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SYSTEMATIC REVIEWS AND META-ANALYSES

Epidemiological and biological associations between cardiovascular disease and kidney stone formation: A systematic review and meta-analysis

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Abstract *Aims:* Previous studies find kidney stone formers (KSF) are at greater risk of developing cardiovascular disease (CVD). The underlying mechanisms are poorly understood, and many clinicians are unaware of this connection. We will:

1 Provide an up-to-date review of epidemiological data.
2 Clearly define CVD outcomes to understand conditions associated with kidney stone formation (KSF).
3 Review hypothesised biological pathways to further understand the relationship.

Data synthesis: Our systematic review is registered with PROSPERO (ID CRD42021251477). We searched epidemiological and biological data. The epidemiological search generated 669 papers, narrowed down to 15. There were 4,259,869 participants (230,720 KSFs). KSF was associated with 25% higher risk of coronary artery disease (CAD) (95% confidence interval (CI): 15, 35%), 17% higher risk of stroke/transient ischemic attacks (TIA) (CI:10, 25%) and 39% higher risk of arterial disease (AD) (CI: 17 65%). Significant heterogeneity was found. Female-identifying KSFs had a higher risk of stroke (ratio = 1.10) and CAD (1.20). The biological search generated 125 papers, narrowed down to 14. Potential underlying mechanisms were extracted and discussed, including intimal/medial vascular calcification, oxidative stress via osteopontin (OPN), cholesterol-induced pathology, and endothelial dysfunction.
Conclusions: There is a significant association between KSF and CVD, supporting the consideration of KSF as a systemic, calcium-mediated disease. Clinicians will benefit from being aware of this connection.

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1. Introduction

There is significant variation in the prevalence of kidney stones worldwide, ranging from 1 to 5% in Asia to 7–15% in North America [1]. The prevalence of stones is likely to increase in the coming decades, with changes in lifestyle and dietary habits [2]. Kidney stones are increasingly being viewed as a systemic condition. One factor that supports this is the link between kidney stones and cardiovascular disease (CVD), distinct from the well-established connection between chronic kidney disease (CKD) and CVD [3]. Studies have found higher risk of myocardial infarction [4], coronary heart disease [5], vascular calcification [6] and stroke [7] in KSF. Many practising clinicians might be unaware of this connection.

Previous systematic reviews and meta-analyses have been performed on this topic [8–11], but they are limited by their size, inadequate categorisation of cardiovascular outcomes and lack of exploration of biological mechanisms underlying the connection [12,13]. Some reviews also did not include sex-based subgroup analyses, despite previous papers suggesting the risk of CVD could be higher in female identifying kidney stone formers (KSF) [5].

Several studies have proposed mechanisms linking the pathogenesis of kidney stones and vascular calcification (a known risk factor for CVD). Including these mechanisms in a systematic review will support the established epidemiological association and will help identify pathways that could be targeted therapeutically.

Our study aims to:

i. Provide an up-to-date epidemiological review of the association between KSF and CVD
ii. Clearly define cardiovascular outcomes to understand the types of CVD that are most strongly associated with KSF, analysing coronary artery disease (CAD), strokes/transient ischemic attacks (TIAs) and arterial disease (AD) (an endpoint that has been under-reported in previous reviews)
iii. Review the hypotheses and evidence on biological mechanisms linking KSF and CVD

2. Materials and methods

The PRISMA-S criteria for reporting systematic reviews were applied [14].

2.1. Search strategy

LM performed the initial epidemiological search in MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials on 6 April 2021. AM performed the initial biological search in MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials and Web of Science on 9 April 2021. The search was repeated on 18 June 2023 to identify more recent literature. See *Supporting Information 1* for details of the search methodology used.

2.2. Inclusion criteria

We applied the following inclusion criteria to the epidemiological papers: cohort, case-control or cross-sectional study design (for the AD outcome); assess selected cardiovascular outcomes in KSFs; reference population who were not KSFs; present relative risks with 95% confidence intervals.

We applied the following inclusion criteria to the biological papers: assess a biochemical pathway/pathophysiological mechanism; address both CVD and KSF.

2.3. Data extraction

See Supporting Information (Methods) for a detailed breakdown of the data extracted from each paper. Both reviewers independently screened and excluded studies using the eligibility criteria.

2.4. Quality assessment

The quality of the epidemiological studies was assessed using the Newcastle-Ottawa scale [15]. This assigns an epidemiological study a score out of 10, assessing the selection, comparability, and outcome. Studies that receive a *Bad Quality* score would not be included. Studies that received a *Fair Quality* score would be included but removed in sensitivity analyses. Publication bias was assessed through inspection of funnel plots. See *Supporting Information (Methods)* for more detail on these methods.

2.5. Statistical analysis

See *Supporting Information (Methods)* for a breakdown of the statistical analysis performed. Separate analyses were performed for the three categories of cardiovascular outcomes. When data was available, subgroup analyses on biological sex were performed. In the CAD and stroke/TIA categories, cross-sectional studies were excluded. In the AD analysis, cross-sectional studies were included, as literature on this topic was mostly non-longitudinal. The biological mechanisms underlying the connection between kidney stones and cardiovascular disease identified from the biological search were analysed as a narrative synthesis.

3. Results

3.1. Epidemiological study

3.1.1. Search

Our initial search generated 669 papers, and one further study was identified. There were 449 papers after duplicate removal. These papers underwent title/abstract screening. Twenty-six papers then underwent full-text review and data-extraction. Thirteen papers were included after full text review. Two further eligible papers

were identified during the repeated search (Fig. 1) (see Fig. 2).

These fifteen papers were made up of 17 cohorts, with 4,259,869 participants and 230,720 KSF. Seven papers assessed CAD, eight assessed stroke/TIA, and four assessed AD. All studies were *Good Quality* using the Newcastle Ottawa scale. See *Supporting Information (Results)* for the characteristics of included studies.

3.1.2. Kidney stones and coronary artery disease

Seven papers assessed CAD. The most common outcome in this category was acute myocardial infarction. The number of individuals included were 3,767,648 (114,809 KSFs). Our analysis revealed significantly higher risk of CAD in KSF relative to non-KSF (pooled hazard ratio (HR) = 1.25 (95% CI: 1.15, 1.35)). This analysis had significant heterogeneity (I^2: 68% ($p < 0.0001$)). This is likely due to the large variability in cohort size and characteristics. See *Supporting Information (Results)* for the funnel plot.

Sensitivity analysis was performed by removing Alexander et al. due to a very large sample size (n = 3,195,462) [7]. The pooled HR remained significant (HR = 1.28; 95% CI: 1.15, 1.43). Studies that included sex-based analyses were included in a sub-group analysis. The relationship between KSF and CAD remained significant for men and women, but the association was 1.20 times greater for women (pooled HR women = 1.43 [95% CI: 1.25, 1.63]; pooled HR men = 1.19 [95% CI: 1.10, 1.29]).

3.1.3. Kidney stones and strokes/TIA

Eight papers assessed strokes/TIA. When available, separate HRs for haemorrhagic and ischemic stroke were included. The number of individuals included were 4,057,942 (204,043 KSFs). Our analysis revealed a statistically significantly higher risk of stroke/TIA in KSFs relative to non-KSFs (pooled HR = 1.17 (95% CI: 1.10, 1.25)). This analysis had significant heterogeneity (I^2: 86% ($p < 0.00001$). See *Supporting Information (Results)* for the funnel plot.

Alexander et al. was removed in sensitivity analysis, and the results remained significant (pooled HR = 1.18 [95% CI: 1.10, 1.26]) [7]. Lin et al. did not provide adjusted HRs and sensitivity analysis was performed removing this study (pooled HR = 1.22 (95% CI: 1.14, 1.30)) [16]. Studies that included sex-based analyses were included in a sub-group analysis. The relationship between KSF and strokes/TIA remained significant for men and women, but the association was 1.10 times greater for women (pooled HR women = 1.20 [95% CI: 1.14, 1.27]; pooled HR men = 1.09 [95% CI: 1.04, 1.14]).

3.1.4. Kidney stones and arterial disease

Four papers assessed AD. Outcomes included atherosclerosis determined by carotid intima-media thickness, carotid score, arterial stiffness measured by brachial-ankle pulse-wave velocity and the use of pooled cohort equations to predict 10-year risk for atherosclerotic CVD. The number of individuals included were 17,520 (1456 KSFs). Our analysis revealed statistically significantly higher odds of AD in KSF relative to non-stone formers (pooled odds ratio (OR) = 1.39 (95% CI: 1.17, 1.65)).

Due to inconsistent reporting, a subgroup analysis on biological sex was not performed. However, biological sex was addressed by some of the papers. Glover et al. found

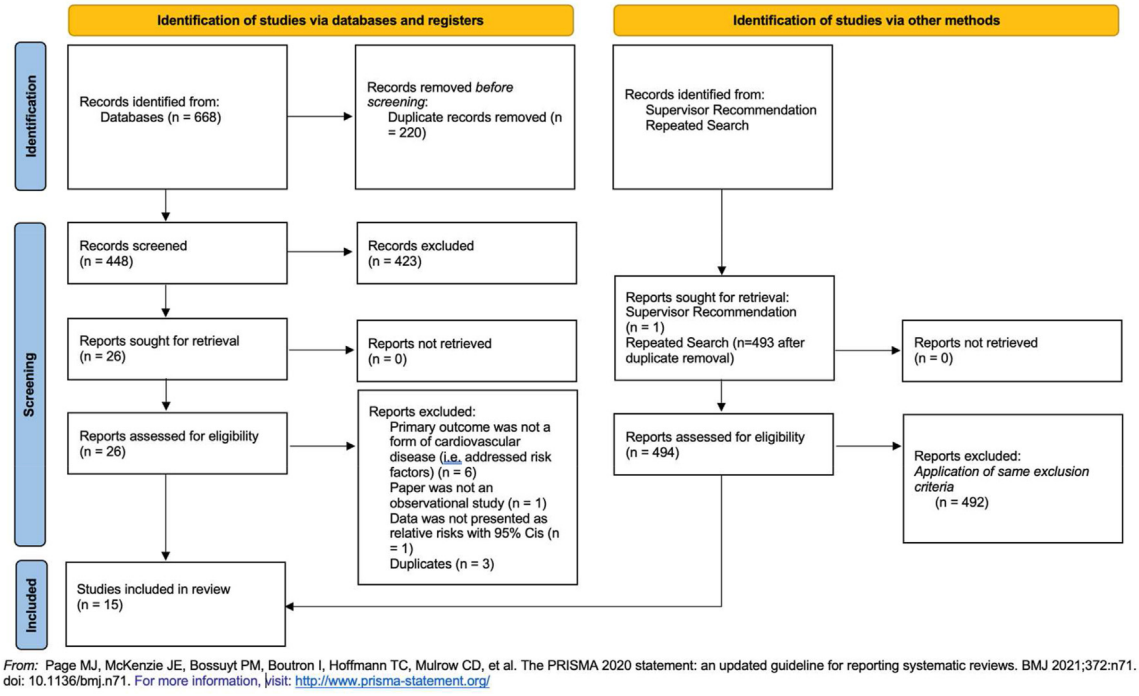

Figure 1 PRISMA Flowchart for the epidemiological search.

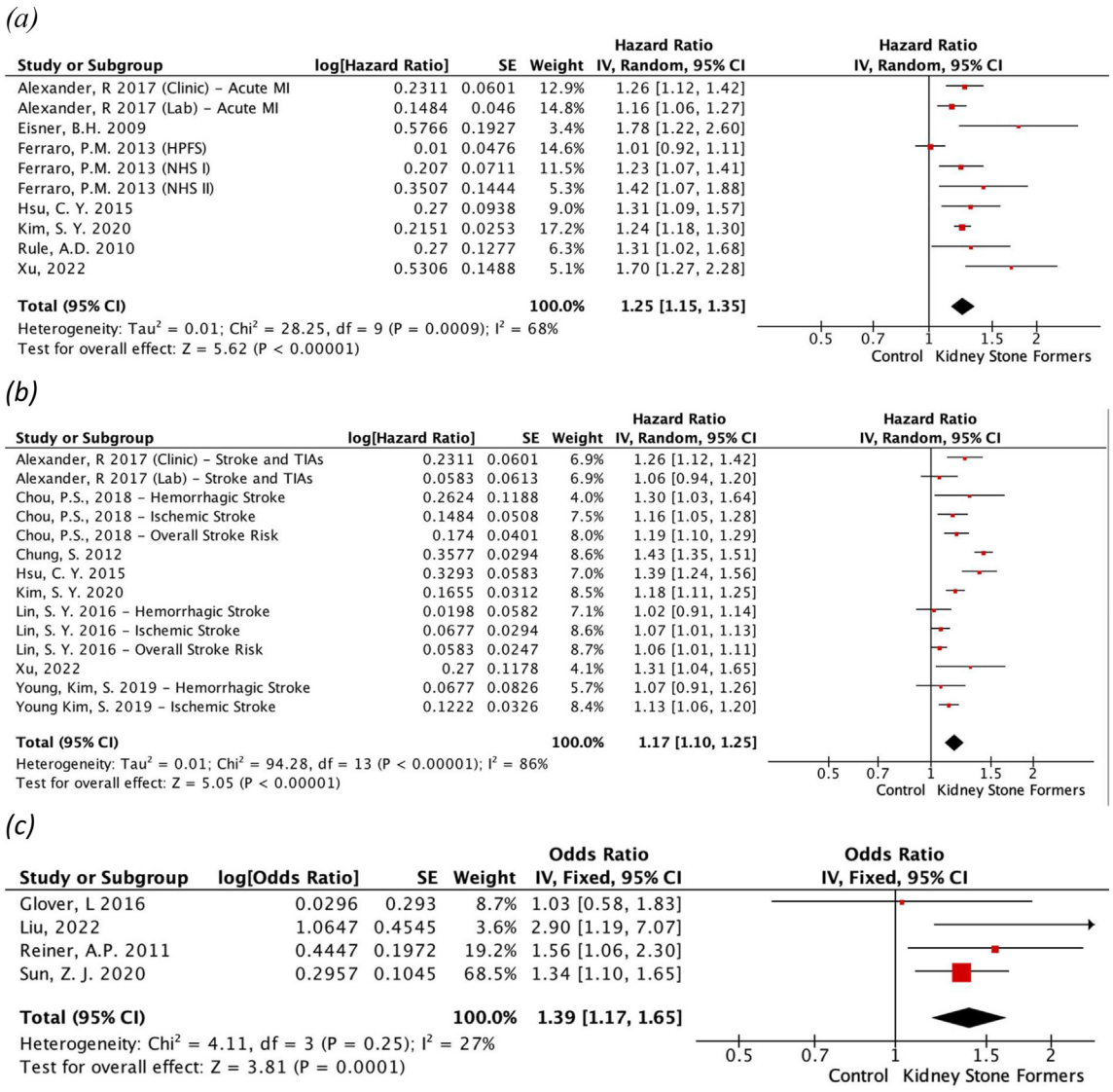

Figure 2 (a) Kidney stone formation and coronary artery disease – forest plot, (b) Kidney stone formation and strokes/TIA - forest plot, (c) Kidney Stone Formation and arterial disease – forest plot.

no significant sex interaction between kidney stones and atherosclerotic CVD [17] but Sun et al. found that the risk of arterial stiffness was 1.21 greater for women [12].

3.2. Narrative synthesis of hypothesised biological pathways

3.2.1. Search

The initial search generated 125 papers, reduced to 78 after duplicate removal. These papers then underwent title/abstract screening. 40 papers underwent full-text analysis, and a further 26 papers were excluded. The PRISMA flowchart in *Supporting Information (Results)* diagrammatically represents the literature screening process.

3.2.2. Circulating biomarkers and mediators of calcification

With 80% of kidney stones consisting of calcium oxalate, calcium phosphate or both, studies have shown that these calcium-containing stones are most clearly linked with the development of atherosclerotic cardiovascular disease [18]. Of the remaining types of stones, approximately 10% are thought to consist of uric acid with an increased association with metabolic syndrome [19]. However, the results of this review indicated that the pathophysiological mechanisms behind kidney stone formation and concurrent atherosclerotic CVD might be more aptly attributed to pathways that affect calcium balance in renal tubules and vascular tissue.

Several circulating biomarkers and calcification mediators were identified, but two were considered important in the calcification process based on experimental evidence from in-vitro and in-vivo studies: OPN and fetuin-A.

OPN is a potent inhibitor of high-phosphate load-induced nephrocalcinosis and vascular calcification [20]. It is also involved in inhibiting formation, growth and accumulation of calcium oxalate (CaOx) crystals while having an anti-lithogenic effect [21]. OPN binds to

hydroxyapatite and becomes part of a mineralised matrix at calcification sites as seen in atherosclerotic plaques [22]. In vascular tissue, this process often includes inflammatory mechanisms involving macrophage activation, leading to calcification [21].

Fetuin-A inhibits the formation and expansion of hydroxyapatite crystals. It binds to calcium and phosphate to form calciprotein particles that transport calcium precipitates to osseous tissue or the reticulohistiocytosis system [22]. Dysregulation of this process in the kidneys could lead to ectopic calcification and Randall's plaque formation with calciprotein particles as precursors. In vascular smooth muscle cells (VSMCs), fetuin-A inhibits the formation of matrix vesicles that lead to intracellular calcification.

3.2.3. Overview of mechanisms of ectopic calcification

We determined 4 mechanisms that led to ectopic/extra-osseous calcification seen in vascular tissue calcification and KSF.

i. Intimal and medial vascular calcification mechanisms
ii. Mechanisms of oxidative stress through the action of OPN
iii. Cholesterol-induced atherosclerosis and nephrolithiasis
iv. Mechanistic links between endothelial dysfunction and urolithiasis

3.2.4. Intimal and medial vascular calcification

Medial vascular calcification is observed in arteriosclerosis; intimal vascular calcification is typically associated with atherosclerosis. There is a distinction between arteriosclerosis and atherosclerosis by their causative mechanisms, both of which are associated with vascular smooth muscle cell (VSMC) activity and differentiation into cells resembling osteoblasts/chondrocytes [22].

Intimal calcification is clearly associated with VSMC apoptosis, which could be mediated by oxidative stress. Apoptotic cells tend to be surrounded by calcium deposition sites. The apoptotic process is also linked to the expression of OPN, which is a mediator of KSF and oxidative stress [23]. This suggests a commonality between the pathways affecting KSF and intimal vascular calcification which contributes to atherosclerosis. Intimal vascular calcification mechanisms are also more closely associated with injury-inflammation responses.

Medial calcification mechanisms are also linked to the differentiation of VSMCs into osteogenic cells. However, in medial calcification, these cells form bone-like deposits in the tunica media rather than tunica intima [23]. The mechanism of medial calcification is also associated with the secretion of vesicles by VSMCs or epithelial cells near calcification sites. These same vesicles have been identified in early stages of KSF and are associated with Randall's plaques. Therefore, there is sufficient evidence of there being a common mechanism underlying CVD and KSF.

The three mechanisms described below could be connected to medial or intimal calcification, thereby linking KSF and either atherosclerosis or arteriosclerosis.

3.2.5. Mechanisms of oxidative stress and activity of OPN

Oxidative stress has been observed in both atherosclerosis (which involves intimal calcification) as well as in KSF [24]. It is mediated by the activity of OPN [20]. In the case of stone formation, OPN's increased expression exacerbates the problem as it facilitates the mechanism of KSF [24] (Fig. 3).

This apoptosis could contribute to mineralisation linked to the accumulation of calcium in apoptotic cells [22]. In atherosclerosis, the mechanism involving OPN is similar to that in kidney tubules. This can be deduced from analysis of atherosclerotic plaques with OPN expression near foam cells and macrophages [24], indicating that the inflammatory response in atherosclerosis and KSF could be key in deriving common mechanistic factors.

3.2.6. Cholesterol-induced atherosclerosis and nephrolithiasis

The role of cholesterol in the formation of atherosclerotic plaques has been extensively studied. However, there seems to be a link between increased cholesterol ingestion and the formation of kidney stones. In clinical settings, an association between enteric hyperoxaluria (caused by increased dietary intake, fat malabsorption and/or increased gastrointestinal oxalate permeability) and KSF has been established [25]. Animal studies show that an increase in dietary cholesterol is associated with increased OPN expression in renal tubular cells followed by stone formation. It has been hypothesised that excess cholesterol ingestion leads to the binding of intestinal bile acid to cholesterol [24], which frees oxalic acid (Fig. 4) which is absorbed in the intestine, leading to increased urinary oxalic acid (waste product of oxalate) secretion which contributes to stone forming conditions in renal tubules [24] (see Fig. 5).

3.2.7. Endothelial dysfunction and urolithiasis

One study [24] suggested a mechanism that causes endothelial dysfunction as well as urolithiasis.

Hyperoxaluria leads to the formation of CaOx crystals, which triggers oxidative stress (as detailed above). This affects endothelial cells' ability to maintain homeostasis which leads to both renal tubular cell apoptosis and atherosclerosis in relation to endothelial dysfunction [26].

An alternate theory [26] focuses on local vascular damage and KSF. A local incident on renal tissue causes vascular insults that leads to renal tubular cell ischaemia. This contributes to the formation of Randall's plaques and stone nidus which, through poorly understood cascades, leads to atherosclerosis. The injury-inflammation response is apparent in this mechanism, further suggesting the link between intimal vascular calcification seen in atherosclerosis and KSF.

4. Discussion

To the best of our knowledge, this is the largest systematic review on this topic, with 4,259,869 participants, including 230,720 KSF. Kidney stones were associated with a 25%

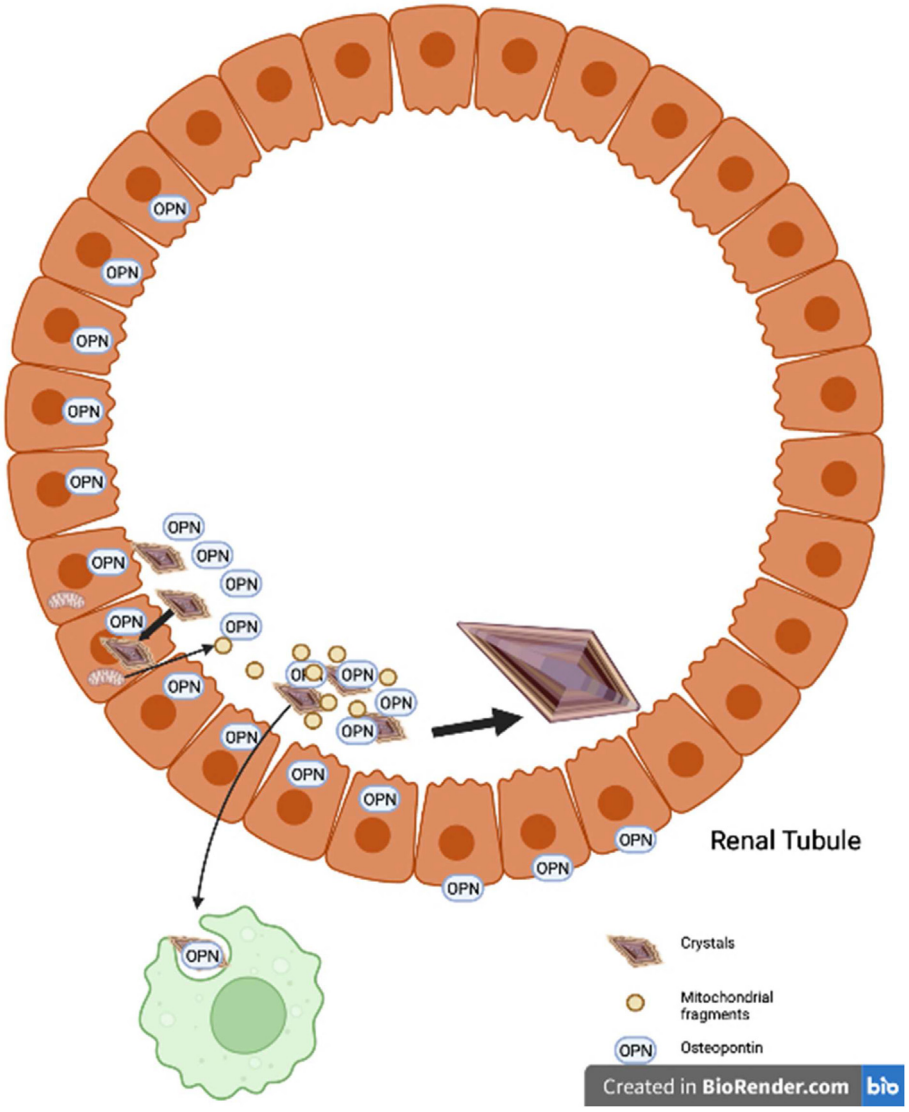

Figure 3 (Adapted) Urinary stone formation by action of OPN and macrophages [24]. Calcium oxalate (CaOx) crystals nucleate, grow and adhere to epithelial renal tubule cells (RTC) due to OPN activity. Crystals are ingested by RTC where they cause insufficient opening of mitochondrial permeability transition pores (mPTP). Subsequent mitochondrial collapse leads to oxidative stress which triggers apoptosis and further OPN expression. Macrophages are activated due to inflammatory response (also seen in intimal vascular calcification/atherosclerosis) for phagocytosis of CaOx crystals. CaOx crystal build-up cannot be phagocytosed, leading to aggregation with OPN and epithelial debris. Aggregates are secreted into renal tubular lumen, forming stone nuclei that develop into kidney stone.

higher risk of developing CAD, a 17% higher risk of developing strokes/TIA, and 39% higher risk of having AD, an association not noted in previous reviews. These are adjusted estimates, indicating that the relationship between KSF and CVD remains even when the influence of potential confounders is removed, emphasising the systemic nature of kidney stones. This paper supports the findings of previous epidemiological studies that found KSF were at increased risk of acute coronary syndrome (myocardial infarction) [4], both ischemic and haemorrhagic stroke [5] and increased arterial stiffness [6]. Our review also clearly defined the cardiovascular outcomes of KSF aiming to categorise specific cardiovascular events. We also coupled a review of biological mechanisms to gain a greater understanding of the relationship, something that previous systematic reviews have not done.

There are three possible explanations underlying this connection; (i) CVD mechanisms lead to stone formation, (ii) stone forming mechanisms lead to CVD or, (iii) common risk factors that trigger mechanisms leading to both diseases.

Most of the mechanisms found in this study linked kidney stone formation to intimal vascular calcification seen in atherosclerotic plaques. The main similarities between these two distinct conditions included common calcification mediators such as OPN [24], the induction of oxidative stress [24,26] and the injury-inflammation response involving macrophages [26]. These mechanisms also included the formation of stone niduses through mechanisms that involved Randall's plaques [26]. A recent review found a strong correlation between endothelial dysfunction, urolithiasis and CVD, suggesting that it may be a modifiable

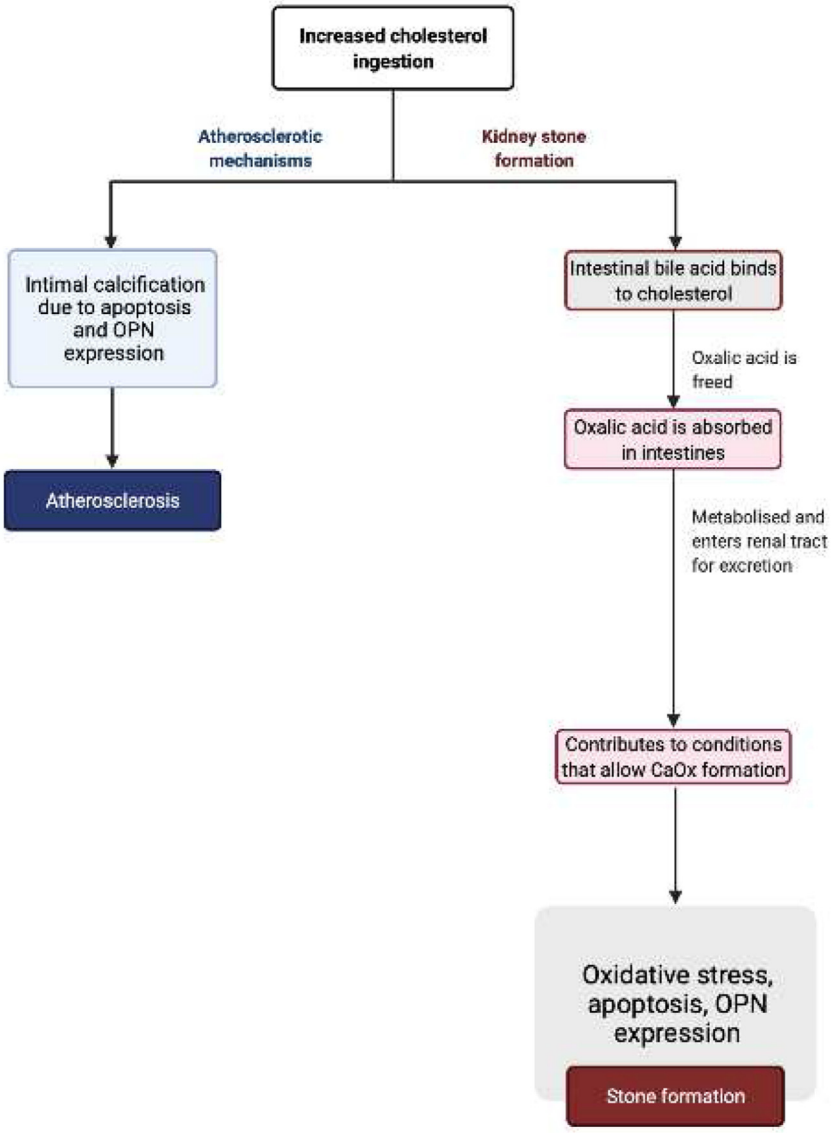

Figure 4 Cholesterol intake and stone formation.

intermediate between the two conditions [27]. Studies that only described the effect of OPN in vitro or in animal models [20,22,29] noted that it was OPN deficiencies that led to increased vascular and renal tubular calcification. However, these same studies, along with those that described mechanisms [23,25] also pointed out that there was significant OPN expression in vascular calcified deposits and kidney stones. This could indicate that both OPN dysregulation due to injury/inflammation and OPN deficiency could lead to increased ectopic calcification.

We have attempted to define the distinction between the mechanisms in intimal and medial vascular calcification. However, it is possible that both occur simultaneously in some conditions (e.g. hyperoxaluria, injury etc.). Our epidemiological data show a clear link between atherosclerosis-mediated (intimal calcification) CVD and kidney stone formation. TIA. Ultimately, further research is required to establishing the contribution of arteriosclerosis to KSF. Biomarker-identifying studies utilising animal models for stone disease such as *Drosophila melanogaster* [28] would be most useful in systematically obtaining evidence for the mechanisms discussed in this paper. Using animal models would also allow us to effectively map the development of CVD and kidney stones across the lifespan of the animals used, providing further insight into the risk factors for both conditions.

The influence of common risk factors, such as obesity [29,30], hypertension [31,32] and dyslipidaemia [33,34] still could underly this connection. Although the effect of these on our data has been minimised by using adjusted incidence ratios, the possibility that this relationship may be one of common risk factors has not been eliminated. Indeed, our biological search indicated that the coexistence of cholesterol-induced atherosclerosis and

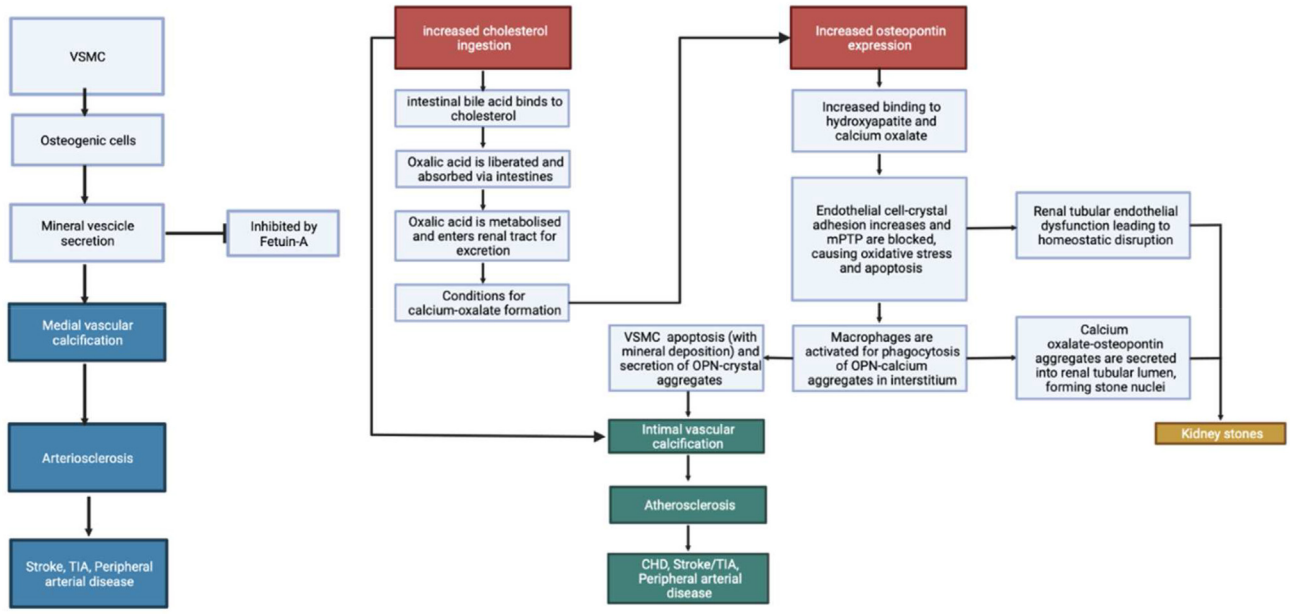

Figure 5 Overview of the discussed mechanisms that contribute to both cardiovascular disease and kidney stone formation.

nephrolithiasis could explain the link between the two conditions [24]. Establishing causal mechanisms of CVD and KSF would help inform whether this is a relationship mediated by pathophysiological mechanisms or common risk factors, which will have direct implications for treatment and management of patients.

We consistently found that female KSF were at higher risk of developing CVD across all outcomes. Ferraro et al. noted that the increased risk of CHD in KSF was observed in two cohorts of women, but not to a statistically significant level in men [35]. Peng et al. found that CHD risk in KSF may be higher in men, whereas stroke risk may be higher in women with kidney stones [9]. This finding is of importance for clinicians in deciding to screen KSFs for CVD risk.

There are limitations of this study. The inclusion of cross-sectional studies in the AD analysis may have been affected by reverse causation (i.e. potentially misclassifying those patients who may have developed an adverse CVD outcome before their kidney stone). The exclusion of cross-sectional studies in the CAD and strokes/TIA portion of the review minimises the effect of this temporal bias on our overall results. Significant heterogeneity was also observed in the epidemiological analysis. The heterogeneity was expected, given the breadth of data which was sought for the review, and the diversity of the patient cohorts (both in outcomes assessed and size). In the biological analysis, it is possible that some literature may have been omitted due to our strict inclusion criteria. We did not explore the different types of kidney stones or different metabolic profiles and their associated CVD risk. This was due to a lack of consistent reporting from the epidemiological studies on the stone type and metabolic data. Ferraro et al. suggest a correlation between calcium phosphate content of stones and increased CVD risk [35]. Bargagli et al. also found that those stone formers who were also diagnosed with CVD had lower urinary excretions of citrate and magnesium, and a lower urine pH [36]. However, Valencia et al. found no relationship between stone composition and CVD in their study population [37].

5. Conclusion

KSF is linked to a broad range of adverse cardiovascular events, including CAD, strokes/TIA and AD, independent of common risk factors. We have combined the epidemiological and biological aspects of CVD and KSF into a comprehensive overview of this pathophysiological connection. Ectopic calcification pathways and injury-inflammation responses may represent common mechanisms leading to intimal and/or medial vascular calcification and stone formation, which could be further exacerbated by the presence of common risk factors. An awareness of this connection is vital for clinicians, and a comprehensive understanding will improve diagnosis, management and the development of novel therapeutic approaches.

Declaration of competing interest

PMF received consultant fees and grant support from Allena Pharmaceuticals, Alnylam, Amgen, AstraZeneca, BioHealth Italia, Gilead, Otsuka Pharmaceuticals, Rocchetta, Vifor Fresenius, and royalties as an author for UpToDate. SHM has received consultant fees from Alnylam, Dicerna and Sanofi.

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This review is registered with PROSPERO, ID CRD42021251477.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2023.09.011.

What is new?

- This is the largest, and most up-to-date systematic review and meta-analysis conducted on this topic, including 4,259,869 participants, 230,720 of whom were kidney stone formers
- This study found a 25% higher risk of coronary artery disease, a 17% higher risk of strokes/transient ischemic attacks and a 39% higher risk of peripheral arterial disease in kidney stone formers compared to non-kidney stone former controls., independent of common risk factors The peripheral arterial disease analysis, to our knowledge, has not been assessed in a systematic review before.
- Our study found that this association was 1.20 times greater for coronary artery disease, and 1.10 times greater for stroke in female-identifying kidney stone formers, which is a subgroup analysis that not all systematic reviews have included
- Our systematic review is the first to couple an in-depth, systematic review of the biological mechanisms underlying this pathway, identifying potential mechanisms linking the two, including intimal/medial vascular calcification, oxidative stress via osteopontin (OPN) effects, cholesterol-induced pathology, and endothelial dysfunction
- Our work should highlight to clinicians this important connection between these two common conditions, and clinicians should also be aware of the subgroup of female-identifying kidney stone formers who are at greater risk of this association. Our work should also indicate the value in including in-depth biological analyses alongside epidemiological work to contextualise findings and inform further research.

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