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REVIEW ARTICLE

Metabolic diagnoses of recurrent stone formers: temporal, geographic and gender differences

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ABSTRACT

Background: Metabolic factors underlying the recent increase in stone prevalence over the past decades are not well understood. Herein, we evaluate temporal, geographic and gender-specific trends in metabolic risk factors in recurrent kidney stone formers.

Patients and Methods: A systematic literature review of metabolic risk factors for stone formation was conducted, inclusive of the last four decades. Studies with inadequate 24 h urine metabolic data, pediatric or those with less than 50 patients were excluded. The primary outcome was prevalence of each metabolic risk factor, compared between studies published prior to the year 2000 vs those following. Geographic and gender differences were secondary outcomes.

Results: Twenty-eight articles met inclusion criteria, of which 10 ($n = 1578$) were published prior to the year 2000 and 18 ($n = 8747$) were published thereafter. Comparing these groups, an increase in hyperoxaluria (29% vs 33%; $p = 0.002$), hypercalciuria (35 vs 36%; $p = 0.446$), hyperuricosuria (17% vs 22%; $p < 0.0001$), low urine volume (28 vs 38%; $p < 0.0001$) and hypocitraturia (23% vs 44%; $p < 0.0001$) was observed. The prevalence of hyperoxaluria, hypercalciuria, hyperuricosuria and hypocitraturia were significantly higher in males. There were also significant geographical differences, with higher prevalence of hyperoxaluria and hypocitraturia in non-Western countries and higher prevalence of hypercalciuria in Western countries. Prevalence of hyperoxaluria is increasing in the US.

Conclusion: Prevalence of metabolic risk factors for nephrolithiasis significantly increased in recent years. These findings are hypothesis-generating and may provide valuable insight into the epidemiology, prevention and management of recurrent stone disease. Dietary modifications and innovative medical therapies are needed to decrease metabolic risk factors underlying nephrolithiasis.

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Introduction

Nephrolithiasis, or kidney stone disease, is highly prevalent worldwide, with rates ranging from 7–13% in North America, 5–9% in Europe and 1–5% in Asia [1,2]. Commonly a non-isolated event, those with kidney stone disease have a 35–50% probability of forming recurrent stones [3,4], thus presenting a substantial financial burden to healthcare systems and detriment to patient quality-of-life by way of their diagnosis, treatment and management [5,6].

Investigations of risk factors contributing to stone formation and recurrence have gained urgency in contemporary research, as recent studies have introduced a globally increasing prevalence of kidney stone disease in the last few decades [2,7,8]. As reported by Scales et al. [7] in 2007, the incidence of renal stones increased 14% in the general population and 21% in females from 1997 to 2002. Following, the National Health and Nutrition Examination Survey indicated a concomitant increase in kidney stone prevalence of up to 4% and 10% in males and females from 2012 to 2014, respectively [8]. While these rates are well-documented, however, the root cause of their increase is not well-established, as incidence and recurrence of kidney stones varies widely by geographic location, age and gender [2,7–10].

Hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia and low urine volume are common metabolic risk factors contributing to stone prevalence and recurrence [9,10]. The trends in prevalence of metabolic factors underlying the recent increase in stone prevalence over the past decades are not well understood. Herein, we evaluate chronological, geographic and gender-specific trends in these metabolic risk factors to identify their impact and guide future directions in dietary modifications or directed pharmacotherapy in effort to decrease stone recurrence.

Materials and methods

Literature review and identification of relevant studies

A literature review of peer-reviewed articles was conducted via PubMed. Search terms, and combinations thereof, included: [hyperoxaluria], [hypercalciuria], [hyperuricosuria],

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[hypocitraturia], [low urine volume], [24 h urine test], [kidney stone disease], [urolithiasis] and [nephrolithiasis]. All studies relating to metabolic risk factors in recurrent kidney stone disease published from the years 1980 through 2020 were included in initial screening. This included any and all studies reporting prevalence of hyperoxaluria, hypercalciuria, hyperuricosuria, low urine volume and/or hypocitraturia, based on 24 h urine measurements.

Exclusion criteria were defined a priori, such that studies were omitted from final analysis if they did not have adequate 24 h urine data, had less than 50 patients, involved pediatric patients, or only included healthy patients with no prior history of kidney stone disease. Review articles, meta-analyses, and commentaries were also excluded, but the citation list of each of these papers was searched to ensure the inclusion of all relevant studies. This literature review was performed systematically and independently by authors ST and SD, of which results were pooled accordingly.

Selection of studies

All articles identified during the initial process were reviewed by the study team, utilizing the following stepwise methodology: first, the titles and abstracts were screened such that non-relevant studies were excluded, and second, full manuscripts were reviewed and those with incomplete data on metabolic risk factors, lacking 24 h urine measurements, had a pediatric study population, and/or limited sample size were excluded. Studies evaluating urine parameters for patients on directed pharmacotherapy were also excluded.

Statistical analysis

All statistical analyses were conducted in SPSS v25 © IBM Corporation. Studies identified for inclusion in final analysis were divided into two study groups, based on when the majority of the study population was enrolled: December 1980 to August 2000 vs January 2001 to January 2018.

All trends were evaluated along three axes. Primary, secondary and tertiary outcome measures were the prevalence of metabolic risk factors in recurrent stone formers overall, across geographical locations (i.e. the US vs non-US studies; as well as Western vs non-Western studies), and by gender (i.e. male vs female). Trends were assessed utilizing a two-tailed, unpaired Student T-tests. A p-value less than 0.05 was considered statistically significant and a 95% confidence interval was reported for all differences.

Results

Study selection

Study selection results are depicted in Figure 1. Two hundred and seventy-nine records were initially identified through the PubMed database search, of which 25 were duplicates. After review of the titles and abstracts, 201 were excluded and the 53 remaining were screened for all relevant data, yielding a total of 28 articles and 10,325 patients [9,11–37]. Per the date ranges for patient enrollment, 10 studies ($n = 1578$ patients) were characterized to be prior to the year 2000 and 18 studies ($n = 8747$ patients) were characterized to be following the years after. Table 1 summarizes patient characteristics and rates of metabolic diagnoses reported in all included studies, stratified by the year of patient enrollment.

Chronologic trends

Table 2 depicts the prevalence of metabolic risk factors in studies prior to and following the year 2000. Studies with patients after 2000 reported higher rates of hyperoxaluria (+4%, 95% CI = 2–6%, $p = 0.002$), hyperuricosuria (+5%, 95% CI = 3–7%, $p < 0.0001$), low urine volume (+10%, 95% CI = 8–12%, $p < 0.0001$) and hypocitraturia (+21%, 95% CI = 19–23%, $p < 0.0001$). Hypercalciuria was not significantly different between the two groups ($p = 0.446$).

Gender-related differences

Gender-related differences in metabolic risk factors are displayed in Table 3. Men were observed to have significantly higher rates of hyperoxaluria (+16%, 95% CI = 12–20%, $p < 0.0001$), hypercalciuria (+18%, 95% CI = 16–22%, $p < 0.0001$), hyperuricosuria (+22%, 95% CI = 19–26%, $p < 0.0001$) and hypocitraturia (+16%, 95% CI = 13–20%, $p < 0.0001$).

Geographic trends

Table 4 illustrates geographic trends of metabolic risk factors in Western countries vs non-Western countries. Studies conducted in Western countries found significantly higher prevalence of only hypercalciuria (+12%, 95% CI = 10–15%, $p < 0.0001$) and lower prevalence of hyperoxaluria (−24%, 95% CI = 21–25%, $p < 0.0001$), hypocitraturia (−37%, 95% CI = 35–40%, $p < 0.0001$) and low urine volume (−31%, 95% CI = 28–34%, $p < 0.0001$) when compared to non-Western countries.

Studies conducted inside of the US reported a higher prevalence of hyperoxaluria (+8%, 95% CI = 6–10%, $p < 0.0001$), low urine volume (+11%, 95% CI = 8–14%, $p < 0.0001$) and lower prevalence of hypocitraturia (−13%, 95% CI = 11–15%, $p < 0.0001$) and hypercalciuria (−3%, 95% CI = 0–6%, $p = 0.029$) when compared to all other studies.

Discussion

Because kidney stone formation and recurrence are dependent on the physicochemical properties of urine, changes in urine composition can contribute to an increased incidence of nephrolithiasis [2,10,38,39]. Based on our systematic review, rates of hypocitraturia, hyperoxaluria, hyperuricosuria and low urine volume have increased from 4 to 21% following the year 2000, coinciding with previously-reported increasing prevalence of nephrolithiasis.

There are several mechanisms by which these findings suggest metabolic risk factors to be important contributors

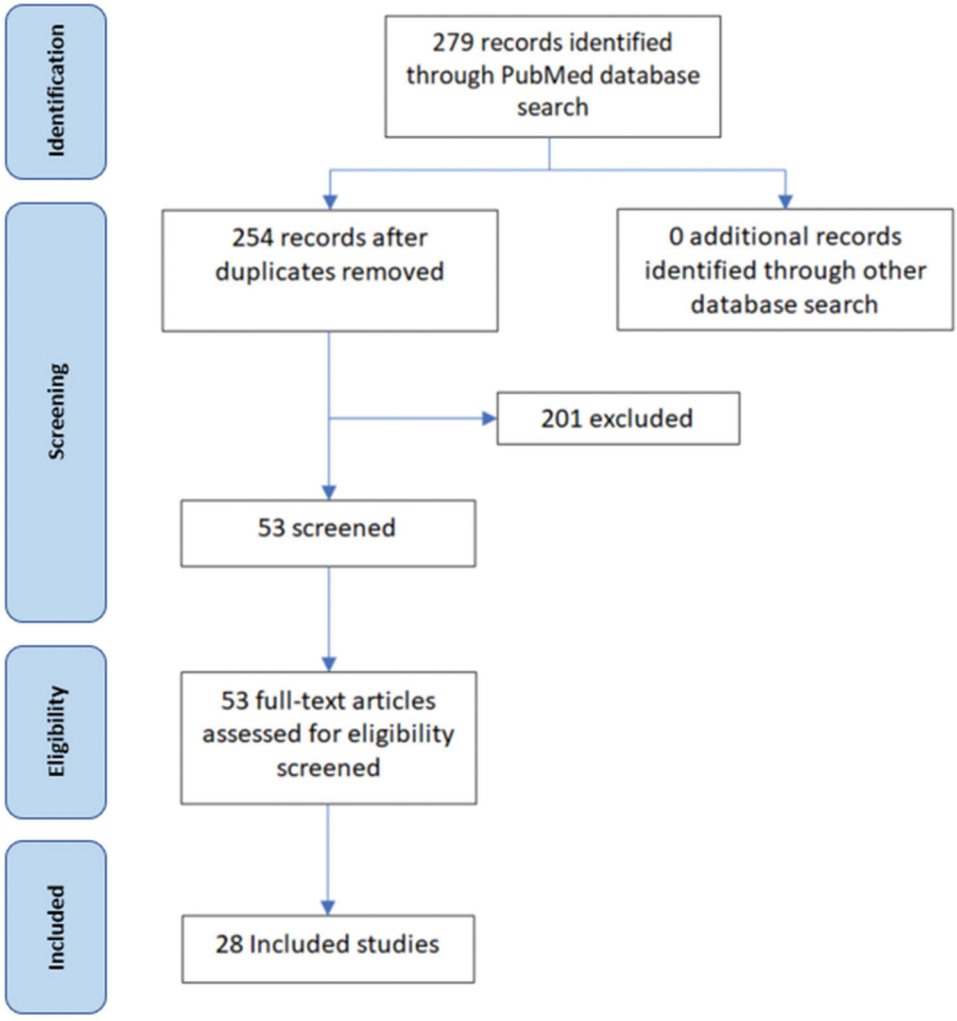


Figure 1. Summary of study selection methods.

to rising rates of recurrent stone formation. First, nephrolithiasis is well-known to be highly sensitive to metabolic disorders such as diabetes mellitus, overweight/obesity, and metabolic syndromes [40–43]. A study by Taylor et al. [41] on body size, weight and weight gain reported 1.4–1.9-times increased risk of nephrolithiasis when comparing patients weighing more vs less than 220 lbs and those who gained 35+ lbs since age 21 vs those maintaining body weight. Even further, work by Redina et al. [42] shows kidney stones to disproportionately affect patients with comorbid diabetes mellitus or overweight/obesity. These findings are further supported by the growing obesity epidemic in the US, coinciding with chronologic and geographic trends of increasing nephrolithiasis since 2000 and in the US [1,2,7,8].

Second, metabolic imbalances can also be explained by variations in dietary habits. As socioeconomic status improves, for example, people tend to 'upgrade' their diet by converting to a more Western-style diet high in salt and animal proteins, thus resulting in lower urine pH, increased urinary calcium and increased risk of uric stone formation [44–46]. Other contributing factors to higher prevalence of nephrolithiasis in Western countries may also include higher average temperatures, higher sunlight indexes and lower latitudes [47,48]. Furthermore, Maloney et al. [19] evaluated the impact of ethnic backgrounds on metabolic abnormalities, finding that all ethnic groups from the same geographic regions had similar metabolic profiles. The lack of variation among ethnic groups further supports findings of underlying geographic differences, such as diet [19].

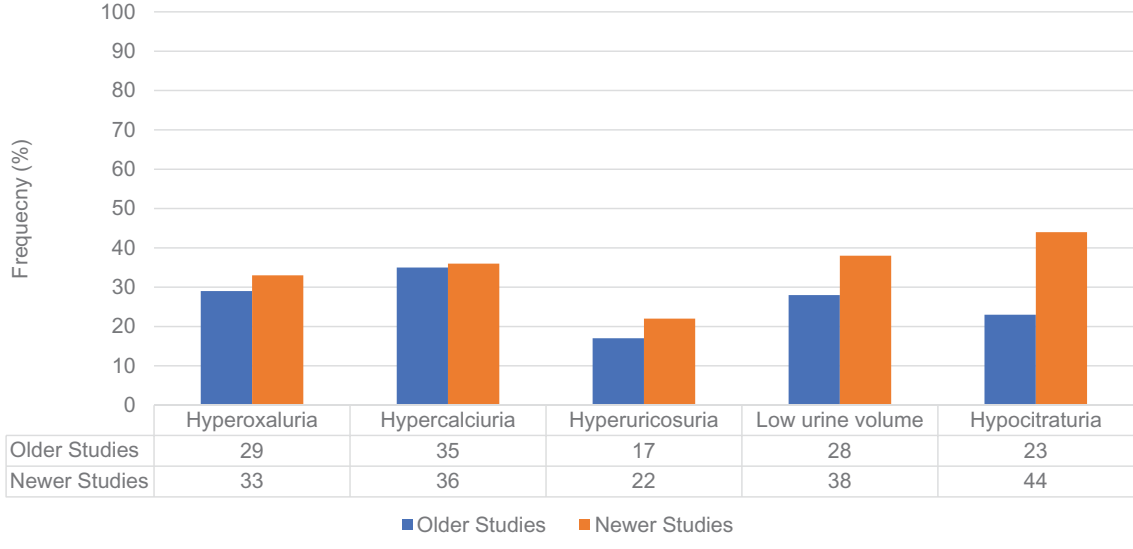
Last, metabolic risk factors may also offer an explanation for gender differences in nephrolithiasis. A study by Bazyar et al. [49] in 2019 found men to more commonly consume diets low in fruits and vegetables and high in animal protein, thus independently contributing to an increased risk of both calcium and uric stones. These results are consistent with the present study, as the prevalence of metabolic risk factors was found to be significantly higher in men and in alignment with increased nephrolithiasis [49]. Furthermore, as more women adopt low-carbohydrate and high-protein diets in contemporary times, the attendant increased risk of hypercalciuria and hypocitraturia with high intake of animal proteins may increase the risk of kidney stone formation and recurrence [50,51]. Not only do these changes in dietary patterns provide an explanation for an increased prevalence of metabolic imbalances, but these gender-specific trends are also consistent with an increasing female-to-male ratio in nephrolithiasis prevalence [7,8].

Table 1. Summary of study characteristics and rates of metabolic diagnoses in included studies, stratified by year of data collection.

Authors	Data collection year(s)	Cohort nationality	Mean age (years)	*n*	Hyperoxaluria (%)	Hypercalciuria (%)	Hyperuricosuria (%)	Hypocituria (%)	Low urine volume (%)
Studies prior to 2000									
Curhan et al. [12]	1976–1994	US	61	297	4	33	3	4	4
Jaeger et al. [15]	1982	Switzerland	NR	79	28	54	14	NR	NR
Baggio et al. [11]	1983	Italy	NR*	88	49	14	13	NR	NR
Curhan et al. [12]NPFS	1986–1994	US	59	341	14	25	9	2	4
Curhan et al. NHS II [12]	1989–1994	US	42	169	7	38	8	3	15
Laminiski et al. [16]	1991	South Africa	40	207	30	NR	36	32	NR
Hatch [13]	1992	US	NR*	115	30	24	9	35	72
Hess et al. [14]	1997	Switzerland	NR*	75	32	39	23	29	32
Yagisawa et al. [17]	1999	US	NR*	119	38	65	24	41	NR
Yagisawa et al. [18]	1999	Japan	NR*	88	58	22	33	35	39
Studies after 2000									
Ferraro et al. [24]	1995–2012	London	NR*	2861	8	38	18	23	6
Kumar et al. [30]	1999–2001	India	NR*	56	61	49	8	78	NR
Amaro et al. [21]	2000–2001	Brazil	NR*	158	24	74	20	37	NR
Stichantrakul et al. [37]	2000–2001	Thailand	49.5	79	1	15	7	70	10
Amaro et al. [22]	2000–2012	Brazil	NR*	735	NR	51	31	35	NR
Spivacow et al. [36]	2000–2013	Argentina	45	2156	3	46	13	11	NR
Kirac et al.	2003–2006	Turkey	NR*	108	77	38	21	16	43
Wu et al. [9]	2003–2012	China	NR*	507	31	26	19	94	46
Serra et al. [34]	2004	Portugal	47	87	40	24	33	23	20
Siener et al. [35]	2005	Germany	47.4	107	14	25	41	57	58
Eisner et al. [23]	2006–2010	US	46.6	240	33	43	45	23	NR
Ortiz-Alvarado et al. [32]	2007–2009	US	50.3	314	30	NR	NR	NR	NR
Hadian et al. [26]	2007–2010	Iran	NR*	232	40	24	15	25	NR
Otto et al. [33]	2007–2014	US	NR*	392	37	38	25	34	63
Abu-Ganem et al. [25]	2010–2015	Israel	44.1	260	24	41	17	60	60
Ahmad et al. [20]	2011–2012	Pakistan	38	200	65	44	14	41	NR
Kang et al. [28]	2011–2015	Korea	50.3	286	8	19	21	68	NR
Hussein et al.[27]	2013	Malaysia	NR*	96	61	15	20	57	NR

Table 2. Prevalence (in %) of metabolic risk factors in recurrent stone formers stratified by date of subject enrollment 1980–1999 vs 2000–2018.

	Prior to 2000 (Total = 1578) *n* (%)	Following 2000 (Total = 8747) *n* (%)	Diff.	95% CI Lower	95% CI Upper	*p*
Hyperoxaluria	458 (29)	2887 (33)	4%	2%	6%	0.002
Hypercalciuria	552 (35)	3149 (36)	1%	−2%	4%	0.446
Hyperuricosuria	268 (17)	1924 (22)	5%	3%	7%	<0.0001
Low urine volume	442 (28)	3324 (38)	10%	8%	12%	<0.0001
Hypocitraturia	363 (23)	3849 (44)	21%	19%	23%	<0.0001



We caution the conclusion that the increased prevalence of nephrolithiasis is explained solely by increases in these metabolic risk factors alone. We recognize other possible explanations for increased prevalence of kidney stones and their recurrence, among of which include increased availability of radiographic imaging, increased accessibility of healthcare and global warming. However, the findings of the current study are complementary and may provide at least a partial

Table 3. Frequencies (in %) of metabolic risk factors in recurrent stone formers stratified by gender.

	Total	Males *n* (%)	Females *n* (%)	Diff.	95% CI Lower	95% CI Upper	*p*
Hyperoxaluria	1002	647 (35)	355 (19)	16%	12%	20%	<0.0001
Hypercalciuria	2011	1244 (48)	767 (30)	18%	16%	22%	<0.0001
Hyperuricosuria	1265	865 (42)	400 (20)	22%	19%	26%	<0.0001
Low Urine Volume	826	516 (59)	310 (35)	24%	19%	29%	<0.0001
Hypocitraturia	1551	961 (42)	590 (26)	16%	13%	20%	<0.0001

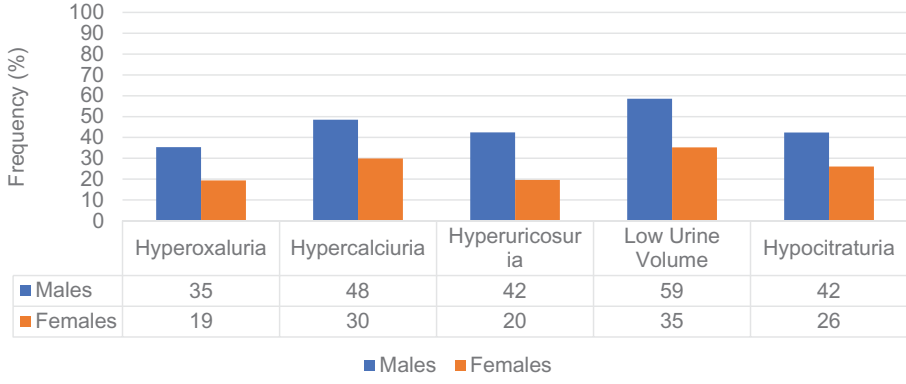


Table 4. Frequencies (in %) of metabolic abnormalities in recurrent stone formers stratified by location of study: Western vs non-Western countries.

	Western Countries Total	Western Countries *n* (%)	Non-Western Countries Total	Non-Western Countries *n* (%)	Diff.	95% CI Lower	95% CI Upper	*p*
Hyperoxaluria	7598	940 (12)	2119	755 (36)	−24%	21%	25%	<0.0001
Hypercalciuria	8019	3307 (41)	1912	551 (29)	12%	10%	15%	<0.0001
Hyperuricosuria	8019	1465 (18)	2119	419 (20)	−2%	0%	3%	0.115
Low Urine Volume	4444	656 (15)	1042	478 (46)	−31%	28%	34%	<0.0001
Hypocitraturia	7852	1615 (21)	2119	1235 (58)	−37%	35%	40%	<0.0001

explanation for the rise in kidney stone formation and recurrence, as well as offering a potential avenue for their prevention and management. Optimization of 24 h urine tests and neutralization of metabolic imbalances via dietary modifications, supplementation and/or increased fluid consumption, for instance, are easily accessible and have multi-pronged benefits outside of stone formation – all while having the added benefit of reducing the risk of nephrolithiasis [52–54].

In this regard, the current results should be considered within the context of several limitations. First, the articles included in our review were heterogeneous and we were thus unable to account for variations in definitions for each of the metabolic risk factors, patient cohorts and demographics. In this regard, any report of body mass index, body weight differences and other comorbidities and their impact on recurrent stone formation varied significantly between studies and, due to this lack of uniform reporting in the individual studies, we are unable to control for these differences in the present study. We also highlight that a temporal change in metabolic factor awareness may have confounded these results and differences in documentation were not considered as a contributor to the trends described. As raw data was not available for the included studies, we were unable to quantitatively control for these differences. Finally, the geographic variation in increased awareness for these factors may have also led to variations in different metabolic abnormalities and the efficiency of their treatment.

As the present study only draws on patient populations from previously published studies, generalizability of these trends may be limited to patients seeking care at tertiary care centers, academic institutions and specialty care centers. As future studies on metabolic risk factors impacting stone formation are pursued, we recommend the inclusion of a control group of non-stone formers pin metabolic assessment to increase validity of the results in the same geographical set-up.

Conclusion

The prevalence of metabolic risk factors contributing to nephrolithiasis has significantly increased in recent years. These increases remain more prevalent in males, particularly for risk factors of hyperoxaluria and hyperuricosuria. When compared to non-Western countries, Western countries show higher rates of hypercalciuria. These findings are hypothesis-generated as they closely correlate with previously reported chronologic, geographic and gender-based trends in patients with kidney stone disease. Further studies exploring the relationship between metabolic risk factors and urinary stone disease may provide added insight into the management and prevention of recurrent stone patients.

Disclosure statement

The authors have no conflicts of interest to disclose.

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