The urinary microbiome in association with diabetes and diabetic kidney disease: A systematic review

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Abstract

Background: The urinary microbiome, or urobiome, is a novel area of research that has been gaining attention recently, as urine was thought to be sterile for years. There is limited information about the composition of the urobiome in health and disease. The urobiome may be affected by several factors and diseases such as diabetes, a disease that often leads to kidney damage. Thus, we need to understand the role of the urobiome to assess and monitor kidney disease related to diabetes over time.

Methods: We conducted a systematic review to summarize knowledge about the urobiome in association with diabetes mellitus and diabetic kidney disease. The search was conducted in several electronic databases until November 2024.

Results: Eighteen studies were selected including cross-sectional case-control studies, cross-sectional surveys and one prospective longitudinal study. In total, the urobiome of 1,571 people was sequenced, of which 662 people had diabetes, and of these 36 had confirmed diabetic kidney disease; 609 were healthy individuals, 179 had prediabetes or were at risk of type 2 diabetes mellitus and 121 did not have diabetes but had other comorbidities. Eight studies analysed data from females, one was focused on male data, and the other nine had mixed female-male data. Most of the studies had a small sample size, used voided midstream urine, and used 16S rRNA sequencing.

Conclusion: This systematic review summarizes trends seen throughout published data available to have a first baseline knowledge of the urinary microbiome, and its microbiota, in association with diabetes including the decreased richness and α-diversity in urinary microbiota in individuals with diabetes compared to healthy controls and the decreased α-diversity with the evolution of kidney disease independently of the cause.

Keywords: urinary microbiome; urinary microbiota; urobiome; albuminuria; diabetes; kidney disease

1. Introduction

Microbial communities living within us comprise viruses, bacteria, archaea, and small eukaryotes like fungi and protists [1]. These communities are symbiotic microbial networks that can perform vital functions in the host and whose metabolites, or the lack of them, have influence in human health and diseases [2–4]. The intricate structure of these microbial ecosystems within their ecological niche, their taxonomy and functional composition, are known as the microbiome [5]. Similarly to our fingerprints, each microbiome in the gut, vagina, skin or urinary tract are highly unique and they are influenced by the environment, host genetics, lifestyle and there may be other factors influencing the microbiome for which we currently lack understanding [4]. Dysbiosis is a state where the microbiome is disrupted or altered, or both, impeding normal functionality or causing low-grade inflammation that may play a role in the onset and/or development of several diseases [5]. The human gut microbiome is seen as a "hidden" metabolic organ for human wellbeing affecting immunity, neural, endocrinal or metabolic pathways [4,6]. Gut dysbiosis has been related to several diseases but if it is cause or effect of these diseases is a question that remains unclear [4,7,8]. While our understanding of the gut microbiome is evolving but limited, the knowledge about other microbiomes is even more scarce. This is particularly true for the urinary tract microbiome, or urobiome, which was long believed to be sterile until a decade ago [9,10]. The urobiome is characterized by a low biomass relative to the gut microbiome, and its composition remains largely unexplored [9,11]. Evidence suggests that the urobiome differs between males and females: associated with lactobacilli in females, whereas in males is linked to *Corynebacterium* or *Staphylococcus* [9,11,12].

Diabetes, a disease characterized by elevated levels of glucose in the blood, is a leading cause of cardiovascular disease, blindness or kidney damage [13]. Diabetes, especially type 2 diabetes mellitus (T2DM), has become a global health emergency whose prevalence have been rising for decades affecting 537 million people globally in 2021, including 6.7 million related deaths [13,14]. The incidence of diagnosed diabetes in adults is stabilising in some high-income countries, but

incidence in children is still increasing [15–18]. Impaired glycaemia contributes to enhanced risk of infections, and it may explain why diabetic individuals have higher risk of urinary infections, pyelonephritis and urosepsis [19]. Not only individuals with diabetes have higher glucose, albumin and other proteins in urine which may affect the urobiome composition, enhance bacterial growth of some species and may influence the diversity of the urobiome; but also they have high glucose in urine which compromises the immune response and uroepithelial integrity [19]. However, we have limited information about the composition of the urobiome related to diabetes. In addition, damage in the kidney blood vessels, because of diabetes or other causes, may decline the estimated glomerular filtration rate (eGFR) which impacts urinary functions as these organs are connected through the ureters to the urinary bladder [20]. Development of diabetic nephropathy may further turn in chronic kidney disease (CKD) or end stage renal disease (ESRD), the former associated with diabetes but also other comorbidities while the latter is mostly caused by diabetes [20].

As there is a clear knowledge gap regarding the role of the urobiome in diabetes and diabetic kidney disease (DKD), the aim of this systematic review is to gather available data and synthetise the main findings about the urobiome, particularly, the urinary microbiota in association with diabetes and kidney conditions derived from diabetes such as CKD or ESRD.

2. Materials and methods

2.1 Search strategy

The comprehensive literature search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [21]. It was registered under accession number of 565545 in the International Prospective Register of Systematic Reviews (PROSPERO) hosted by the National Institute for Health and Care Research of the University of York (United Kingdom). A comprehensive literature search on different databases was conducted from 1st January 2000 until 28th November 2024. The search included the following terms [("urobiome" OR "urinary

91 microbiome" OR "urinary microbiota" OR "urinary tract microb*" OR "urine microb*" OR "urogenital
92 microbiome" OR "urogenital microbiota") AND ("kidney disease*" OR "chronic kidney disease" OR
93 "diabetes" OR "albuminuria" OR "diabetic nephropathy" OR "end stage renal disease*" OR "renal
94 disease*")]. We used the 'TITLE-ABS-KEY' search in SCOPUS and Cochrane Central Register of
95 Controlled Trials databases, the 'Keyword' in advanced search in MEDLINE-Ovid and EMBASE
96 databases, while 'ALL FIELDS' were used in Web of Science and PUBMED databases (**S1 Table**). This
97 search wanted to identify relevant clinical urinary microbiome studies associated with diabetes
98 and/or kidney impairment published from 1st January 2000 until 28th November 2024.

99 2.2 Study selection

100 We included studies that evaluated the urobiome sequencing any type of urine samples (urinary
101 bladder, urinary kidney or urogenital samples [22]) in relation with diabetes and conditions that
102 affect kidney functionality, and which can lead to chronic kidney disease or end stage renal disease.
103 Studies were excluded if they were review articles, editorials, comments, systematic reviews, books,
104 conference abstracts or any other type of article without full data available. The inclusion criteria
105 were: (i) analyses studying the bacterial species of urine; (ii) analyses of individuals with diabetes
106 and/or albuminuria and/or diabetic CKD and/or diabetic end-stage renal disease; (iii) human clinical
107 samples; and (iv) perform DNA sequencing through 16S ribosomal DNA gene or shotgun next
108 generation sequencing.

109 2.3 Data extraction, assessment of quality and risk of bias

110 Throughout this synthesis, we used the PRISMA and PROSPERO frameworks and we incorporated
111 the associated guidance at each stage. Following the removal of duplicates, the first step was the
112 screening of studies by article type. After removal of non-suitable studies, the second step included
113 a screening of studies by title and/or abstract for relevance. Those that seemed relevant were the
114 preliminary selected publications and they were finally screened based on full-text information.

Studies lacking full-text availability or with missing or unclear information were excluded from the evaluation (**Fig 1**). Two independent authors (T.G and Y.T.L) screened studies by title and abstract and, if discrepancies arose, they were discussed until they reached a common agreement. Preliminary selected publications were fully screened by T.G., reviewed by Y.T.L, and if they fulfilled the inclusion criteria, they were selected for this systematic review. Studies quality and risk of bias were assessed on participant selection, exclusion criteria, data measurements and analysis [23,24]. A determination of "low risk" or "high risk" bias according to the Cochrane and the National Heart, Lung and Blood of the United States (NHLBI) guidelines was assessed by T.G. and independently checked by Y.T.L and J.Ä. [23,25]. Any disagreement was discussed and resolved between these authors.

Fig 1: Flow diagram of selected studies. Diagram showing how studies in this systematic review about the urinary microbiota and diabetes were selected.

3. Results

3.1 Selected studies

In total, eighteen studies were included including cross-sectional case-control studies, cross-sectional surveys and one prospective longitudinal study (**Table 1** and **S2 Table**). These studies altogether sequenced the urinary microbiome of 1,571 people, some participants were part of the same cohort studied and were included multiple times [26–29]. Of these individuals 662 had diabetes, 609 were healthy individuals, 179 had prediabetes or were at risk of diabetes, and 121 did not have diabetes but had other comorbidities. Among the 662 diabetic individuals, 36 individuals had diabetic kidney disease [30–32] while one studied CKD patients, most of them with diabetes, but did not mention the primary cause of CKD [33]. Sixteen of the studies used voided midstream urine samples, or a modification of this collection technique, to avoid as much as possible skin or genitalia microorganisms (**S2 Table**). The remaining two studies analysed urinary bladder microbiota

140 (catheterised urine) and, among these two, one was focused only on males (**Table 1**). Eight studies
141 included only female samples (four of these used the same cohort data); and nine studies had mixed
142 female-male data (**Table 1**). All studies except one used 16S sequencing which included twelve
143 studies with small sample sizes with less than 100 individuals, including five studies with less than 50
144 participants (**Table 1**). The only one that used shotgun sequencing had a small sample size (n = 29)
145 (**S2 Table**). Participants of these 18 studies were adults; individuals with diabetes ranged between 50
146 and 72 years old on average, and healthy controls were similar in age but slightly younger (if age was
147 significantly different between groups, it is stated in the comments in **Table 1**). Selected studies had
148 comprehensive exclusion criteria which are detailed in **S2 Table** and they were assessed for risk of
149 bias in **S3 Table**. Moreover, as articles considered confounding factors, such as age, BMI or other
150 relevant clinical factors; those that were statistically significant between groups are pointed up in
151 the comments of **Table 1.**

152 3.2 Diversity and richness indexes

153 Among the 11 case-control studies, 9 reported richness and α-diversity analyses of which
154 three of the studies observed a decrease in richness and α-diversity, one a decrease in richness, two
155 a decrease in α-diversity, one observed an increase in α-diversity but this study assessed kidney
156 stones patients with and without diabetes, and two studies did not observe differences in richness
157 or α-diversity in the urobiome of the individuals with diabetes compared to those without diabetes
158 (**Table 1**). Among the studies assessing only diabetic individuals, one study observed lower α-
159 diversity in diabetic individuals with pyuria, one study observed lower richness in patients with
160 diabetic peripheral neuropathy, one study did not observed differences in α-diversity when
161 assessing urinary interleukin-8; and one study observed increased richness in diabetic individuals
162 compared to diabetic individuals with hyperlipidaemia but decreased richness if compared to
163 diabetic individuals with hypertension. Lastly, the two studies assessing CKD reported a decrease of
164 α-diversity as CKD worsened independently of the primary cause of CDK (diabetes or other). Indexes

165 calculated in each study are detailed in **S4 Table** and the main ones are detailed in **Table 1.** Only
166 seven studies reported β-diversity analyses with variable results (**Table 1**); 4 reported differences in
167 β-diversity, of which 2 described different urotypes [33–36]; while 3 did not see differences in β-
168 diversity[27,37,38].

169 3.3 Differences in microbial taxa

170 Significant results in microbial species for diabetic adults (statistical significance set to $p<$
171 0.05) of each article are summarised in **Table 1** and all details can be found in **S5 Table**. Comprising
172 all studies, most of the bacterial species were identified at the genus level; few at species level and
173 some at higher taxonomy levels. The relative abundance of 69 different bacteria was decreased, of
174 53 was increased in the urine of diabetic individuals while bacteria such as *Enterococcus,*
175 *Stenotrophomonas, Klebsiella* or Actinobacteriota had increased or decreased relative abundance
176 depending on studies (**S5 and S6 Tables** and **Table 1**).

177 Overall, we could observe that the genus *Lactobacillus,* and at species level *Lactobacillus iners*, had
178 increased relative abundance in diabetic individuals in 6 and 2 studies, respectively; and it was
179 related to poor glycaemic control and with presence of interleukin-8 in urine [27,28,34–36,39].
180 Three studies reported a decrease in relative abundance of the family *Bifidobacteriaceae* in urine of
181 individuals with diabetes which includes the genera *Bifidobacterium* and *Gardnerella;* while one
182 study reported the absence of the genus *Gardnerella* in individuals with diabetes and hyperlipidemia
183 *(*note: *Gardnerella* is included now in the genus *Bifidobacterium*)[27,28,30,40]. In addition, depletion
184 of the family *Peptoniphilaceae* in urine of T2DM patients was reported in several selected studies. In
185 fact, studies reported decreased relative abundance of this family being relevant genera
186 *Peptoniphilus*, *Anaerococcus, Finegoldia, Murdochiella* and *Gallicola*, which were reported decreased
187 abundant in four, three, two, one and one article, respectively [26,27,35,36]. The genus *Parvimonas,*
188 which belongs to this family as well, was increased in relative abundance in diabetic individuals
189 compared to non-diabetics only in the elderly cohort [39]; while its relative abundance was

190 increased in the diabetic cohort compared to the diabetic plus hypertension cohort [28]. Lastly,
191 three studies reported increased relative abundance of *Escherichia* (*Escherichia-Shigella),* a well-
192 known genus causing urinary tract infections (UTI), which was related to poor glycaemic control and
193 in two studies this genus was related to urinary symptoms or pyuria in urine (even though
194 individuals did not have an active UTI) [32,35,41].

195 Taxonomic classification of bacteria identified in selected studies was updated according to Genome
196 Taxonomy Database release 220 (https://gtdb.ecogenomic.org/) at higher taxonomical levels (e.g.
197 phylum) but at lower levels was maintained to preserve clarity of the conclusions. For the most
198 accurate taxonomic annotation refer to details in **S6 Table**.

199 **Table 1: Characteristics and results of selected studies.**

Article	Coun-try	Total adult	Healthy vs diabetic adults	Age: mean ± SD	Context	Indexes results in diabetic individuals	Main findings and/or differences in relative abundance of diabetic individuals in urine	Other significant details or relevant information
Case-control studies with controls and diabetic individuals								
[34]	China	30	0 vs 15	Kidney stones and T2DM: 56 ± 11 Kidney stones alone: 55 ± 12	Urinary microbiota in the renal pelvis of patients with kidney stones plus T2DM and those with kidney stones alone	No differences in richness (Chao index) ↑ α- diversity (Shannon index) β-diversity: the group with kidney stones alone and with kidney stones and T2DM clustered and could be differentiated	↑*Sphingomonas* ↑*Propionibacterium* ↑ *Corynebacterium* ↑ *Cellulosimicrobium* ↑ *Methylophilus* ↑ *Lactobacillus* ↑ *Enhydrobacter* ↑ *Chryseobacterium* ↑ *Haemophilus* ↑ *Allobaculum*	The relative abundance of *Enhydrobacter, Chryseobacterium,* and *Allobaculum* genera exhibited correlations with fasting blood glucose and HbA1c values.
[42]	Italy	75	25 vs 50	H males: 62 ± 7 H females: 57 ± 6 T2DM males: 65 ± 9 T2DM females: 64 ± 10		No differences in richness or α-diversity (observed species, Chao, and Shannon indexes)	NS [Statistical differences in prevalence (males and females): *Bifidobacterium breve, Corynebacterium pyroviciproducens, Lactobacillus gasseri* , and *Streptococcus agalactiae* were more prevalent in healthy controls. *Campylobacter ureolyticus, Corynebacterium coyleae, Corynebacterium glucuronolyticum, Enterococcus faecalis, Escherichia coli, Lactobacillus iners, Peptoniphilus grossensis,* and *Veillonella atypica* were more prevalent in T2DM individuals]	Total bacterial load and the abundance of total Bacillota were found to be elevated in patients with diabetes compared with the healthy control group, this was also true for females but not males. *Actinotignum schaalii, Bifidobacterium scardovii, Facklamia hominis, Negativicoccus succinicivorans,* and *Peptoniphilus lacrimalis* were less prevalent in T2DM males. *Aerococcus christensenii, Anaerococcus hydrogenalis, Brevibacterium ravenspurgense, Corynebacterium aurimucosum, Gardnerella vaginalis, Mobiluncus curtisii, Prevotella buccalis, Prevotella colorans,* and *Veillonella montpellierensis* were more prevalent in T2DM females whereas *Facklamia ignava* and *Winkia neuii* were less prevalent in T2DM females.

[31]	China	34	15 vs 19	H: 44 ± 8 T2DM: 60 ± 9	T2DM with diabetic kidney disease	↓ α - diversity in T2DM (Shannon and Simpson indexes)	↓Bacillota ↓ Bacteroidota ↑ Pseudomonadota ↑Acidobacteriota	Clinical characteristics between H and T2DM differed significantly in age; BMI; SBP; urea; uric acid; creatinine; natriuretic peptide; HbA1c (all ↓in H); and HDL and albumin (both ↑ in H). HbA1c was positively correlated with Acidobacteria and eGFR was positively correlated with Bacillota, Clostridiales, Clostridia, *Lactobacillaceae* and *Lactobacillus*.
[43] [£]	South Korea	691	368 vs 164	59 ± 6 (average of all groups and periods)	4-year longitudinal study of sequencing extracellular microbial vesicles. Also, 164 prediabetics and 35 people transitioned	↓ α - diversity (Shannon index) in all groups (possible effect of aging)	↓ unclassified *Lachnospiraceae* GU174097_g	Low abundance of GU174097_g was a risk factor for T2DM development, and it was associated with T2DM progression. GU174097_g decreased ketone bodies levels; and thus reduced HbA1c levels.
[37] [Ω]	Czech Repu-blic	58	0 vs 14	65 ± 14 (all)	Catheterized urine samples from men collected under anesthesia from the bladder prior to urological surgery. 14 individuals had diabetes (36 did not have diabetes and for 8 it was unknown)	↓richness (OTUs, ACE and iChao2 indexes) ↓ α - diversity (Shannon and Simpson indexes) β - diversity was no different	No statistical differences of specific taxa between T2DM and non-T2DM individuals	Lower richness was also associated with: (1) ≥75 years; (2) High cholesterol and/or hyperlipidemia; (3) antibiotic prophylaxis. Smokers had higher α - diversity. No significant differences in α - diversity for hypertension or CKD. β – diversity was different between individuals with (1) CKD vs no CKD; (2) severe vs mild urinary symptoms; and (3) antibiotic prophylaxis vs without
[40] [¥]	Turkey	60	15 vs 15	H: 42 ± 11 Obese: 42 ± 9 Pre-DM: 50 ± 9 T2DM: 54 ± 8	T2DM, prediabetic (n=15), obese (n=15) and H groups	NS	↓ *Bifidobacterium* (same was observed for obese and prediabetics)	Clinical features statistically different: FBG between all groups; HbA1c between all groups except for H and obese individuals; BMI between all groups except for prediabetics and both obese and T2DM. Age was significantly lower in both H and obese vs T2DM individuals. Triglycerides and HDL were significantly lower in H vs both prediabetics and T2DM individuals
[36]	United States	136	49 vs 87	H: 51 ±11 T2DM: 51 ± 11	Females with T2DM	β – diversity: Both H and T2DM clustered in 4-5 urotypes Urotypes in T2DM:	↑ *Lactobacillus* ↓ *Corynebacterium* ↓ *Staphylococcus* [T2DM differences in presence/absence:	H and T2DM groups differed significantly in FBG and HbA1c (both ↓in H). HbA1c was positively correlated with *Lactobacillus* and negatively associated with *Prevotella* and *Corynebacterium* in all cohort; and

						Lactobacillus and *Enterobacteriaceae* vs H females: *Gardnerella* and mixed	*Lactobacillus* was more present while *Corynebacterium, Anaerococcus, Finegoldia* and *Peptoniphilus* were less present]	negatively associated with *Prevotella* also in the T2DM group. Prevalence of *Lactobacillus* increased with weight; and most of participants were obese.
[35]	China	58	26 vs 32	H: 58 ± 9 T2DM: 57 ± 8	Females H and T2DM. T2DM microbiota were also assessed for lower urinary symptoms and levels of HbA1c	Richness and α – diversity were no different (OTUs, observed species, Chao, ACE, Shannon and Simpson indexes) β - diversity was different between H and T2DM	↑ *Escherichia-Shigella* ↑ *Klebsiella* ↑ *Aerococcus* ↑*Delftia* ↑*Enterococcus* ↑*Alistipes* ↑*Stenotrophomonas* ↑ *Micrococcus* ↑ *Deinococcus* ↓ *Gallicola* ↓*Arcobacter* ↓*Arcanobacterium* ↓*Kocuria* ↓ *Murdochiella* ↓ *Solitalea* ↓ *Peptoniphilus*	FBG was ↑ in T2DM compared to H group. HbA1c was ↑ in T2DM with urinary symptoms vs T2DM without. The diabetic group with urinary symptoms (compared to the group without) had lower richness, different β – diversity; and: ↑*Escherichia-Shigella* ↑ *Campylobacter* ↑ *Megasphera* ↓ *Prevotella* ↓ *Dialister* ↓ *Anaerococcus* ↓ *Fusobacterium* ↓ *Prevotella_6,* ↓ *Mycoplasma* ↓ *Peptoniphilus* ↓ *Porphyromonas* ↓ *Fodinicola* ↓ *Brevundimonas* The diabetic group with high HbA1c compared to the diabetic low HbA1c group had lower α – diversity, different β – diversity, and: ↑*Escherichia-Shigella* ↑ *Lactobacillus* ↓ *Prevotella* ↓ *Campylobacter* ↓ *Dialister* ↓ *Anaerococcus* ↓ *Peptoniphilus* ↓ *Porphyromonas* ↓ *Fodinicola*
[39]	China	100	50 vs 50	Elderly: 72 ± 7 Non-old: 50 ± 8	Elderly vs non-elderly cohorts. Half of the females of each cohort had T2DM	↓ richness (OTU and Chao indexes) in elderly with T2DM No differences in α - diversity (Shannon and Simpson indexes) between the	Elderly with T2DM (compared to elderly without): ↓ *Nitrospirae* ↓ *Odoribacter* ↓*Aeromonas*	T2DM females treated with metformin. *Lactobacillus* had a decreased trend in T2DM patients with FBG > 10 mmol/l. *Lactobacillus iners* was not associated

						elderly with and without T2DM	↓*Clostridium* ↓*Enterobacter* ↓*Butyricimonas* ↓*Enterococcus* ↓ *Erwinia* ↓ *Fusobacterium* ↓ *Klebsiella* ↓ *Lachnobacterium* ↓*Stenotrophomonas* ↓*Phascolarctobacterium* ↑*Eggerthella* ↑ *Parvimonas* ↑*Bdellovibrio* ↑*Hydrogenophaga* ↑***Lactobacillus iners***	with FBG. Elderly related differences: (1) relative abundance of Bacillota (Firmicutes) increased with BMI; (2) relative abundance of Bifidobacteria was negatively correlated with age; (3) *Lactobacillus* decreased with age but was not associated with pH; (4) ↑ abundance of *Sphingobium* and *Bosea;* and (5) ↓ abundance of *Sneathia; Geobacillus; Shuttleworthia; Bacillus; Gemella; Bdellovibrio; Hydrogenophaga; Proteus; Novosphingobium.*
[26]	China	140	70 vs 70	Matched H and T2DM individuals. 70% > 56 years or older; only 8% younger than 45 years	Authors matched individual characteristics between the H and the T2DM groups	↓ richness (number of OTUs, observed species, ACE and Chao1 indexes) ↓ α-diversity (Shannon index)	↑ Actinobacteria ↑ *Porphyromonas* ↑ *Flavobacteriales* ↑ *Collinsella* ↓ *Akkermansia muciniphila* ↓ Bacteroidota ↓ *Prevotellaceae* ↓ *Prevotella* ↓*Pseudomonadales* ↓*Peptoniphilus* ↓ *Citrobacter* ↓Actinobacteriota ↓ *Synergistota* ↓*Acinetobacter* ↓*Campylobacter* ↓*Campylobacterales* ↓ *Staphylococcus* ↓ *Anaerococcus* ↓ *Halomonas* ↓ *Finegoldia* ↓ *Streptococcus* ↓*Veillonella* ↓*Clostridium* ↓*Corynebacterium*	Actinobacteria increase was associated with higher BMI; increased FBG and urine glucose. *Akkermansia muciniphila* decrease was associated with FBG and urine glucose. Urine glucose, FBG, urine infections, hypertension and hyperlipidemia were statistically ↑ in T2DM compared to H group. Authors studied hypertension and hyperlipidemia in article by [28]; inflammatory markers in article by (Ling et al. 2017) and the effect on diet in article 7 [29].
[32] Ω	United States	29	8 vs 6	H: 35 ESDR T1DM: 51 ESDR T2DM: 64 (all ESRD: 53)	Transplant ESRD patients. Kidney damage caused by 4 primary diagnoses: other, T1DM, T2DM, and hypertension. 15 individuals had	↓ α-diversity (Shannon and inverse Simpson indexes) ↓ richness (observed species) β-diversity: primary diagnoses had no significant differences in bacterial	↑ *Enterococcus faecalis* ↑ *Enterococcus faecium* ↑ *Enterococcus sp.* ↑ *Escherichia coli* ↑ *Escherichia sp.* ↓ *Cutibacterium acnes* ↓ *Corynebacterium*	↑ Bacillota and ↓Actinobacteria because *Enterococcus* belongs to the former phylum while as *Mobiluncus* belongs to the latter. Both groups had similar folate metabolism (which is the target of trimethoprim-sulfamethoxazole) but

						non-diabetic ESRD. Trimethoprim - sulfamethoxazole was given prophylactically	composition; but all had with the H	↓*Mobiluncus curtisii*	had differences in specific enzymes. Dihydrofolate synthase/folypolygluta-mate synthase was increased in transplant groups.
Studies with diabetic individuals only									
[41]		Taiwan	7	0 vs 7	T2DM No-pyuria: 59 ± 6 T2DM Pyuria: 60 ± 7	All 7 individuals with T2DM and SGLT2 therapy; 3 with pyuria in urine; 4 without	↓ α - diversity in T2DM with pyuria compared with T2DM without pyuria (Shannon index)	↑*Escherichia-Shigella* in individuals with pyuria	7 T2DM individuals with negative standard urine cultures. eGFR stage II (60–89 mL/min) mildly impaired kidney function
[38]		China	30	0 vs 30	T2DM with diabetic peripheral neuropathy: 56 ± 8 T2DM only: 55 ± 7	Among the 30 females with T2DM, 17 females also had diabetic peripheral neuropathy	↓richness in DPN group (OTUs, observed species, ACE and iChao2 indexes) α – diversity was no different (Shannon and Simpson indexes) β – diversity was no different	Group with DPN: ↑ *Mycoplasmataceae* ↓Propionibacteriaceae ↓ Pseudobdellovibrioinaceae ↓Sphingobacteriaceae	T2DM females: 17 with DPN and 13 without. Both groups did not differ in clinical characteristics.
*	[28]	China	70	0 vs 70	T2DM: 56 ± 14 T2DM + hypertension: 70 ± 9 T2DM + hyperlipidemia: 54 ± 11 T2DM + both: 70 ± 10	Only analysis of the T2DM individuals from article 13 that had different clinical features. The T2DM cohort was divided: 28 had T2DM; 24 had T2DM + hypertension; 7 had T2DM + hyperlipidaemia; 11 had T2DM and both hypertension + hyperlipidaemia	↑ richness compared to the hyperlipidemia only group (number of reads and number of OTUs) ↓ richness compared to hypertension groups (number of reads and number of OTUs) No differences in α - diversity (Shannon and Simpson indexes) between the groups	<u>Compared to T2DM + hypertension group, the group **with only** T2DM had:</u> ↑ *Lactobacillus iners* ↑ *Acinetobacter rhizosphaerae* ↑ *Acinetobacter schindleri* ↑*Lactobacillus* ↑*Enterobacter* ↑*Klebsiella* ↑*Shuttleworthia* ↑*Sneathia* ↑ *Parvimonas* ↑*Megasphera* ↑*Erwinia* ↓ *Kocuria palustris* ↓ *Aeromonas* ↓ *Roseburia* ↓ *Ruminococcus* <u>Compared to T2DM + hyperlipidemia, the group **with only** T2DM had:</u> ↓ *Faecalibacterium* ↓ *Collinsella* ↓ *Oscillospira* (diagnostic factor to differentiate both groups)	The T2DM cohort was divided: 28 T2DM; 24 T2DM + hypertension; 7 T2DM + hyperlipidemia; 11 T2DM + hypertension + hyperlipidemia. The duration of T2DM was significantly shorter in the two groups without hypertension. The four most abundant bacteria in all groups were Proteobacteria, Bacillota, Bacteroidota and Actinobacteria. The fifth varied from Fusobacteria (inT2DM and T2DM with both conditions), Synergistota (group with hypertension) and Acidobacteria (group with hyperlipidemia). Predominant genera: in T2DM *Lactobacillus, Prevotella,* and *Acinetobacter;* in T2DM + hyperlipidemia *Lactobacillus, Prevotella* and *Halomonas*; in T2DM + hypertension *Prevotella, Streptococcus*, and *Bacteroides*; and in T2DM + hypertension + hyperlipidemia *Prevotella, Lactobacillus* and *Bacillus*.

								<u>Compared to T2DM + hypertension and hyperlipidemia, the group **with only** T2DM had:</u> ↑*Acinetobacter rhizosphaerae* ↑ *Shuttleworthia* ↓*Gemella* ↓*Prevotella* <u>Compared to T2DM + hypertension and hyperlipidemia, the group with T2DM + hyperlipidemia had:</u> ↑*Acinetobacter rhizosphaerae* ↑*Faecalibacterium* <u>Compared to T2DM + hypertension, the group with T2DM + hyperlipidemia had:</u> ↑ *Klebsiella* ↑ *Novosphingobium* ↑ *Lactobacillus* ↑ *Enterobacter* <u>The two groups with hypertension did not show differences</u>	The groups with hypertension had presence of *Eggerthella lenta* but this species was absent in the group with only diabetes; while *Gardnerella* was absent in the hyperlipidemia group but it was present in the other groups. Several bacteria correlated with FBG, blood pressure and lipidic profiles. *Atopobium* was positively correlated with FBG in the T2DM group. *Allobaculum* and *Odoribacter* were negatively correlated with diastolic pressure in the hypertension and hypertension plus hyperlipidemia groups, respectively. *Rikenella* and *Dorea* were positively correlated with triglycerides in the hyperlipidemia group and with LDL in the hypertension plus hyperlipidemia group, respectively.
*	[27]	China	70	0 vs 70	T2DM with IL-8 in urine: 66 ± 14 T2DM without IL-8 in urine: 59 ± 11	T2DM females whose levels of IL-8 were evaluated. IL-8 is a potential biomarker for diagnosing of urinary infections	α – diversity was no different between T2DM females with and without IL-8 in urine (Shannon and Simpson indexes) β-diversity: the group with Il-8 and without IL-8 in urine clustered together and could be differentiated	T2DM females without IL-8: ↓*Bifidobacteriaceae* ↓*Shuttleworthia* ↓ *Thermales* ↓ *Streptococcus anginosus* ↓ *Acinetobacter rhizosphaerae* ↓ *Acinetobacter schindleri* ↓ *Lactobacillus iners* ↓ *Akkermansia muciniphila* ↓ *Mobiluncus* ↓ *Peptoniphilus* ↓ *Corynebacterium* ↓ *Gemella* ↓ *Enterococcus* ↓ *Geobacillus* ↑ *Prevotella copri* ↑ *Prevotella stercorea* ↑*Bacteroides uniformis* ↑*Coprococcus eutactus* ↑ *Faecalibacterium*	*Ruminococcus* was positively associated with urinary IL-8. Urinary IL-8 was high in T2DM patients with ↑ *Pseudomonas* and ↑ *Klebsiella*. Clinical features between the T2DM with IL-8 and without IL-8 in urine differed in age, BMI and pH, white blood cells, leukocyte esterase, protein, glucose, and nitrites in urine (all characteristics ↑ in the group with IL-8)

								↑ *Megamonas* ↑ *Comamonas* ↑*Pseudomonas* ↑*Phascolarctobacterium*	
* ♂	[29]	China	140 ♂	70 vs 70	Matched H and T2DM individuals. 70% > 56 years or older; only 8% younger than 45 years	T2DM association with urinary IL-8 and evaluation of the effect of diet on urinary microbiota	NS	NS	*Ruminococcus* was positively associated with urinary IL-8 (results from Ling et al. 2017). Water weakened the positive relationship between *Ruminococcus* and IL-8 in urine while fiber, vitamin B3 and vitamin E enhanced the positive relationship.
Case-control studies with individuals that have kidney or renal disease									
[30]		Portu-gal	46	0 vs 14	57 ± 11	All individuals with CKD and on peritoneal dialysis; the rest had other comorbidities	↓ α - diversity (Shannon index) as CKD-PD worsened (independently of the cause)	↓*Atopobium* ↓ *Dermabacter* ↓*Gardnerella*	Apart from diabetes in CKD patients, significance was found for sex: *Lactobacillus* linked to females; *Staphylococcus* and *Anaerococcus* to males.
[33]		United States	77	23 vs 54	Males: 77 ± 8 Females: 71 ± 8	All individuals with CKD but no dialysis (70% of them with diabetes)	↓ α - diversity (Shannon index) as CKD worsened (independently of cause). Richness and α – diversity were no different between diabetic and non-diabetic CKD individuals (Chao; Inverse Simpson and Shannon indexes).	NS	Richness and α – diversity were no different by age or obesity status. β – diversity: Different urotypes. Urinary incontinence and ↑ eGFR was associated with ↑ α-diversity.

BMI = body mass index; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end stage renal disease; FBG = fasting blood glucose; H = healthy controls; HbA1c = glycosylated haemoglobin; IL-8= interleukin 8; NS = Not stated; OTU = operational taxonomic unit; PD = peritoneal dialysis; SBP = systolic blood pressure; (TX)DM = (type X = 1 or X = 2) Diabetes mellitus; SD = standard deviation; vs = versus; * = studies that used data from participants/cohort of article 13 authored by Liu et al. 2017 [26]; £ = sequencing of microbiota extracellular vesicles; ¥ = primers for phylum Firmicutes; and genera *Bacteroides* and *Bifidobacterium;* Ω = some or all individuals used antibiotic prophylaxis. ♀ = only females; ♂ = only males; ↓ = lower; ↑ = higher.

207 # 4. Discussion

208 This study has assessed the urinary microbiota related to diabetes and diabetes-related
209 kidney diseases through a systematic review. This work has summarised statistically significant
210 results reported by selected studies with a threshold of $p \leq 0.05$. The main findings of this study
211 were: (1) a decreased richness and α-diversity in urinary microbiota in individuals with diabetes
212 compared to healthy controls; (2) α-diversity was not different within diabetic individuals, except if
213 they showed urinary symptoms (e.g. urgency to pee) although they did not have a (diagnosed)
214 urinary infection; (3) α-diversity decreases with the evolution of kidney disease independently of
215 the primary cause (e.g. kidney disease primarily caused by diabetes or hypertension or other
216 pathology); (4) β-diversity urinary microbiota composition between healthy controls and diabetic
217 individuals results were conflicting between studies and may depend on the stage of the disease
218 and/or the grade of kidney damage; (5) patients with T2DM shared the depletion of *Peptoniphilus,*
219 *Anaerococcus, Finegoldia* and *Gallicola* (all formerly part of the genus *Peptostreptococcus* and inside
220 the *Peptoniphilaceae* family), or *Lachnospiraceae* that are butyrate-producing bacteria; (6) patients
221 with diabetes shared the enrichment of pro-inflammatory microbes such as Pseudomonadota
222 (formerly Proteobacteria) and of bacteria of order Lactobacillales such as *Lactobacillus* or
223 *Enterococcus*; (7) cohort sizes were small (from a few samples to more than one hundred) and the
224 only one study that was large (nearly seven hundred samples) had data restricted to extracellular
225 microbial vesicles; (8) except in two studies, voided midstream urine samples were analysed and
226 those are often referred as urogenital samples due to likely cross-contamination with skin or
227 genitalia microbiota during collection; and, (9) although data showed similar trends, some bacterial
228 phyla, families, and genera had controversial results, probably due to the lack of resolution of these
229 studies using 16S sequencing.

230 One of the main findings of this systematic review is the depletion of the family *Peptoniphilaceae* in
231 urine of T2DM patients as a trend. The most relevant genera of this family for the urobiome being
232 *Peptoniphilus*, *Anaerococcus, Finegoldia, Murdochiella, Parvimonas* and *Gallicola*. These genera are

233 gram-positive obligate anaerobic cocci that have been described as producers of short-chain fatty
234 acids such as butyrate (*Peptoniphilus*, *Anaerococcus,* and *Gallicola*) and acetate (*Peptoniphilus,*
235 *Parvimonnas, Gallicola* and *Finegoldia)* or lactate *(Murdochiella)* [44]. *Parvimonas* increased in
236 relative abundance in diabetic individuals compared to non-diabetics only in the elderly cohort [39];
237 while its relative abundance was increased in the diabetic cohort compared to the diabetic plus
238 hypertension cohort [28]. In the latter, if diabetes is accompanied by other factors such as
239 hypertension, there is decreased abundance of this genus pointing to a depletion as the health
240 status worsens. *Peptoniphilus* and *Anaerococcus* abundance may be associated to glycosylated
241 haemoglobin HbA1c as diabetic individuals with high HbA1c had decreased relative abundance of
242 these two genera in urine compared to diabetic individuals with low HbA1c [35]. Generally, adults
243 with diabetes and/or chronic kidney disease show lower abundance of short-chain fatty acids
244 producing bacteria in the gut compared to healthy controls [4,45]. This systematic review reveals
245 that diabetic individuals have similar trends in their urinary and urogenital microbiota with lower
246 relative abundance of short-fatty acid butyrate-producing bacteria of the family *Peptoniphilaceae*.
247 Butyrate is the main source of colonocyte metabolism, it is an enhancer of the integrity of the
248 epithelium, and it decreases inflammation in the mucosa while promoting electrolyte absorption in
249 the gut [46]. Moreover, dissociated butyric acid has an antibacterial effect [46] and butyryl-CoA
250 regulates transcription and modifies proteins [46,47]. We hypothesize that butyrate could also
251 promote epithelium integrity and reduce inflammation in the urinary tract. Hence, depletion of
252 butyrate-producing bacteria such as *Peptoniphilus*, *Anaerococcus,* and *Gallicola* in diabetic
253 individuals could induce inflammation and contribute to the high onset of urinary infections in
254 diabetic individuals in the urinary tract and induce inflammation in the renal blood vessels which
255 could worsen kidney disease. This theory will need further studies to be tested, and it could help to
256 understand if these molecules could be used to improve urinary functionality in association with
257 diabetes and kidney disease.

258 Higher relative abundance of *Lactobacillus* associated with diabetes was a common trend of this
259 systematic review. *Lactobacillus* have been described as a genus that is common in the urobiome of
260 females and whose difference between females and males has been attributed to the hormone
261 oestrogen, which plays a crucial role in glycogen production [11,48]. Oestrogen fluctuations with age
262 and menopausal status may affect the female urobiome [49], as the genus *Lactobacillus* metabolizes
263 glycogen, and as a byproduct of it there is lactic acid which acidifies the environment modulating the
264 growth of other bacteria [11]. The acidic environment has been assumed significant for the
265 protective role that lactobacilli play in both the vaginal and urinary microbiomes of women [9,48].
266 However, the genus *Lactobacillus* seems to be more abundant in the urine of diabetic individuals
267 according to this systematic review. In line with these findings, history of diabetes was associated
268 with increased odds of growing Lactobacilli when using expanded quantitative urine culture in
269 catheterised urine of women [50]. *Lactobacillus iners*, which has been described as a transitional
270 species that colonizes the vagina after an ecological disturbance [51], was found enriched in the
271 urine of T2DM females [28,39] and in the same cohort with higher levels of inflammatory
272 interleukin-8 in urine [27]. Other species of this genus such as *Lactobacillus crispatus* and
273 *Lactobacillus gasseri* have been associated with lack of lower urinary tract symptoms and lack of
274 urgency urinary incontinence, respectively; and levels of *Lactobacillus* in the vagina are reported to
275 be associated with menopausal status and with reduced risk of UTI [36]. Although lactobacilli have
276 generally been considered beneficial and the normal microbiota of the urobiome and vagina, there is
277 increasing evidence that some *Lactobacillus* spp. may be pathogenic or related to urinary symptoms
278 [52,53]. The association between the different species of *Lactobacillus* and their role in T2DM needs
279 further investigation, considering that age, oestrogen, HbA1c and/or BMI could also be important
280 factors affecting the abundance of this genus. In this context, HbA1c was positively correlated with
281 *Lactobacillus.* Individuals with T2DM and high HbA1c had higher abundance of this genus compared
282 to those with T2DM and low HbA1c levels [35,36]. Another point to consider is that the genus
283 *Lactobacillus* is naturally resistant to widely used antibiotics and T2DM individuals often have

284 multiple infections that require the use of them [35]. Thus, we could hypothesize that antibiotic
285 therapy may imbalance the urobiome allowing *Lactobacillus* to grow excessively which may induce
286 inflammation.

287 Diabetic, prediabetic and obese individuals had lower abundance of the genus *Bifidobacterium* in
288 urine; and the abundance of this genus was negatively correlated with age [39,40]. In this line, T2DM
289 patients with hyperlipidemia lacked *Bifidobacterium* (former *Gardnerella*) [28]. This was also true for
290 the former genus *Gardnerella,* that is now included in the genus *Bifidobacterium,* that have
291 decreased abundance in CKD patients with diabetes [30]. *Bifidobacterium* (*Gardnerella*) was a
292 common urotype in healthy females compared to diabetic females that had *Lactobacillus* or
293 *Enterobacteriaceae* urotypes [36]. *Bifidobacteriaceae* had decreased relative abundance in diabetic
294 females without interleukin-8 in urine in the study by Ling et al; but this group had also lower age
295 and BMI compared to the group with interleukin-8 [27]. These results may imply that diabetes but
296 also age, BMI or levels of interleukin-8 could influence the relative abundance of *Bifidobacterium* in
297 urine [27].

298 The role of the genus *Prevotella* in the urinary microbiota is unclear. Although HbA1c was negatively
299 correlated with *Prevotella* in T2DM patients [36] and Chen et al. reported a decrease of this genus in
300 individuals with diabetes with high urinary symptoms [35], other studies have found that this genus
301 was more prevalent in T2DM [42] or that urotypes and enrichment of *Prevotella* was associated with
302 urinary incontinence patients [12,54]. Therefore, similarly to findings with the genus *Lactobacillus,*
303 we will likely need higher resolution studies, preferably shotgun metagenomics, to identify which
304 species or strains of these genera may play different roles in the urobiome.

305 UTIs are common in diabetic patients and are associated with poor glycaemic control, which
306 compromises kidney function and impairs quality of life [55]. That is why many selected articles also
307 examined urinary symptoms, as hospitalization for UTIs caused by diabetes is more than twice as
308 common as hospitalizations for UTIs caused by other factors. The use of sodium–glucose

309 cotransporter 2 inhibitors as therapy for diabetes may contribute as these drugs reduce glucose
310 reabsorption, thus lowering the level on blood, but causing glycosuria in urine which could increase
311 the risk of UTIs in those patients [56]. Hyperglycaemia and diabetes has been shown to reduce
312 psoriasin and occludins levels in the urinary tract leading to be more prone to urinary tract infections
313 [19]. Moreover, psoriasin is an antimicrobial peptide with a broad protective role against *Escherichia*
314 *coli* and *Enterococcus* urinary infections, two of the most common pathogens causing UTI in
315 diabetics [19]. In addition, low-grade inflammation with higher concentration of proinflammatory
316 cytokines and the depletion of producers of short-chained fatty acids such as butyrate, which has
317 beneficial effects on the host [57], may affect mucosa integrity, bacterial translocation and host–
318 urine microbiota interactions in T2DM patients.

319 The results of this systematic review have also highlighted that urinary microbiota diversity seems
320 lower in CKD or ESRD and it drops as the disease progresses independently of the primary cause
321 [30,33]. Diabetes progression to kidney damage reduces eGFR and as eGFR declines the excretion of
322 uromodulin follows the same trend. Uromodulin, an urinary antimicrobial peptide whose function is
323 to stick to bacteria forming larger particles which enhance their excretion by the kidney, is produced
324 exclusively in the renal tubules and is affected by the decline of renal function [33] which may also
325 influence bacterial growth, microbiota diversity and risk of UTI.

326 4.1 Strengths and limitations

327 To our knowledge, this review represents the first comprehensive analysis of the current
328 understanding of the urobiome, specifically the urinary microbiota, in the context of diabetes. One
329 notable strength of this review is the identification of emerging trends within the urobiome across
330 multiple studies where the majority had low risk of bias assessment. For instance, this is the first
331 article to highlight the significance of the *Peptoniphilaceae* family within the urobiome of diabetic
332 individuals, which has frequently been reported as less prevalent or reduced in relative abundance

333 in urine of diabetic individuals. Additionally, this work is strengthened by its systematic approach,
334 adhering to PRISMA and PROSPERO guidelines, ensuring standardized and reproducible results.

335 However, we also recognize some limitations. First, we were unable to perform meta-analyses due
336 to the considerable heterogeneity of the included studies and the small sample size in most of them.
337 Second, the included studies have some methodological limitations such as the collection method of
338 the urine, the small sample size of the studies, being the vast majority cross-sectional, and mostly
339 they processed samples using 16S sequencing. Only two studies analysed catheterized urine,
340 reflecting the microbiota of the bladder or renal pelvis, while most of the studies relied in voided
341 midstream collection techniques that may also capture microbiota from the genitalia or skin (Linda
342 Brubaker et al., 2021). Since most studies employed 16S sequencing, the resolution of the results is
343 limited and there may be discrepancies depending on the region sequenced (most of them used the
344 V3-V4 region or only the V4 region of the 16S rDNA gene). This limitation means that the same
345 genera identified across different studies could refer to distinct bacterial species, potentially
346 explaining some discrepancies in the findings. Moreover, microbial taxa such as fungi or small
347 prokaryotic taxa that may also contribute to the urobiome community are often not captured in
348 these studies, as they must sequence the eukaryotic 18S rDNA gene. Another limitation is the
349 evolving taxonomical classification of bacteria. Taxonomic reclassification may have occurred since
350 the original articles were published. Where possible, we have updated higher-level classifications
351 (e.g., from Firmicutes to Bacillota) while maintaining the original nomenclature at lower levels to
352 preserve the clarity of the conclusions (e.g., *Gardnerella* instead of *Bifidobacterium*). For the most
353 accurate taxonomic annotation, we refer readers to the Genome Taxonomy Database release 220
354 (https://gtdb.ecogenomic.org/), with detailed information provided in **S6 Table**. Therefore, the
355 generality of these findings may be treated as trends, with caution, and these hypotheses should be
356 tested in larger size studies and analysed using high resolution shotgun sequencing.

357 # 5. Future perspectives

358 There are significant knowledge gaps regarding the role and impact of the urobiome in both
359 health and disease. This an emerging field that has attracted increasing attention in recent years, but
360 the influence of the urobiome on conditions such as diabetes and diabetic kidney disease remains
361 largely unexplored. While this systematic review has identified common trends across studies—such
362 as the depletion of *Peptoniphilaceae* and the increased abundance of *Lactobacillus* in the urine of
363 diabetic adults—the evidence remains insufficient due to the small sample sizes of most studies and
364 the limited resolution provided by 16S sequencing.

365 To advance urobiome research, large-scale population-based studies are urgently needed, along
366 with the application of higher-resolution techniques like shotgun metagenomics to more precisely
367 characterize the urinary microbiome. Longitudinal studies will also help to understand the changes
368 in the urinary microbiome in diabetes and diabetic kidney disease progression, including the role of
369 the urobiome in early stages of diabetes development. These approaches could identify generalized
370 results including specific microbial species that play critical roles in maintaining a healthy urobiome,
371 as well as those involved in the onset and progression of diseases such as diabetes and conditions
372 affecting kidney function. In the future, the applicability of this knowledge may help us to investigate
373 the influence of diet on the urobiome in diabetes and the potential for probiotics, postbiotics or
374 other interventions to modulate the urobiome in relation to diabetes and diabetic kidney disease.

375 **Supplementary information:** The supplementary files include one file with S1 to S6 tables with the
376 following captions, and another file with S7 Table which includes all documents retrieved in this
377 search.

378 **S1 Table: Details of the databases and search strategy used in this systematic review.**
379 **S2 Table: Main characteristics of selected studies.**
380 **S3 Table: Quality and risk of bias assessment of selected studies based on Cochrane and NHLBI.**
381 **S4 Table: Specific diversity, evenness and richness indexes used in selected studies.**

S5 Table: Characteristics and results of selected studies.

S6 Table: Taxonomic classification of bacteria identified in selected studies according to GTDB release 220.

A separate file contains:

S7 Table: Original records retrieved from Pubmed, SCOPUS, MEDLINE-Ovid, EMBASE, Web of Science and Cochrane Central Register of Controlled Trials databases.

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406 **Data Availability Statement:** Data presented and gathered in this systematic review are fully shown

407 in this manuscript or in the supplementary information including the full record retrieval in S7 Table.

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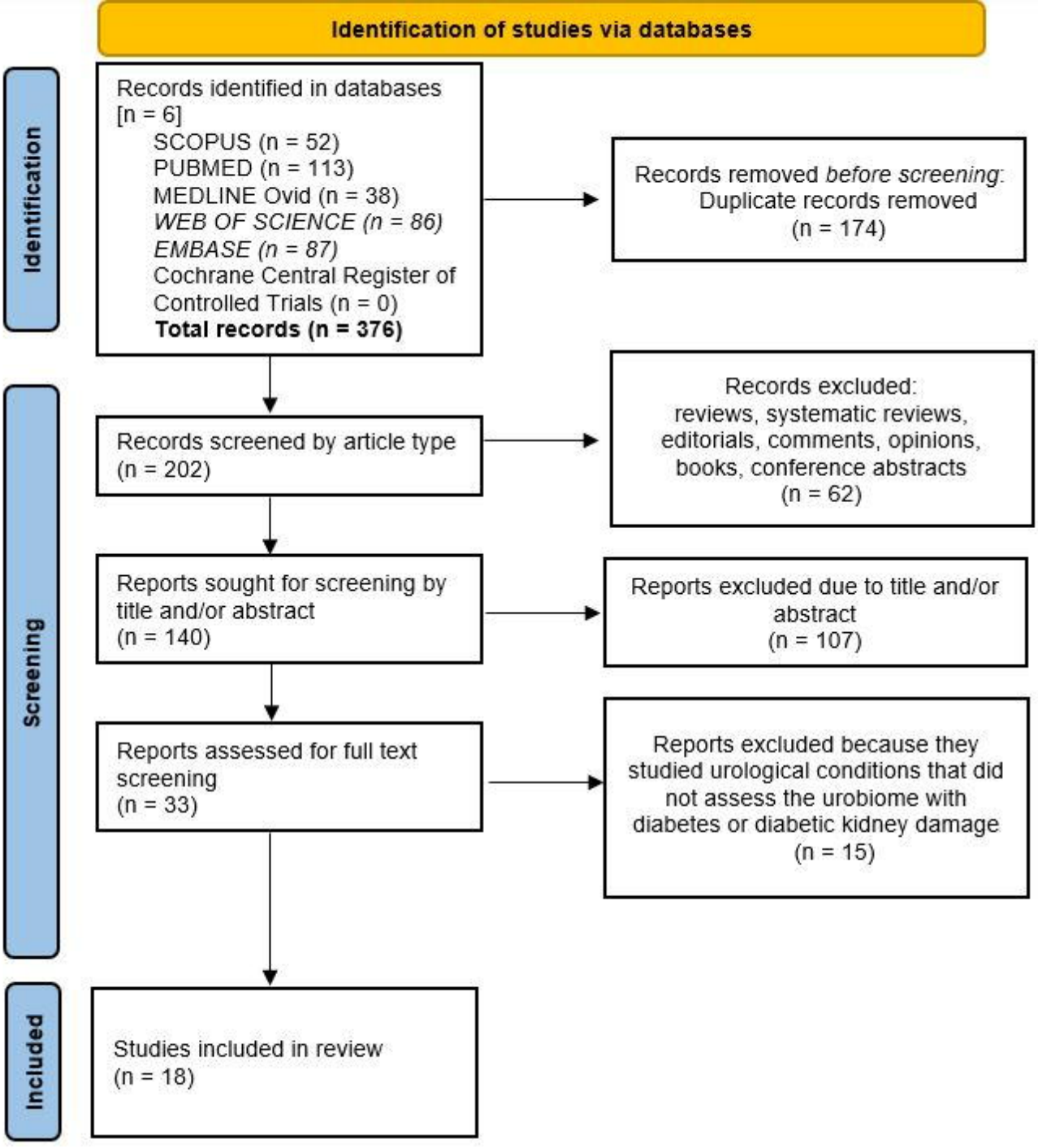
Identification of studies via databases
Identification
Records identified in databases
[n = 6]
SCOPUS (n = 52)
PUBMED (n = 113)
MEDLINE Ovid (n = 38)
WEB OF SCIENCE (n = 86)
EMBASE (n = 87)
Cochrane Central Register of Controlled Trials (n = 0)
Total records (n = 376)
Records removed before screening:
Duplicate records removed
(n = 174)
Screening
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(n = 202)
Records excluded:
reviews, systematic reviews, editorials, comments, opinions, books, conference abstracts
(n = 62)
Reports sought for screening by title and/or abstract
(n = 140)
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(n = 107)
Reports assessed for full text screening
(n = 33)
Reports excluded because they studied urological conditions that did not assess the urobiome with diabetes or diabetic kidney damage
(n = 15)
Included
Studies included in review
(n = 18)