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Effects of coffee consumption on serum uric acid: systematic review and meta-analysis

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ABSTRACT

Objective: Study results on the effects of coffee consumption on serum uric acid (UA) have been conflicting. The aim of this study is to analyze the literature regarding the effect of coffee consumption on serum UA.

Methods: We searched MEDLINE, EMBASE, the Cochrane library, and KoreaMed for all articles published before January 2015. Studies with quantitative data on coffee consumption and serum UA level were included. Coffee consumption and serum UA level were identified with/without the risk of gout. Results: Nine studies published between 1999 and 2014 were included, containing a total of 175,310 subjects. Meta-analysis demonstrated that coffee has a significantly lowering effect on serum UA, where there are gender differences in the amount of coffee required to lower serum UA. Women (4–6 cups/day) need more coffee to lower serum UA than men (1-3 cups/day). Meta-analysis showed that coffee intake

correlation with the amount of daily coffee intake for both genders. Conclusions: This is the first systematic review on the effects of coffee consumption on serum UA. Based on our study, moderate coffee intake might be advocated for primary prevention of hyperuricemia and gout in both genders.

of 1 cup/day or more was significantly associated with reduction of the risk of gout, with a negative

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Coffee is one of the most popular beverages in the world [1-3]. There is evidence that consumption of coffee within a moderate range (3-5 cups per day) is not associated with increased longterm health risks among healthy individuals. Consistent evidence demonstrates that coffee consumption is associated with reduced risk of type 2 diabetes and cardiovascular disease in adults. Therefore, according to the Scientific Report of the 2015 Dietary Guidelines Advisory Committee, moderate coffee consumption can be incorporated into a healthy dietary pattern, along with other healthful behaviors [4].

Traditionally, serum uric acid (UA) has been related to gouty arthropathy [5]. Hyperuricemia is associated with a variety of medical conditions, such as hypertension, insulin resistance, and cardiovascular and renal diseases, as well as gout [6–11].

UA is also known as a central nervous system antioxidant [12]. Elevated serum UA level is reported to be associated with better cognition and a lower risk of dementia [13]. There is some

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neurological disorders, such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis [11,14]. Therefore, serum UA has varied biological significance and must be assessed for reasons other than just gout [5].

evidence that reduced serum UA levels are associated with various

Coffee consumption has been reported as either increasing [15] or decreasing serum UA [3,16–19]. Thus, the aim of this systematic review and meta-analysis is to analyze for the first time the literature exploring the effect of coffee consumption on serum UA and the risk of gout.

Materials and methods

This study is based on the Cochrane Methods, and reporting follows the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statements [20].

Data sources and searches

In January 2015, we performed a comprehensive literature search of electronic databases, including MEDLINE, EMBASE, and

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the Cochrane Library. We also conducted searches in a regional electronic bibliographic database (KoreaMed). No restrictions were imposed in terms of the publication language, time, or status. Electronic database searches used both free text words and Medical Subject Headings. The search strategy was adapted as appropriate for all other databases searched (Appendix), taking into account differences in indexing terms and search syntax for each database. We identified further relevant studies for possible inclusion by reviewing the reference lists of the studies identified by our initial search strategies.

Study selection

The inclusion of all studies was independently decided by four reviewers (KYP, SHK, SYY, and JBJ) based on predefined inclusion and exclusion criteria. Discrepancies were resolved by discussion between the reviewers. Study selection included two levels of screening. Four reviewers independently screened the titles and abstracts of identified studies. We retrieved the articles of any citation identified by the reviewers for full-text review. Two reviewers then assessed the reports to ensure that they met the inclusion criteria detailed below.

Studies were included in our systematic review if they met all of the following three inclusion criteria: (1) original studies with the aim of evaluating the association between coffee consumption and serum UA level or coffee consumption and risk of gout; (2) studies providing quantitative data on coffee consumption and serum UA level; and (3) human study. If the data from the same or a similar population had been published in more than one study, the most complete and relevant study was chosen for analysis.

Data extraction

Two reviewers (KYP and SYY) independently performed data extraction using a predefined form. Any disagreement unresolved by discussion was reviewed by a third author. The following variables were extracted from the studies: (1) demographic characteristics, including first author's name, year of publication, country where the study was performed, study design, total number of participants, mean age, and proportion of men and women; (2) coffee intake (cups/day); and (3) serum UA levels (mg/dl). If the information regarding the presence of gout was available, it was extracted.

For coffee consumption, the measurement of intake varied among studies. Cups/day was chosen as the standard measure. The amount of coffee intake was assigned to three levels: <1 cup/day, 1–3 cups/day, and of ≥ 4 cups/day. Serum UA value was extracted in the units of milligrams per deciliter (mg/dl). Therefore, we performed the conversion from μ mol/L to conventional units (mg/dl) using a factor of 0.01681 (1 mg/dl = 59.48 μ mol/L). Gout was defined using the American College of Rheumatology survey criteria [21].

Data analysis

Meta-analysis was done to examine the effect of coffee consumption on both serum UA level and risk of gout. Subgroup analysis was done according to gender. Sensitivity analyses were conducted to assess the influence of an individual study on the pooled estimate, by omitting studies having high risk of bias or increasing heterogeneity. Sensitivity analysis was also done according to the type of study, such as a cohort or cross-sectional study.

Assessment of methodological quality

Assessment of risk of bias

Three reviewers (KYP, SHK, and SYY) independently assessed the methodological qualities of each study using the risk of bias for non-randomized studies in meta-analysis suggested by the Newcastle-Ottawa Scale [22]. Any discrepancies were addressed by a joint re-evaluation of the original article by a fourth author.

Statistical analysis

Meta-analysis was performed using Review Manager software (RevMan 5.2, 2012), which was supplied by the Cochrane Collaboration. The dichotomous data such as the risk of gout were analyzed by calculating a pooled risk ratio (RR), using the Mantel–Haenszel method. Continuous data such as serum UA level were analyzed by calculating a pooled weighted mean difference using the inverse variance method. We examined the presence of heterogeneity across studies using the l^2 statistic to quantify the percentage of variability that can be attributed to the between-study differences. l^2 value above 50% was considered significantly heterogeneous, but values for all reports were calculated via the random effect model due to the inherent limitations of non-controlled studies.

Results

Identification of studies

Nine studies were included in this analysis [1–3,15,16, 18,19,23,24]. The screening process for study selection is listed in a flow diagram (Fig. 1).

Study characteristics

A total of 175,310 subjects were included in nine studies. Six articles [1-3,15,19,23] including 171,605 cases were from cohort studies. Three articles [16,18,24] including 3,705 cases had a cross-sectional study. The characteristics of the studies and of their participants are shown in Table 1.

Assessment of risk of bias

The assessment of the risk of bias for the nine studies is shown in Table 2. The overall quality of studies was good, ranging from 6 to 8, except for one study [24].

Meta-analysis of the effect of coffee intake on serum UA

Meta-analysis was conducted to examine the effect of coffee intake on serum UA (Fig. 2). Coffee intake of 1-3 cups/day and 4-6 cups/day did not show significant differences in serum UA compared to coffee intake of < 1 cup/day. The highest amount of daily coffee intake in each study also did not show significant differences in serum UA compared to the lowest amount of daily coffee intake (Fig. 2A).

We conducted sensitivity analysis to assess the influence of an individual study on the pooled estimate, by omitting studies having high risk of bias [24] or increasing heterogeneity [23]. The result of meta-analysis done by removing two studies showed significant reduction in serum UA with the highest amount of coffee intake compared to that with the lowest amount [5 studies, 11,109 subjects, -0.23 mg/dl (95% CI: -0.45 to -0.01); p = 0.04; Fig. 2B]. There was no significant difference in serum UA in the meta-analysis done by removing either of two studies (Supplementary Fig. 1). Another sensitivity analysis was performed

K.Y. Park et al. / Seminars in Arthritis and Rheumatism ■ (2016) ■■■-■■■

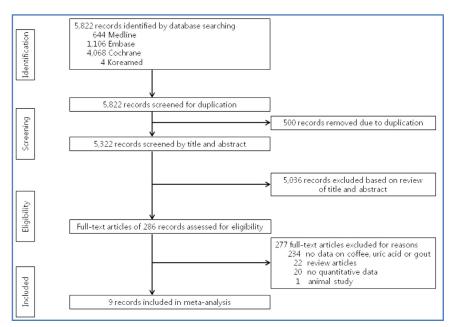


Fig. 1. Flow diagram of study selection.

to assess influence of type of study, such as cohort or cross-sectional study. Sensitivity analysis did not show any significant reduction in serum UA with any amount of coffee intake on meta-analysis including only cohort studies (Fig. 2C). Sensitivity analysis showed significant reduction in serum UA with 4–6 cups/day [1 study, 1,082 subjects, -0.32 mg/dl (95% CI: -0.52 to -0.12), p=0.002] and the highest amount of coffee intake, [2 studies, 3,133 subjects, -0.36 mg/dl (95% CI: -0.55 to -1.17), $I^2=46\%$; p=0.0002] compared to coffee intake of <1 cup/day and the lowest amount of coffee intake, respectively, on meta-analysis including only cross-sectional studies (Fig. 2D).

Meta-analysis of the effect of coffee intake on serum UA according to gender

Serum UA was significantly higher in men than in women, regardless of the amount of coffee intake (Supplementary Fig. 2). Meta-analysis of the effect of coffee intake on serum UA was conducted according to gender (Fig. 3). Men showed significantly lower serum UA level with coffee intake of 1–3 cups/day than with $<1~\rm cup/day$ [3 studies, 7,794 subjects, $-0.12~\rm mg/dl$ (95% CI: $-0.17~\rm to$ -0.08), $I^2=41\%$; p <0.00001; Fig. 3A]. However, serum UA level did not show a significant difference with coffee intake of 4–6 cups/day compared to $<1~\rm cup/day$. The highest amount of coffee intake in each study also did not show a significant difference in serum UA compared to the lowest amount of coffee intake.

Since we identified one study [23] that significantly increased heterogeneity, sensitivity analysis was conducted by excluding this study, and demonstrated a significant reduction in serum UA with coffee intake of both 1–3 cups/day [2 studies, 5,655 subjects, $-0.09 \, \text{mg/dl}$ (95% CI: $-0.14 \, \text{to} -0.03$); p = 0.005] and 4–6 cups/day [2 studies, 3,830 subjects, $-0.21 \, \text{mg/dl}$ (95% CI: $-0.38 \, \text{to} -0.04$); p = 0.02] compared to $< 1 \, \text{cup/day}$. The highest amount of coffee intake also showed significant reduction in serum UA compared to that with the lowest intake [3 studies, 3,412 subjects, $-0.21 \, \text{mg/dl}$ (95% CI: $-0.37 \, \text{to} -0.04$); p = 0.01; Fig. 3B].

Women showed significant reduction in serum UA with coffee intake of 4–6 cups/day compared to <1 cup/day [1 study, 3428 subjects, -0.11 mg/dl (95% CI: -0.20 to -0.02); p=0.02; Fig. 3C]. However, women did not show significant differences in serum UA when coffee intake of <1 cup/day was compared with 1–3 cups/day. The highest amount of coffee intake in each study also did not show significant differences in serum UA compared to the lowest amount of coffee intake. Sensitivity analysis was conducted by excluding one study [23] that increased heterogeneity, and demonstrated significant reduction in serum UA with coffee intake of 4–6 cups/day [1 study, 3,428 subjects, -0.11 mg/dl (95% CI: -0.20 to -0.02); p=0.02] compared to <1 cup/day (Fig. 3D).

Another sensitivity analysis was performed to assess the influence of type of study, such as a cohort or cross-sectional study. Sensitivity analysis showed significant reduction in serum UA with different amounts of coffee according to type of study in men. While the cohort study for men showed significant reduction in serum UA with 1–3 cups/day, the cross-sectional study for men demonstrated significant reduction in serum UA with 4–6 cups/day (Supplementary Figs. 3A and B). Since there was only one cross-

Table 1Study characteristics of nine studies analyzed in this review

References, country	Study design	Total number of participants (men:women)	Mean age (years)	The method used to measure uric acid
Bae et al., South Korea [23]	Cohort study	9400 (3564:5836)	61.9	Not reported
Teng et al., Singapore [15]	Cohort study	483 (214:269)	57.6	Uricase method
Pham et al., Japan [19]	Cohort study	11,662 (4964:6698)	62.6	Uricase method
Choi and Curhan USA [2]	Cohort study	89,433 (0:89,433)	46	Not applicable
Choi and Curhan USA [3]	Cohort study	14,758 (6906:7852)	45	Uricase method
Choi et al., USA [1]	Cohort study	45,869 (45,869:0)	54	Not applicable
Olak-Bialon et al., Poland [18]	Cross-sectional study	1955 (1384:571)	36	Not reported
Yuan, 2000, China [24]	Cross-sectional study	96 (-:-)	_	Uricase method
Kiyohara et al., Japan [16]	Cross-sectional study	1654 (1654:0)	52	Uricase method

Table 2Quality assessment of the included studies based on Newcastle-Ottawa Scale.

References	Selection	Comparability	Outcome
Bae et al. [23]	4	1	3
Teng et al. [15]	4	1	3
Pham et al. [19]	4	1	3
Choi and Curhan et al. [2]	2	1	3
Choi and Curhan et al. [3]	4	1	2
Choi et al. [1]	2	1	3
Olak-Bialon et al. [18]	4	2	1
Yuan et al. [24]	0	1	0
Kiyohara et al. [16]	4	1	3

sectional study for women, sensitivity analysis was done only for a cohort study. It showed that there was a significant reduction in serum UA with 4–6 cups/day (Supplementary Fig. 3C).

Meta-analysis of the effect of coffee intake on risk of gout

Two studies [1,2] were analyzed with one [1] exclusively in men and one [2] in women. The multivariate-adjusted RR of risk of gout was 0.85 (95% CI: 0.72–0.99, $I^2=23\%$; p=0.04) for 1–3 cups/day, and 0.50 (95% CI: 0.36–0.70, $I^2=36\%$; p<0.0001) for ≥ 4 cups/day. However, the multivariate-adjusted RR was 0.97 for <1 cup/day that did not show significant change. This indicates that coffee intake of 1 cup/day or more is related to significant reduction in the risk of gout for both genders, with a negative correlation with the amount of daily coffee intake, where coffee intake ≥ 4 cups/day reduced the multivariate RR to 0.50 (Fig. 4).

Discussion

Findings from this meta-analysis indicated that there is a lowering effect of coffee on both serum UA and the risk of gout in both genders. Women need more coffee intake to lower serum UA than men do. Coffee intake of 1 cup/day or more was related to significant reduction in the risk of gout for both the genders, with

a negative correlation with the amount of daily intake, where coffee intake ≥ 4 cups/day reduced the multivariate RR to 0.50.

UA is the final product of purine metabolism and is synthesized by xanthine oxidase from xanthine [25]. The level of serum UA is dependent on both genetic and non-genetic factors like diet and lifestyle that modulate synthesis and excretion of UA, and dietary modification has been used for treatment and prevention of hyperuricemia and gout. Avoidance of foods with a high purine content such as meat and seafood has been recommended. Based on the current study, individuals with hyperuricemia and gout can be advised that coffee consumption can modify serum UA.

The mechanism by which serum UA is lowered by coffee remains still unknown. Since coffee is a complex beverage containing over 1,000 compounds [26], it is difficult to identify a single mechanism. Although coffee's UA lowering mechanism is not our destination and should be another issue to be reviewed by other researcher, chlorogenic acid can provide us one mechanism. Chlorogenic acid, one of the major polyphenols in coffee [27] is known to have an inhibitory effect on xanthine oxidase [28]. Therefore, it is plausible that various other polyphenols in coffee have inhibitory effects on xanthine oxidase similar to chlorogenic acid [29].

Women had significantly lower serum UA than men. Since women also need more coffee to lower serum UA, the mechanism by which gender difference affects this quantity must be identified. Menopausal women reportedly have higher serum UA levels than premenopausal women, and postmenopausal hormone replacement is associated with lower serum UA [30,31]. These findings suggest a protective role of estrogen against hyperuricemia and gout [30,31]. It was reported that estrogen therapy significantly decreased serum UA levels in trans-sexual men. Therefore, a lower serum UA level in women than in men might be related to the difference in estrogen levels. Baseline lower serum UA levels in women might require more coffee to further lower serum UA.

This study also has several limitations. First, there is potential bias in using the results of observational studies as potential confounding factors. Moreover, type of coffee, brewing method, and presence of additives are potential confounding factors for the effect of coffee on serum UA along with type of diet, concurrent systemic disease, and nutritional profile. There are many types of

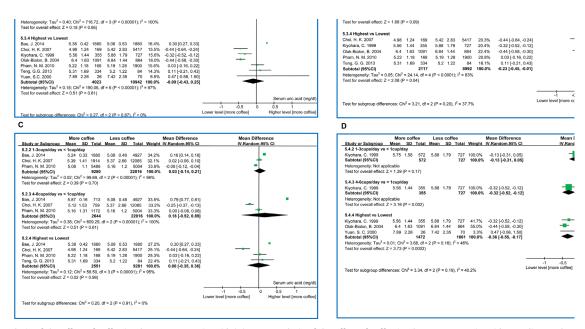


Fig. 2. Meta-analysis of the effect of coffee intake on serum uric acid. (A) Meta-analysis of the effect of coffee intake on serum uric acid according to the amount of coffee intake. (B) Sensitivity analysis by omitting two studies [23,24]. (C) Sensitivity analysis for the cohort studies. (D) Sensitivity analysis for cross-sectional studies. SD, standard deviation; CI, confidence interval; IV, the inverse variance method; Random, the random effect model.

K.Y. Park et al. / Seminars in Arthritis and Rheumatism ■ (2016) ■■■-■■■

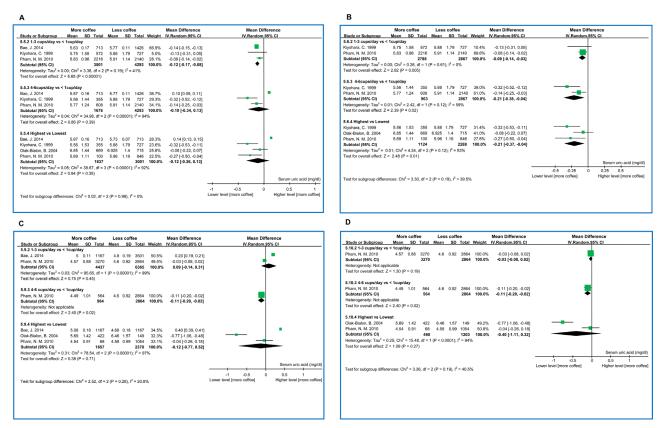


Fig. 3. Meta-analysis of the effect of coffee intake on serum uric acid according to gender. (A) Meta-analysis of the effect of coffee intake on serum uric acid for men. (B) Sensitivity analysis by omitting one study [23] which increased heterogeneity for men. (C) Meta-analysis of the effect of coffee intake on serum uric acid for women. (D) Sensitivity analysis by omitting one study [23] which increased heterogeneity for women. SD, standard deviation; CI, confidence interval; IV, the inverse variance method; Random, the random effect model.

coffee beans, as well as instant coffee made commercially by drying prepared coffee. There are several brewing methods [32]. Sugar/sweeteners and milk/creamers are added as desired. Sugar/sweeteners are associated with higher serum UA [33] and higher risk of gout [34], whereas dairy is associated with lower serum UA [35] and lower risk of gout [36]. This will also serve to confound

the effect of coffee on serum UA. Coffee made by a combination of all of these factors is served in different sizes of cups. This diversity of coffee products was partly reflected in the overall high heterogeneity of this study. However, since few studies reported brewing method and size of cups, we could not perform subgroup analyses according to the type and exact volume of coffee. Second, our

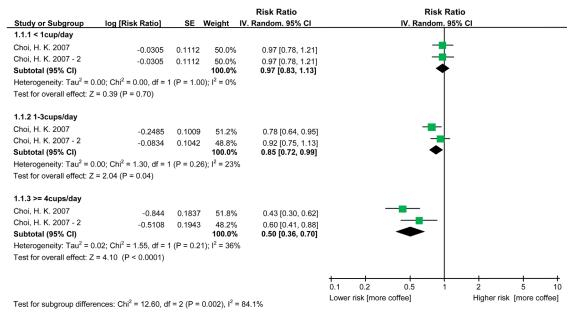


Fig. 4. Meta-analysis of the effect of coffee intake on risk of gout. Coffee intake of 1 cup/day or more showed significant reduction of the risk of gout for both gender, with negative correlation with the amount of daily coffee intake, where coffee intake ≥ 4 cups/day reduce multivariate RR to 0.50. SE, standard error; CI, confidence interval; IV, the inverse variance method; Random, the random effect model.

meta-analysis showed significant heterogeneity. Between-study heterogeneity is common in meta-analysis, and exploring the potential sources of between-study heterogeneity is an essential component of meta-analysis. Characteristics such as study design, publication year, and country of study could be sources of heterogeneity. Sensitivity analyses by the type of study design and risk of bias were conducted to explore the source of heterogeneity. Crosssectional studies seemed better in terms of reflecting serum UA related to current coffee intake than cohort studies. Even with elimination of an article with high risk of bias, the between-study heterogeneity persisted in subgroups, suggesting the presence of other unknown confounding factors. The high heterogeneity of the report of Bae et al. [23] in the current study might be related to the fact that the coffee consumption pattern in Korea is quite different from other counties. In Korea, an instant coffee mix that contains non-dairy creamer and/or sugar still accounts for a significant portion of coffee consumption [37], although the consumption of brewed coffee is increasing. Instant coffee is reported to be associated with a higher risk of metabolic syndrome in Korean adults [38], and high consumption of instant coffee in Korea might show a heterogeneous effect on serum UA compared with brewed coffee. Third, since meta-analyses are influenced by publication bias, we tried to decrease bias by searching four major databases with no language restriction. Lastly, the different methods of determining the serum UA level along with varying test sensitivities among different studies may influence the statistical power.

Accordingly, the overall results must be interpreted with an appropriate degree of caution. Moreover, although coffee has lowering effect on serum UA, the effect is smaller when compared to that of UA-lowering drugs such as allopurinol. Every increment of 100 mg of allopurinol was reported to decrease serum UA by approximately 1 mg/dl [39], while the largest lowering effect of coffee on serum UA was -0.36 mg/dl [95% CI: -0.55 to -1.17] with the highest amount of coffee intake shown in Fig. 2D. Therefore, there is no doubt that the use of UA-lowering drugs is a primary approach in the management of gout. Further prospective studies should be conducted to verify the effect of coffee on serum UA. Even with these limitations, moderate coffee intake might be advocated for primary prevention of hyperuricemia or gout in both genders.

Appendix A. Supplementary information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.semarthrit.2016. 01.003.

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