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REVIEW ARTICLE

Erectile dysfunction in hyperuricemia: A prevalence meta-analysis and meta-regression study

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Abstract

Background: Whether and to what extent an association exists between hyperuricemia and erectile dysfunction (ED) has not yet been fully determined.

Objective: To define pooled prevalence estimates and correlates of erectile dysfunction in men with hyperuricemic disorders.

Materials and methods: A thorough search of Medline, Scopus, and Cochrane Library databases was performed. Data were combined using random-effects models and the between-study heterogeneity was assessed by Cochrane's Q and I^2 tests. A funnel plot was used to assess publication bias.

Results: Overall, 8 studies included gave information about 85,406 hyperuricemic men, of whom 5023 complained of erectile dysfunction, resulting in a pooled erectile dysfunction prevalence estimate of 33% (95% Confidence Interval: 13–52%; Iš = 99.9%). The funnel plot suggested the presence of a publication bias. At the meta-regression analyses, among the available covariates that could affect estimates, only type 2 diabetes mellitus was significantly associated with a higher prevalence of erectile dysfunction ($\beta = 0.08$; 95% Confidence Interval: 0.01, 0.15, $p = 0.025$). At the sub-group analysis, the pooled erectile dysfunction prevalence decreased to 4% (95% Confidence Interval: 0%–8%) when only the largest studies with the lowest prevalence of type 2 diabetes mellitus were included and increased up to 50% (95% Confidence Interval: 17%–84%) when the analysis was restricted to studies enrolling smaller series with higher prevalence of type 2 diabetes mellitus.

Conclusions: A not negligible proportion of men with hyperuricemia can complain of erectile dysfunction. While a pathogenetic contribution of circulating uric acid in endothelial dysfunction cannot be ruled out, the evidence of a stronger association between hyperuricemia and erectile dysfunction in type 2 diabetes mellitus points to hyperuricemia as a marker of systemic dysmetabolic disorders adversely affecting erectile function.

KEYWORDS
diabetes, gout, impotence, metabolic syndrome, sexual function, uric acid

1 | INTRODUCTION

Erectile dysfunction (ED) is defined as the persistent inability to achieve and/or maintain a penile erection sufficient for satisfactory sexual performance.[1] Among the organic etiologies of ED, the vascular causes remain the most frequent.[2,3] Besides sharing common risk factors with cardiovascular disease (CVD), ED is also regarded as an independent risk predictor for CVD.[4] The exposure to conventional risk factors for CVD, such as smoking, obesity, diabetes, hypercholesterolemia, and hypertension, promotes endothelial dysfunction with decreased nitric oxide (NO) bioavailability, ultimately resulting in a systemic disease of all vascular beds.[3–7] All these features, as a whole, take the form of metabolic syndrome (MetS), a high CVD-risk dysmetabolic profile also including an increase in circulating levels of uric acid (UA) in many cases.[8–11]

High levels of UA, the end product of dietary and endogenous purine metabolism, have been associated with endothelial dysfunction,[12–16] microvascular diseases,[17] and hypertension.[18,19] Moreover, pilot clinical studies suggest that lowering circulating UA could improve endothelial function while decreasing blood pressure values in hypertensive patients.[20–22] Indeed, in experimental studies, UA decreased endothelial NO bioavailability via different pathways, including direct scavenging, scavenging by UA-induced oxidative stress, and arginase stimulation.[23–26] Interestingly, a stimulating effect of UA on vascular smooth muscle cell proliferation has been also demonstrated in vitro.[27–29] In this light, hyperuricemia has begun to be considered a possible independent risk factor for both CVD and vasculogenic ED. Intriguingly, an experimental model of hyperuricemic rats exhibited ED resulting from a decrease in the expression of NO synthase (NOS) along with an increase in reactive oxygen species in cavernous tissue.[30] Nevertheless, the actual existence and extent of an association between hyperuricemia and ED remain controversial in clinical studies. An independent positive association of UA with ED was found in a Turkish study on 200 hypertensive men,[31] in a case-control study by Salem et al.[32] recruiting 251 patients with newly diagnosed ED, and in a large population study on 1365 Chinese men.[33] On the contrary, in a study by Solak et al., enrolling 312 men with suspected coronary artery disease, although those with ED exhibited significantly higher UA levels, such an association was lost at the multivariable regression model.[34] More recently, in a series of Finnish men from the Harmonica (HArjavalta Risk MONItoring for CArdiovascular disease) Project, UA was not associated with ED in univariate or multivariable analysis.[35]

In order to comprehensively assess the extent of the association between UA and ED, we carried out a systematic review with meta-analysis and meta-regression study to define pooled prevalence estimates and possible correlates of ED in men with hyperuricemia.

2 | METHODS

The study was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[36] It also complies with the guidelines of Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE).[37] The PRISMA-P and MOOSE checklists have been presented as Tables S1 and S2, respectively. The study is registered in the PROSPERO (International Prospective Register of Systematic Reviews) with the number CRD42020188585. (https://www.crd.york.ac.uk/PROSPERO/).

2.1 | Systematic search strategy

A systematic search was performed in MEDLINE, Scopus, and Cochrane Library, including the following free and vocabulary terms: 'uric acid', 'urate', 'hyperuricemia', 'gout', 'erectile dysfunction', 'erection', and 'impotence', using the Boolean functions AND/OR. The search was restricted to English-language studies enrolling human participants, published up to February 2021. If it was not clear from the abstract whether the study contained relevant data, the full text was retrieved. The reference lists of the identified articles were also scrutinized to find possible additional pertinent studies.

2.2 | Inclusion and exclusion criteria

Eligible studies were identified according to a PECOS (Population, Exposure, Comparison/Comparator, Outcomes, Study design) model (Table S3).

Studies were included in the quantitative analysis if they reported the prevalence (or information for its calculation) of any diagnosis of ED (according to a different diagnosis, see Table 1) in subjects with a documented diagnosis of hyperuricemia and/or gout recruited from the general population or from cohorts of patients. Observational studies (case-control, cross-sectional, prospective, and series of cases), as well as intervention studies, were screened for eligibility. Only information about cases (subjects with hyperuricemia and/or gout) was extracted from case-control studies. Only baseline information was extracted from intervention studies assessing the effects of the urate-lowering treatments in patients with hyperuricemia. Duplicates were rigorously checked and removed.

Reviews, meta-analyses, studies lacking to assess the outcomes of interest or with unsuitable design (e.g. assessment of UA levels in men with ED) were excluded. When the population sample was used for multiple publications, the study with the largest number of participants was included.

Two independent reviewers (Maria Totaro and Settimio D'Andrea) evaluated the full text of all selected studies for eligibility, and, where a disagreement occurred, a third reviewer (Arcangelo Barbonetti) took a decision after an open discussion.

2.3 | Data extraction

Data were extracted from the selected studies by three independent reviewers (Maria Totaro, Settimio D'Andrea, and Chiara Castellini) by including the first author, publication year, country/geographic region,

TABLE 1 Characteristics of the included studies

Study	Region	Study design	Mean age of participants (years)	Men with hyperuricemia (*n*)	ED (*n*)	Testosterone levels (nmol/L)	ED diagnostic tool	ED etiopathogenesis	T2DM (*n*, %)	Dyslipidemia (*n*, %)	Hypertension (*n*, %)	CKD (*n*, %)
Gao et al.[33]	China	Cross-sectional study	54.5	339	196	15.2	IIEF-5	NR	61 (17.9%)	NR	NR	NR
Hsu et al.[42]	Taiwan	Retrospective cohort study	49.6	35265	476	NR	ICD-9-CM	Organic: 88.7%, Psychogenic: 11.3%	3016 (8.6%)	10249 (29.0%)	13631 (38.6%)	3201 (9.1%)
Kim et al.[43]	Korea	Cross-sectional study	52.0	80	44	14.3	IIEF-5	NR	NR	59 (73.8%)	26 (32.5%)	NR
Maynard et al.[44]	USA	Cohort study	68.7	256	102	NR	Health professional diagnosis of ED	NR	NR	NR	NR	NR
Roddy et al.[45]	UK	Cross-sectional study	59.9	1292	116	NR	Health register code	NR	NR	NR	NR	NR
Schlesinger et al.[46]	USA	Cross-sectional study	56.7	83	63	NR	SHIM score	NR	12 (14.5%)	43 (51.8%)	54 (65.0%)	32 (38.6%)
Schlesinger et al.[47]	UK	Cohort study	63.6	38438	2290	NR	Health register code	NR	3900 (10.1%)	14740 (38.3%)	19599 (50.9%)	NR
Sultan et al.[48]	UK	Cohort Study	NR	9653	1736	NR	Medical code	NR	1470 (15.2%)	NR	4191 (43.4%)	802 (8.3%)

Abbreviations: CKD, chronic kidney disease; ED, erectile dysfunction; IC9-9-CM, International Classification of Diseases, 9th revision-Clinical Modification; IIEF-5, International Index of Erectile Function Questionnaire-5; NR, not reported; SHIM, sexual health inventory for men; T2DM, type 2 diabetes mellitus.
Values are presented as mean or number (%).

study design, the total number of individuals with hyperuricemia, and the number of those complaining of ED and the diagnostic tool for sexual dysfunction. The mean value of the age of the participants, diagnosis of chronic kidney disease (CKD), and MetS-related comorbidities, including type 2 diabetes mellitus (T2DM), dyslipidemia, and hypertension, were also taken into account, when available. When summary statistics were not fully reported, these were calculated, whenever possible.[38] Where data were missing, incomplete, or inconsistent, the authors were contacted to obtain necessary information.

2.4 | Quality assessment

The quality of the studies was assessed using an adapted Assessment Tool for Prevalence Studies.[39] This tool, designed to assess the risk of bias in prevalence studies, takes into account 10 different items, including representativeness and selection of the study population, the likelihood of non-response bias, the process of data collection, appropriateness of the definition of cases (subjects with ED) as well as of the measurement of the parameter of interest (prevalence of ED). Response options for individual items were either low or high risk of bias and a summary assessment of the overall risk of bias was based on the subjective judgment attributed to the 10 items: 7–10 items with 'low risk' judgment indicated an overall low risk of bias, 4–6 items with 'low risk' judgment indicated an overall moderate risk of bias, and 0–3 items with 'low risk' judgment indicated an overall high risk of bias.

Quality assessment was performed independently by two reviewers (Maria Totaro and Settimio D'Andrea) and any disagreement was resolved by involving a third reviewer (Arcangelo Barbonetti) who re-evaluated the original study.

2.5 | Statistical analysis

The pooled prevalence of ED was estimated by a random-effects model which assumes that the included studies have varying effect sizes, thus providing a conservative estimate of the overall effect. The 95% confidence intervals (CIs) of the prevalence reported in individual studies were estimated from the proportion of cases of ED and the sample size, using the binomial Clopper-Pearson exact method. After ascertaining the non-normal distribution of the original data sets (by the Shapiro-Wilk test), the Freeman-Tukey double arcsine transformation was applied to the primary study data to approximate normality. The final pooled results and 95% CIs were back-transformed and expressed as percentages for an easier interpretation. An inverse variance method was used for weighting each study in the pooled estimates. The Cochran's chi-square (Cochran's Q) test and the I^2 test were used to analyze the statistical heterogeneity between the results of different studies: an $I^2 > 50\%$ and/or $p < 0.05$ indicated substantial heterogeneity.[40] Publication bias was graphically explored through the funnel plot.[41]

Covariates that could affect the estimates, such as the mean age of the participants and the presence of comorbidities (CKD, hypertension, T2DM, dyslipidemia) were included in linear meta-regression models.

Data were analyzed and graphed using the packages 'metafor' and 'ggplot2' of the R statistical software (version 3.6.3, 2020; The R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Study selection and quality assessment

From the electronic search, we retrieved a total of 481 studies and two additional records were found by manual search. After the removal of duplicates, 396 studies were left, of which, 381 were excluded as irrelevant based on title and abstract reading. Hence, as shown in Figure 1,[15] studies were identified, of which 8 met the inclusion criteria.[33,42–48] The study by Chen and colleagues[49] was excluded since the population under investigation was already included in that by Hsu et al.[42] Details of the selected articles are summarized in Table 1.

Quality assessment of the studies is shown in Table 2. Six studies were considered at low/moderate risk of bias, whereas an overall high risk of bias was attributed to the remaining two studies.

3.2 | Synthesis of results and publication bias

As shown in Figure 2, the included studies collectively gave information about ED in 85,406 hyperuricemic men, resulting in a pooled ED prevalence estimate of 33% (95% CI: 13%–52%; $I^2 = 99.9\%$, $p_{\text{for heterogeneity}} < 0.0001$).

The asymmetric shape of the funnel plot pointed to the presence of a publication bias (Figure 3): the largest studies tended to converge around a low pooled estimate (< 20%) at the top of the funnel plot, contrary to smaller studies, displaying a wide scatter of effect estimates around a higher pooled prevalence of ED at the bottom of the distribution.

3.3 | Meta-regressions and sub-group analysis

Meta-regression analyses were carried out to find out covariates that could affect the prevalence estimate. No significant relationship was found between ED and mean age of study populations ($\beta = -0.0019$; 95% CI: −0.049, 0.045; $p = 0.9$), diagnosis of dyslipidemia ($\beta = 0.018$; 95% CI: −0.002, 0.038; $p = 0.08$), CKD ($\beta = 0.0028$; 95% CI: −0.0065, 0.0121; $p = 0.6$), and hypertension ($\beta = 0.0124$; 95% CI: −0.021, 0.045; $p = 0.5$). Instead, a diagnosis of T2DM was significantly associated with a higher prevalence of ED in hyperuricemic men ($\beta = 0.08$; 95% CI: 0.01, 0.15; $p = 0.025$, Figure 4).

A sub-group analysis was carried out according to funnel plot distribution of effect estimates (Figure 3) and T2DM meta-regression results (Figure 4). When the analysis was restricted to the studies by

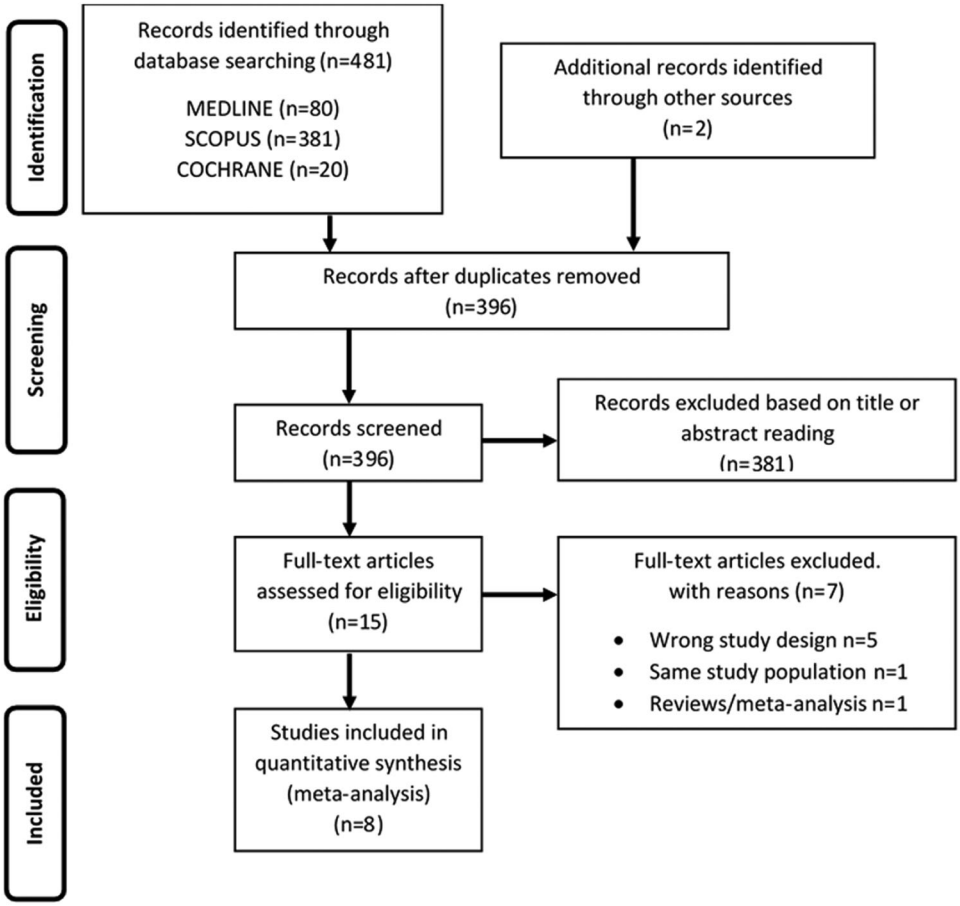


FIGURE 1 Flow diagram showing an overview of the study selection process

TABLE 2 Quality assessment of the included studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Overall
Kim et al.[43]	L	H	H	L	L	L	L	L	L	H	Low risk of bias
Schlesinger et al.[46]	L	H	H	L	L	L	L	L	H	L	Low risk of bias
Sultan et al.[48]	L	H	H	L	H	L	L	L	H	L	Moderate risk of bias
Schlesinger et al.[47]	L	L	H	L	H	L	L	L	H	L	Low risk of bias
Hsu et al.[42]	L	L	L	L	H	L	L	L	H	L	Low risk of bias
Maynard et al.[44]	H	H	H	H	H	H	H	H	H	H	High risk of bias
Roddy et al.[45]	H	H	H	H	H	H	H	H	H	H	High risk of bias
Gao et al.[33]	L	H	H	L	L	L	L	L	L	H	Low risk of bias

H = High risk; L = Low risk.
Q1. Was the study's target population a close representation of the national population in relation to relevant variables.
Q2. Was the sampling frame a true or close representation of the target population.
Q3. Was some form of random selection used to select the sample, OR was a census undertaken.
Q4. Was the likelihood of non-response bias minimal.
Q5. Were data collected directly from the subjects (as opposed to a proxy).
Q6. Was an acceptable case definition used in the study.
Q7. Was the study instrument that measured the parameter of interest (prevalence of sexual dysfunction) shown to have reliability and validity.
Q8. Was the same mode of data collection used for all subjects.
Q9. Was the length of the shortest prevalence period for the parameter of interest appropriate.
Q10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate.
Overall. The summary item on the overall risk of study bias: 7–10 items with 'low risk' judgment = overall low risk of bias; 4–6 items with 'low risk' judgment = overall moderate risk of bias; 0–3 items with 'low risk' judgment = overall high risk of bias.

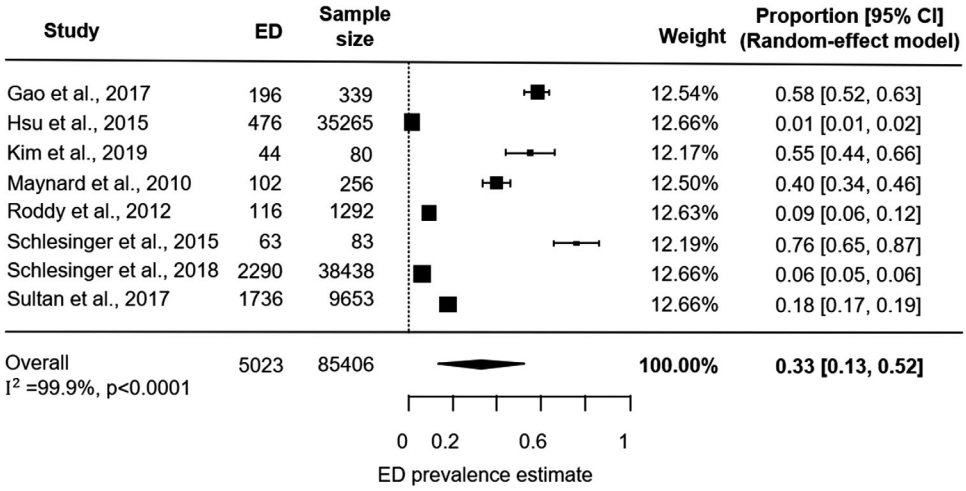


FIGURE 2 Forest plot depicting the pooled prevalence estimate for erectile dysfunction (ED) in hyperuricemic men. The diamond indicates the overall summary estimate and the width of the diamond represents the 95% confidence interval (CI). The boxes indicate the weight of individual studies in the pooled results

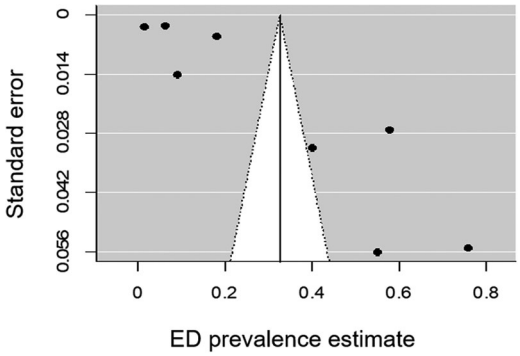


FIGURE 3 Funnel plot of the results from studies assessing the prevalence of erectile dysfunction (ED) in men with hyperuricemia

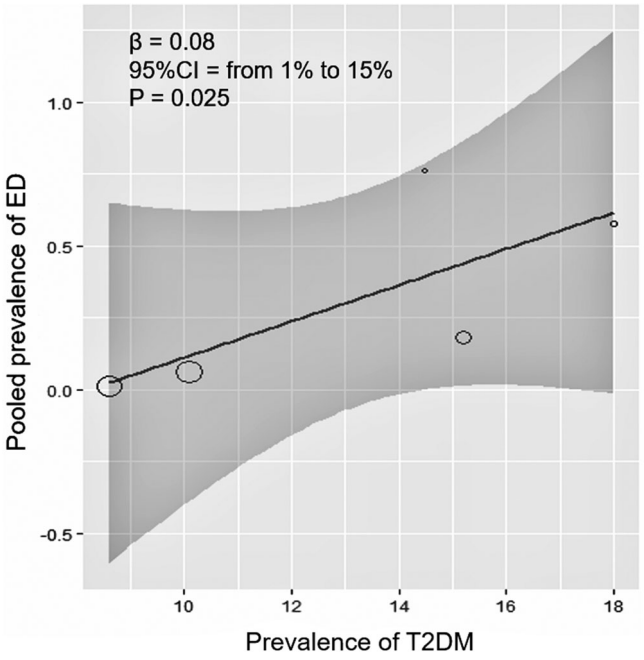


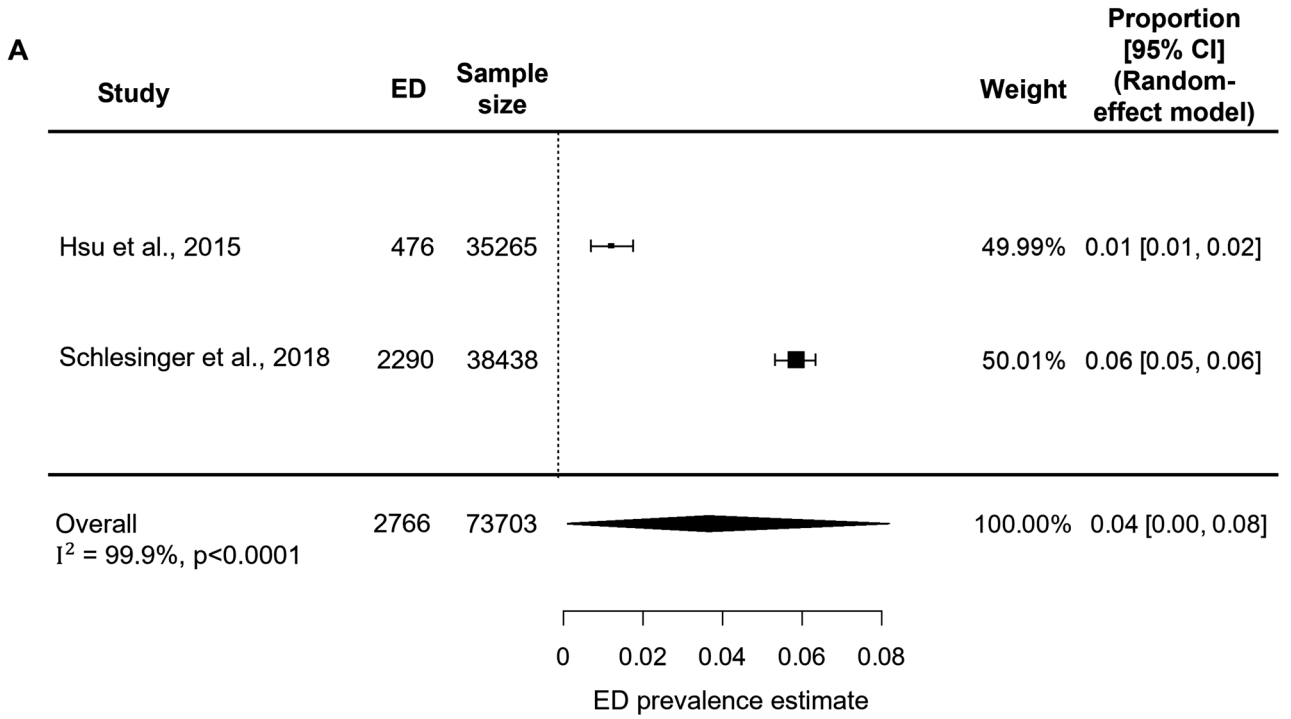
FIGURE 4 Meta-regression bubble plot of the prevalence of erectile dysfunction (ED) in hyperuricemic men as a function of the concomitant diagnosis of type 2 diabetes mellitus (T2DM). The predicted effects (solid line) with corresponding confidence intervals (gray range) are also shown. CI, confidence interval

Hsu et al.,[42] and Schlesinger et al.,[47], reporting both the largest sample size and the lowest prevalence of T2DM, the pooled prevalence of ED dropped to 4% (95% CI: 0%–8%; $I^2 = 99.9\%$, $p_{\text{for heterogeneity}} < 0.0001$, Figure 5A). On the contrary, the pooled estimate increased up to 50% (95% CI: 17%–84%; $I^2 = 99.4\%$, $p_{\text{for heterogeneity}} < 0.0001$) in the sub-analysis that included the studies by Gao et al.,[33] Schlesinger et al.,[46] and Sultan et al.,[48], all enrolling smaller series with a higher prevalence of T2DM (Figure 5B).

4 | DISCUSSION

According to results from the present meta-analysis, overall, ED would be exhibited by 33% of men with hyperuricemia. Indeed, the accuracy of the prevalence estimate was burdened by the large between-study heterogeneity, with prevalence rates among studies ranging from 1%[42] to 76%.[46]

The wide variability of the results is likely to be a reflection of differences in clinical characteristics of the enrolled populations that could exhibit heterogeneous profiles of CVD risk. In particular, hyperuricemic disorders can represent very common features of MetS,[8–11] which results from a constellation of visceral obesity, hypertension, dyslipidemia, and hyperglycemia, up to overt T2DM.[50] All these components, which are linked by a common thread of insulin resistance, are well-known risk factors for endothelial dysfunction/damage and the impairment of the cardiovascular system integrity can result in vasculogenic ED.[51] Therefore, it can be hypothesized that a variable



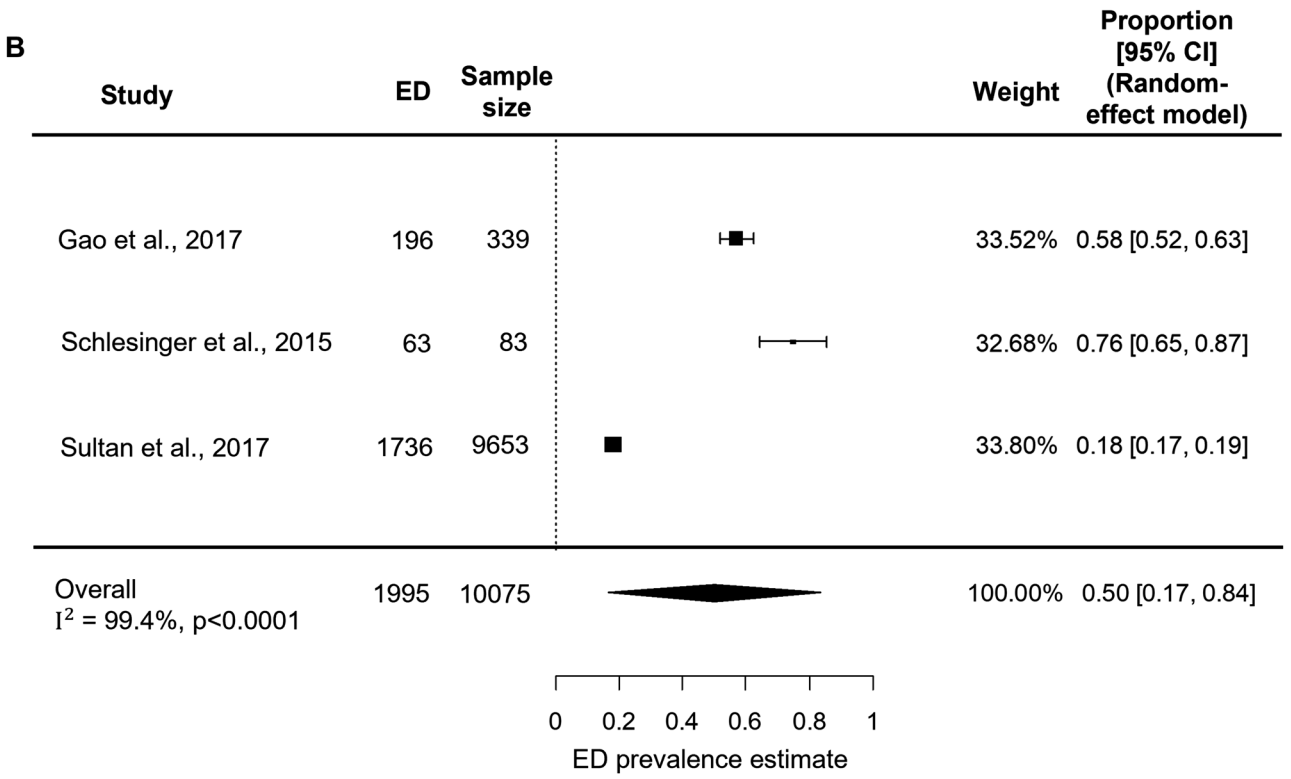


FIGURE 5 Forest plots depicting the results of the sub-group analysis according to sample size and prevalence of type 2 diabetes mellitus (T2DM) of the study populations. The pooled prevalence estimate of erectile dysfunction (ED) in hyperuricemic men was calculated separately for studies with both larger sample sizes and lower T2DM prevalence (A) and for those enrolling smaller series with a higher prevalence of T2DM (B). Diamonds indicate the overall summary estimates and the width of the diamonds represents the 95% confidence interval (CI). The boxes indicate the weight of individual studies in the pooled results

expression of MetS-related CVD risk factors in the study populations has contributed to the high between-study heterogeneity in the prevalence rates of ED among hyperuricemic patients. In this regard, some interesting information arose from the results of meta-regression analyses. The lack of a significant positive association between the prevalence of ED and age is not surprising. Although in the general population, ED gets more prevalent with aging,[52] reflecting both a progressive decline in testosterone levels and poorer cardiovascular health, these latter events also occur in the presence of MetS irrespective of age. In this scenario, a young dysmetabolic (and hyperuricemic) man might display the same risk of developing ED as an elderly man without metabolic disorders.[53] On this basis, the positive association between ED and aging, could become no longer recognizable in patients whose hyperuricemia can be framed by the MetS picture. In the context of MetS, the use of multiple medications, namely antihypertensive drugs, could also contribute to worsening ED: as beta-blockers and diuretic therapy tend to elevate circulating UA levels,[54] it has been hypothesized[55] that such a pharmacological interference could partially explain the reported association between hyperuricemia and ED in hypertensive patients.[31,32] Noteworthy, at the meta-regression analyses, among the main clinical components of MetS, including hypertension, dyslipidemia, and T2DM, only this latter exhibited a significant association with the prevalence of ED in hyperuricemia. At the sub-group analysis, the pooled prevalence of ED decreased to 4% (95% CI: 0%–8%) when only the two studies with both largest sample size and lowest prevalence of T2DM were included,[42,47] whereas the estimate increased up to 50% (95% CI: 17%–84%) when the analysis was restricted to studies enrolling smaller series with higher prevalence of T2DM.[33,46,48] Indeed, diabetes can adversely affect erectile function by different pathogenetic mechanisms, ranging from micro- and macroangiopathy and neuropathy[56] to endothelial dysfunction related to reactive oxygen species, which represent key mediators in the pathophysiology of chronic complications.[57] In long-lasting diabetes, the impairment of renal function could also contribute to increasing circulating UA levels. In fact, UA is mainly produced by the liver and intestinal mucosa as the final breakdown product of purine catabolism and is eliminated by kidneys.[58] In this light, the effect of glomerular filtration rate (GFR) has been suspected to act as a confounding factor in mediating the association between UA and ED.[59] Accordingly, in a study by Solak et al. in 312 patients with coronary artery disease,[34] the significant univariate association between higher UA levels and ED was lost at the multivariable analysis adjusted for GFR. In the present study, at the meta-regression analysis, the presence of CKD did not affect the prevalence rate of ED in hyperuricemic men, although caution should be used when interpreting this finding due to the limited number of studies included. Overall, the results of our meta-regression and sub-group analyses seem to resize the role of hyperuricemia as a possible direct causal factor of endothelial dysfunction leading to ED. Hyperuricemia and ED could simply share common risk factors related to a dysmetabolic habitus. As matters stand, outside the context of T2DM and MetS, the association between hyperuricemia and ED could be unremarkable especially in full-scale investigations. Accordingly, in a recent cross-sectional study enrolling unselected Finnish men, UA was not associated with ED both in univariate and multivariable analysis.[35]

This meta-analysis has some limitations. First, only a few studies were included in the quantitative synthesis, which resulted, indeed, from a strict screening and selection of the literature. However, although only eight articles were selected, they collectively provided information on a relatively large study population, including more than 85,000 hyperuricemic men, of whom 5023 complained of ED. Moreover, the shape of the funnel plot suggested the presence of a publication bias but the inclusion of eight studies only prevented us from performing tests for funnel plot asymmetry. A further major limitation concerns the heterogeneity in the criteria used for the selection of hyperuricemic populations. Hyperuricemia was not always explicitly quantified and different cut-offs were used among the studies. Moreover, a full comparability of findings from the included studies could not be ensured because of the use of different (not always validated) tools for the diagnosis of ED (Table 1), which could introduce a measurement bias. Finally, the dearth of information regarding the etiology of ED and other relevant patients' characteristics, including testosterone levels, GFR, MetS-related CVD risk factors, and antihypertensive medications, did not allow their inclusion in comprehensive meta-regression and sub-group analyses to check their possible contributions in explaining the large between-study heterogeneity.

In conclusion, a not negligible proportion of men with hyperuricemia can complain of ED. While a direct pathogenetic contribution of UA in promoting endothelial dysfunction cannot be ruled out, the evidence of a stronger association between hyperuricemia and ED in diabetic patients points to hyperuricemia as a marker of systemic dysmetabolic disorders adversely affecting erectile function.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

AUTHOR CONTRIBUTIONS

Maria Totaro and Arcangelo Barbonetti conceived the concept and design. Maria Totaro wrote the article under Arcangelo Barbonetti's supervision. Settimio D'Andrea, Antonio Parisi, Sara Palazzi, Federica D'Amato, and Daniele Tienforti were involved in the acquisition of the data. Maria Totaro and Arcangelo Barbonetti were involved in the statistical analysis and interpretation of the data. Settimio D'Andrea, Chiara Castellini, Marco Giorgio Baroni, and Sandro Francavilla were involved in the interpretation of the data and critically reviewed the article. All authors have read and agreed to the published version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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