselouds D[45]	2011	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Tsioufis C[46]	2011	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Park JS[50]	2012	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Wang F[47]	2011	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Brian S[48]	2012	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Krishnan E[49]	2012	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Lee MJ[72]	2012	B(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Liang J[13]	2012	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Shin JY[51]	2012	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8

Appendix 2 Risk of Bias Assessment for Cohort and Cross Sectional Studies of Serum UA and AS (Continued)

Author	Year	Representative of the Sample	Sample Size	No-Respondents	Ascertainment of Risk Factor	Control Important Factor	Control Additional Factor	Assessment of Outcome	Statistical Test	Total Star
Xiong Z[24]	2012	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Zhu C[53]	2012	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Gomez-Marcos M[25]	2013	A(1*)	A(1*)	A(1*)	(c)	A(1*)	A(1*)	A(1*)	A(1*)	7
Kim BJ[72]	2013	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Magalhaes P[55]	2013	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Wang X[26]	2013	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Xie X[58]	2013	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Zhu C[59]	2013	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Elsurer R[60]	2014	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Fang JI[27]	2014	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Mule G[29]	2014	B(*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Valero-Gonzalez S[69]	2014	B(*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Zhang J[1]	2014	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Baena CP[61]	2014	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Fu S[32]	2015	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Mehta T[10]	2015	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Tanindi A[30]	2015	B(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Wijnands JM[2]	2015	B(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8
Zhu WH[33]	2015	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	A(1*)	8

Appendix 3 Exploring Source of Heterogeneity of Mean Difference of Serum UA Between AS and Non-AS by Meta-Regression Analysis

Variable	Coefficient (95% CI)	I^2	*P* Value
Studies that had AS measured by cfPWV			
Original model	0.76 (0.22 to 1.30)	97.08	0.01
Age	-0.01 (-0.06 to 0.03)	82.24	0.56
Male percentage	-0.01 (-0.04 to 0.02)	97.53	0.44
General vs Disease subjects	-0.92 (-1.62 to -0.22)	88.23	0.02
Studies that had AS measured by baPWV			
Original model	0.58 (-0.39 to 1.55)	96.08	0.17
Age	0.08 (-0.01 to 0.19)	95.00	0.07
Male percentage	-0.01 (-0.08 to 0.05)	96.79	0.91
General vs Disease subjects	0.49 (-2.6 to 3.59)	96.90	0.64

Abbreviation: AS, arterial stiffness; baPWV, brachial pulse wave velocity; cfPWV, carotid femoral pulse wave velocity; CI, confidence interval.

Appendix 4 Pooling the Odd Ratios of Serum UA Among AS vs Non-AS

Author, Year	No.				OR (95%CI)
	AS		Non-AS		
	High baPWV	Low baPWV	High Serum UA	Low Serum UA	
Ishizaka N, 2007[3]	69	161	132	590	1.92 (1.36 - 2.69)
Lim JH, 2010[18]	52	241	146	837	1.24 (0.87 - 1.75)
Zhu WH, 2015[33]	1172	915	2985	3395	1.48 (1.32 - 1.61)
Pooled OR					1.49 (1.25 - 1.78)

Abbreviation: AS, arterial stiffness; baPWV, brachial pulse wave velocity; OR; odd ratio; UA, uric acid.

Appendix 5 Exploring Source of Heterogeneity of Odds Ratio of Serum UA Between baPWV by Meta-Regression Analysis

Variable	Coefficient (95% CI)	I^2	*P* Value
Original model	1.52 (0.72 to 2.33)	76.21	0.01
Age	0.04 (-0.26 to 0.35)	60.84	0.33
Male percentage	0.01 (-0.21 to 0.24)	87.48	0.66
General vs Disease subjects	-0.12 (-7.28 to 7.04)	86.67	0.86

Abbreviation: CI, confident interval.

Appendix 6 Exploring the Source of Heterogeneity of Mean Difference of PWVs Between High vs Low Serum UA Groups by Meta-Regression Analysis

Variable	Coefficient (95% CI)	I^2	*P* Value
Studies that had AS measured by cfPWV			
Original model	62.42 (28.04 to 96.81)	99.69	0.003
Age	-3.07 (-10.35 to 4.19)	99.73	0.35
Male percentage	-5.50 (120.82 to 109.80)	99.70	0.91
General vs Disease subjects	65.84 (20.19 to 111.49)	99.02	0.01
Studies that had AS measured by baPWV			
Original Model	89.87(5.87 to 173.89)	94.29	0.04
Age	6.72 (-0.32 to 13.78)	36.91	0.05
Male percentage	-5.50 (120.82 to 109.80)	99.70	0.91
Studies that had AS measured by crPWV			
Original Model	32.69 (-21.76 to 87.15)	99.79	0.15
Age	3.14 (-19.33 to 25.62)	99.73	0.60
Male percentage	1.44 (-1.14 to 4.02)	99.67	0.13
General vs Disease subjects	-61.28 (-95.92 to -26.64)	98.81	0.001

Abbreviation: AS, arterial stiffness; baPWV, brachial pulse wave velocity; cfPWV, carotid femoral pulse wave velocity; CI, confident interval.

Appendix 7 Pooling of Beta Coefficients Between Serum UA and PWV

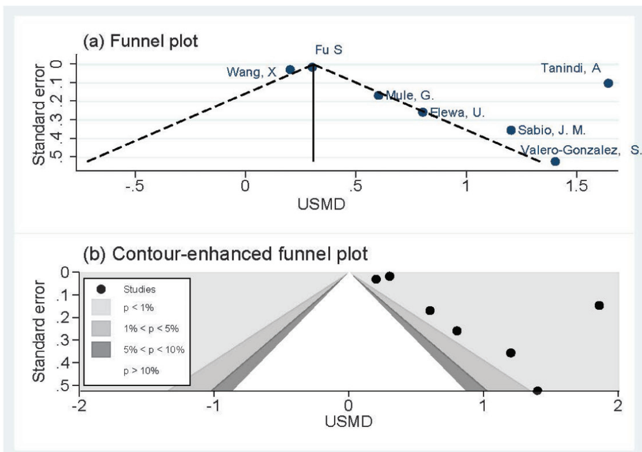
Author, Year	No.	Standardized Beta Coefficient	Standard Error	95% CI
Studies that had AS measured by cfPWV				
Vlachopoulos C, 2010[41]	51	2.89	0.09	2.72 to 3.07
Syrseloudis D, 2011[45]	402	2.61	0.001	2.60 to 2.62
Vlachopoulos C, 2011[14]	1225	5.72	0.002	5.69 to 5.76
Wang F, 2011[47]	2375	2	0.08	1.99 to 2.0
Bian S, 2012[48]	1236	2	0.05	1.99 to 2.0
Gomez-Marcos MA, 2013[54]	366	0.37	0.03	0.21 to 0.53
Magalhaes P, 2013[55]	432	2.14	0.05	2.04 to 2.24
Baena CP, 2015[61]	3578	2.26	0.03	2.21 to 2.32
Pooled beta coefficient		2.51		2.26 to 2.76
Studies that had AS measured by baPWV				
Saijo Y, 2005[17]	4266	4.55	0.01	4.52 to 4.57
Lee MJ , 2012[72]	760	0.84	7.82	-14.48 to 16.16
Zhu C, 2012[53]	638	7.5	0.004	7.49 to 7.51
Xie X, 2013[58]	13 899	1.5	0.03	1.45 to 1.55
Zhu C, 2013[59]	978	6	0.005	5.99 to 6.01
Elsurer R, 2014[60]	339	-0.69	0.03	-0.75 to -0.63
Pooled beta coefficient		3.75		2.24 to 5.25

Abbreviation: AS, arterial stiffness; baPWV, brachial pulse wave velocity; cfPWV, carotid femoral pulse wave velocity.

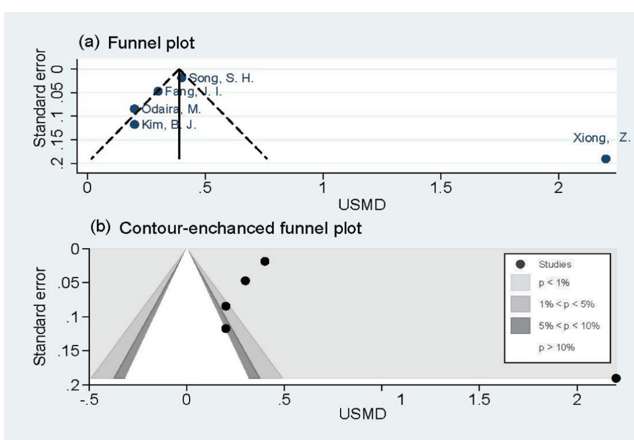
Appendix 8 Exploring the Source of Heterogeneity of Pooling Beta-Coefficient Between Serum UA and PWV by Meta-Regression Analysis

Variable	Coefficient (95% CI)	I^2	*P* Value
Studies that had AS measured by cfPWV			
Original Model	2.51 (1.25 to 3.76)	99.99	0.002
Age	-0.02 (-0.24 to 0.21)	99.98	0.88
Male parentage	0.02 (-0.17 to 0.22)	99.67	0.78
General vs Disease subjects	1.68 (-0.58 to 3.92)	99.98	0.12
Studies that had AS measured by baPWV			
Original Model	3.74 (0.32 to 7.17)	100.00	0.04
Age	0.21 (-0.47 to 0.89)	99.99	0.44
Male percentage	0.07 (-0.19 to 0.34)	99.67	0.45
General vs Disease subjects	-0.82 (-9.94 to 8.29)	100.00	0.81

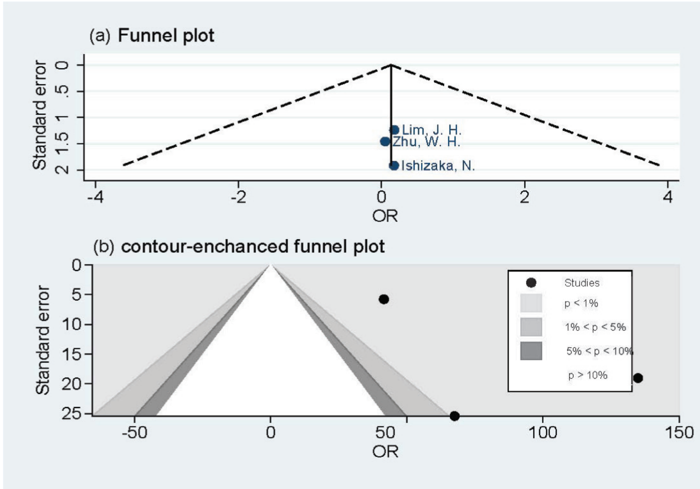
Abbreviation: AS, arterial stiffness; baPWV, brachial pulse wave velocity; cfPWV, carotid femoral pulse wave velocity; CI, confident interval.



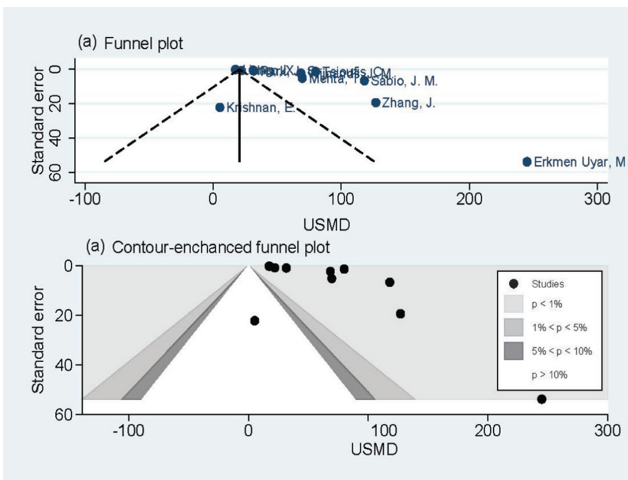
Appendix 9 Funnel Plot and Contour-Enhanced Funnel Plot for Pooling USMDs of Serum UA Between AS vs Non-AS Measured by cfPWV



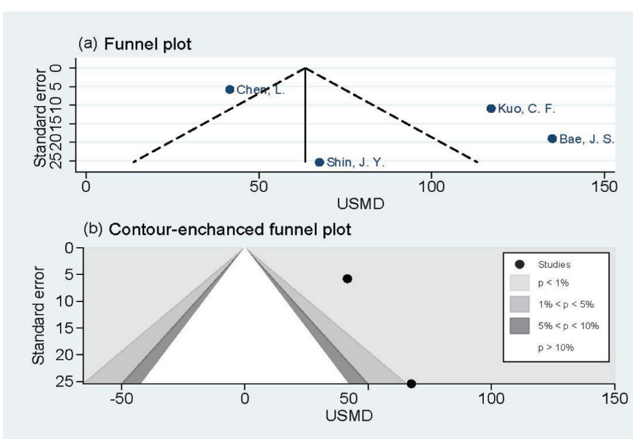
Appendix 10 Funnel Plot and Contour-Enhanced Funnel Plot for Pooling USMDs of Serum UA for AS vs Non-AS Measured by baPWV



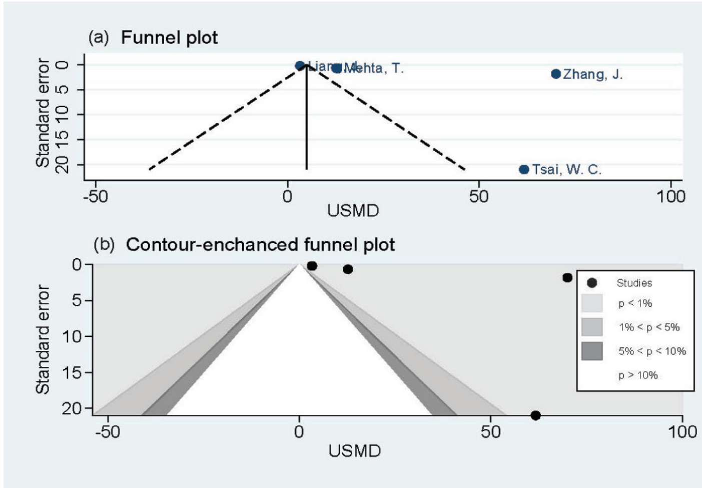
Appendix 11 Funnel Plot and Contour-Enhanced Funnel Plot for Odds Ratio of High vs Low Serum UA Measured by baPWV



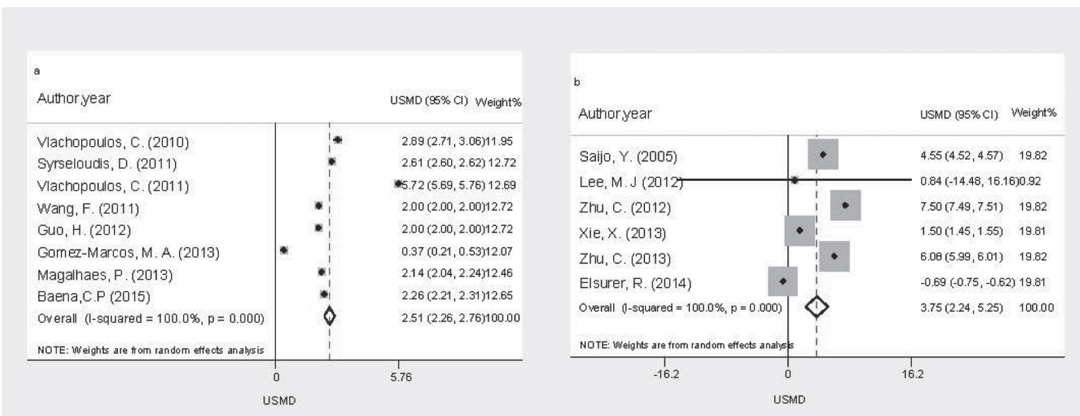
Appendix 12 Funnel Plot and Contour-Enhanced Funnel Plot for Pooling USMDs of cfPWV Between High vs Low Serum UA Groups



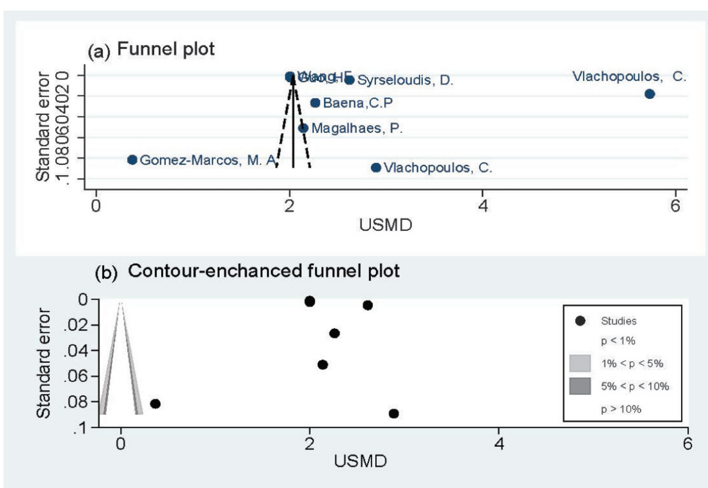
Appendix 13 Funnel Plot and Contour-Enhanced Funnel Plot for Pooling USMDs of AS Measured by baPWV Between High vs Low Serum UA Groups



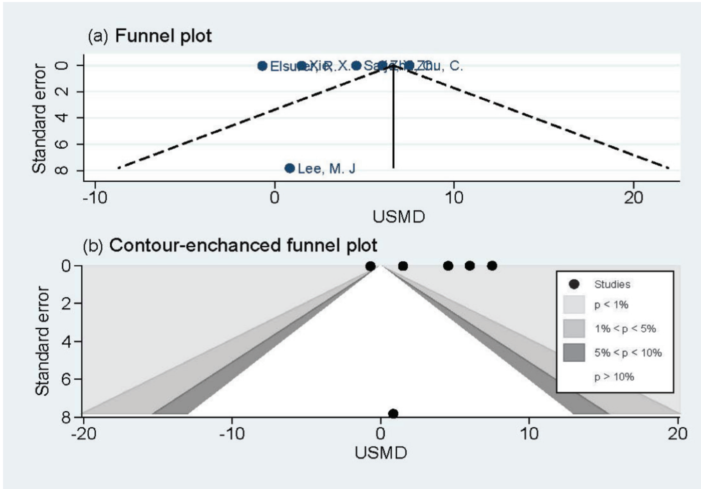
Appendix 14 Funnel Plot and Contour-Enhanced Funnel Plot for Pooling USMDs of AS Measured by crPWV Between High vs Low Serum UA Groups



Appendix 15 Forest Plot for Pooling Beta-Coefficient of Serum UA and cfPWV (a) and baPWV (b)



Appendix 16 Funnel Plot and Contour-Enhanced Funnel for Pooling Beta-Coefficients of Serum UA and cfPWV



Appendix 17 Funnel Plot and Contour-Enhanced Funnel for Pooling Beta-Coefficients of Serum UA and baPWV

Review Article/บทฟื้นฟูวิชาการ

ความสัมพันธ์ระหว่างกรดยูริกและความแข็งของหลอดเลือดแดงในผู้ใหญ่: การทบทวนวรรณกรรมอย่างเป็นระบบและการวิเคราะห์อภิมาน

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บทคัดย่อ

บทนำ: ความแข็งของหลอดเลือดแดงเป็นตัวแทนของการบ่งชี้โรคหลอดเลือดแดงแข็งและโรคหัวใจและหลอดเลือด ซึ่งอาจสัมพันธ์กับระดับของกรดยูริกในเลือด

วัตถุประสงค์: เพื่อทบทวนวรรณกรรมอย่างเป็นระบบของความสัมพันธ์ระหว่างกรดยูริกในเลือดและความแข็งของหลอดเลือดแดง

วิธีการศึกษา: คัดเลือกการศึกษาสังเกตที่ศึกษาผลของระดับกรดยูริกในเลือดและความแข็งของหลอดเลือดแดงในผู้ใหญ่จากฐานข้อมูล MEDLINE และ Scopus ตั้งแต่เริ่มต้นจนถึงวันที่ 30 มิถุนายน พ.ศ. 2559 ค่าความแตกต่างของค่าเฉลี่ยระหว่างระดับกรดยูริกในเลือดระหว่างกลุ่มผู้ป่วยที่มีหลอดเลือดแดงแข็งและค่า Odds ratio ของกรดยูริกในกลุ่มที่ได้ทำการตรวจวัดความแข็งของหลอดเลือดแดง

ผลการศึกษา: งานวิจัยที่ผ่านเกณฑ์คัดเข้า จำนวนทั้งสิ้น 61 เรื่อง และมีจำนวน 44 เรื่อง ได้ถูกรวมค่าความแตกต่างของค่าเฉลี่ยรวมของกรดยูริกในกลุ่มผู้ป่วยที่มีหลอดเลือดแดงแข็งและกลุ่มผู้ป่วยที่ไม่มีหลอดเลือดแดงแข็งจากการตรวจวัดด้วยวิธี Carotid - femoral pulse wave velocity (cfPWV) และ Brachial ankle pulse wave velocity (baPWV) ในงานวิจัยจำนวน 7 เรื่อง และ 5 เรื่อง เท่ากับ 0.76 (95% CI, 0.50 - 1.03) mg/dL และ 0.58 (95% CI, 0.31 - 0.85) mg/dL ตามลำดับ ค่า Odds ratio รวมของกลุ่มที่มีกรดยูริกสูงเปรียบเทียบกับกลุ่มที่มีกรดยูริกต่ำของงานวิจัยที่ตรวจวัดด้วยวิธี baPWV จำนวน 3 เรื่อง เท่ากับ 1.49 (95% CI, 1.25 - 1.78) ค่าความแตกต่างของค่าเฉลี่ยรวมของผู้ป่วยที่มีหลอดเลือดแดงแข็งกลุ่มที่มีกรดยูริกสูงเปรียบเทียบกับกลุ่มที่มีกรดยูริกต่ำของงานวิจัยที่ตรวจวัดด้วยวิธี cfPWV (10 เรื่อง), baPWV (4 เรื่อง) และ Carotid radial pulse wave velocity (crPWV) (4 เรื่อง) เท่ากับ 62.43 (95% CI, 46.94 - 77.88), 86.20 (95% CI, 35.40 - 136.99) และ 32.69 (95% CI, 13.45 - 51.94) cm/s ตามลำดับ ค่ารวมของค่าสัมประสิทธิ์เบต้าของกรดยูริกในผู้ป่วยที่มีหลอดเลือดแดงแข็งที่ตรวจวัดด้วยวิธี cfPWV และ baPWV เท่ากับ 2.51 (95% CI, 2.26 - 2.76) และ 3.75 (95% CI, 2.24 - 5.25) ตามลำดับ

สรุป: ระดับของกรดยูริกมีความสัมพันธ์กับความแข็งของหลอดเลือดแดงอย่างมีนัยสำคัญทางสถิติเมื่อตรวจวัดด้วยวิธี cfPWV, baPWV และ crPWV อย่างไรก็ตาม การรวบรวมมีความแตกต่างกันสูงระหว่างงานวิจัย

คำสำคัญ: กรดยูริก ความแข็งของหลอดเลือดแดง ความเร็วคลื่นชีพจรคาโรติดและโคนขา ความเร็วคลื่นชีพจรแขนและข้อเท้า ความเร็วคลื่นชีพจรคาโรติดและเรเดียล

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