# Meta-Analysis of the Significance of Asymptomatic Bacteriuria in Diabetes

MARJO RENKO, MD, PHD
PÄIVI TAPANAINEN, MD, PHD
PÄIVI TOSSAVAINEN, MD, PHD
TYTTI POKKA, BSC
MATTI UHARI, MD, MSC

**OBJECTIVE** — To evaluate whether asymptomatic bacteriuria (ASB) is more common in patients with diabetes than among control subjects. In addition, we wanted to clarify the clinical significance of ASB in patients with diabetes.

**RESEARCH DESIGN AND METHODS** — We conducted a systematic review and meta-analysis of published data since 1966. Twenty-two studies fulfilled the inclusion criteria of the meta-analysis.

**RESULTS** — ASB was present in 439 of 3,579 (12.2%) patients with diabetes and in 121 of 2,702 (4.5%) healthy control subjects. ASB was more common both in patients with type 1 diabetes (odds ratio 3.0 [95% CI 1.1–8.0]) and type 2 diabetes (3.2 [2.0–5.2]) than in control subjects. The point prevalence of ASB was higher in both women (14.2 vs. 5.1%; 2.6 [1.6–4.1]) and men (2.3 vs. 0.8%; 3.7 [1.3–10.2]) as well as in children and adolescents (12.9 vs. 2.7%; 5.4 [2.7–11.0]) with diabetes than in healthy control subjects. Albuminuria was more common in patients with diabetes and ASB than those without ASB (2.9 [1.7–4.8]). History of urinary tract infections was associated with ASB (1.6 [1.1–2.3]).

**CONCLUSIONS** — We were able to show that the prevalence of ASB is higher in all patients with diabetes compared with control subjects. We also found that diabetic subjects with ASB more often had albuminuria and symptomatic urinary tract infections.

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As the prevalence of both type 1 diabetes and type 2 diabetes increases world wide, factors associated with diabetes and its complications become more important (1,2). Asymptomatic bacteriuria (ASB) refers to the presence of bacteria in bladder urine in an asymptomatic individual. Usually, samples are collected indirectly by clean-voided midstream urine, and growth of the same uropathogen ($\geq 10^5$ cfu/ml) in two consecutive specimens is considered to be a significant indication of the presence of bacteria in bladder urine (3). ASB is found in 2–5% of healthy adult women, is quite unusual in healthy men, and has been claimed to be three to four times more common in women with diabetes than in healthy women (3). A prevalence as high as 30% in diabetic women has been reported (4).

ASB is considered clinically significant and worth treating during pregnancy because treatment effectively reduces the risk of pyelonephritis and preterm delivery (5,6). Although ASB has been found to associate with increased risk of hospitalization for urosepsis in a prospective observational study among women with diabetes (7), the treatment of ASB in one randomized controlled trial did not reduce the risk of symptomatic urinary tract infection (8). Associations between ASB, metabolic control of diabetes, and impaired renal function have been brought up repeatedly (9–15). To evaluate whether ASB is truly more common in patients with diabetes than among control subjects and to clarify the clinical significance of ASB in diabetic subjects we did a systematic literature search and performed a meta-analysis of the published data.

## RESEARCH DESIGN AND METHODS

— We performed a literature search in PubMed for the years 1966–2007 using the following MeSH terms: "asymptomatic bacteriuria" and "diabetes" in order to find all the articles that considered epidemiology, risk factors, and prognosis of ASB in patients with diabetes. Altogether, 112 hits were found. Reviews, commentary articles, and editorials were excluded. On the basis of the title and abstract, 45 articles were found to be original-research articles on the selected topic. All members of the study group read these 45 articles. Studies where ASB was defined as growth of one or two bacteria species for $\geq 10^5$ cfu/ml urine in one or more samples taken from asymptomatic patients were included. After excluding 24 articles in which study design, presentation, or reporting was not adequate, 21 articles were finally accepted and analyzed (Fig. 1). Of the non-English articles, only abstracts in English were reviewed.

We focused on the point prevalence of ASB in diabetic patients and control subjects and the associations of ASB and specific risk and prognostic factors among people with diabetes. Analyses were performed using the Comprehensive Meta-Analysis Program, version 1.0.25. Heterogeneity was assessed and quantified by calculating $I^2$ (inconsistency) values. Without the heterogeneity (test for inconsistency not significant), pooled estimates of odds ratios (ORs) or effect sizes and 95% CIs for the estimates were derived using a fixed-effects model; otherwise, a random-effects model was used (16). The possibility of publication bias was assessed with funnel plots (not shown). The analyses were performed separately for women and men and for patients with type 1 diabetes and type 2 diabetes, whenever possible. The quality of the articles was assessed by all members of the study group, using a scale from 1 to 5, and the summary scoring was then decided after a discussion on the flaws and biases of the study. Because using one figure indicative for the quality of included studies has been shown to be problematic

From the Department of Pediatrics, University of Oulu, Oulu, Finland.
Corresponding author: Marjo Renko, marjo.renko@oulu.fi.
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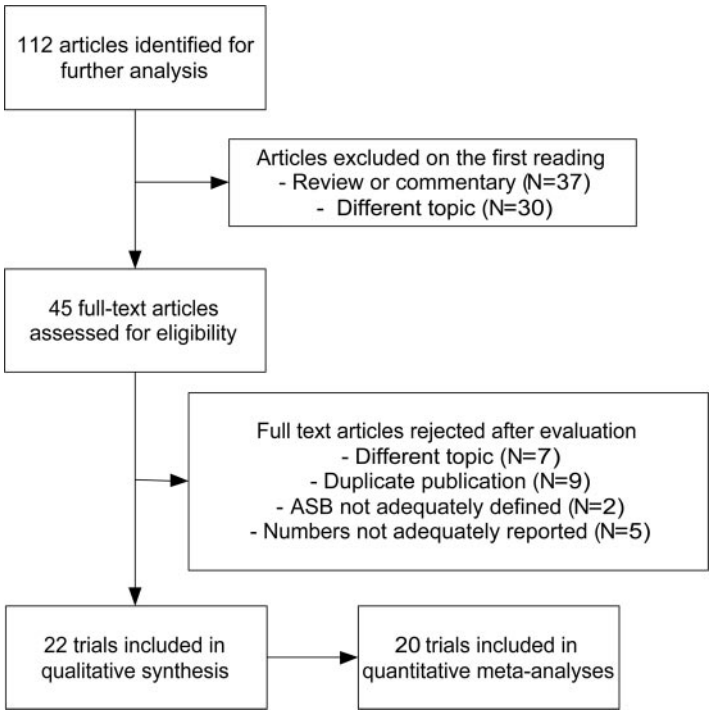


**Figure 1—***Flowchart of the literature search.*

or even misleading, the numbers were not included in the final analyses (17).

**RESULTS** — Twenty-two studies fulfilled the inclusion criteria of the meta-analysis (Table 1). The design was cross-sectional in 16 and follow-up in 5 studies, whereas 10 studies comprised only women. The mean quality score of the studies included in the analyses was 2.6 (range 1–4). The only randomized intervention trial was evaluated separately (8).

In the pooled data, ASB was present in 439 of 3,579 (12.2%) patients with diabetes and in 121 of 2,702 (4.5%) healthy control subjects. ASB was more common in both patients with type 1 diabetes (OR 3.0 [95% CI 1.1–8.0]) and type 2 diabetes (3.2 [2.0–5.2]) than in control subjects. The point prevalence of ASB was higher in both women (14.2 vs. 5.1%; 2.6 [1.6–4.1]) and men (2.3 vs. 0.8%; 3.7 [1.3–10.2]) with diabetes than in healthy control subjects (Figs. 2 and 3). There were only two trials (12,18) that included children and adolescents and comprised 683 subjects and was published by the same study group. In these surveys, ASB was more common in children and adolescents with diabetes (12.9%) than in healthy control subjects (2.7%; 5.4 [2.7–11.0]) (Fig. 4).

The effect of the duration of diabetes on the point prevalence of ASB was reported in four studies (9,10,13,19) all comprising only women. The mean duration of diabetes was longer in patients with ASB than in those without ASB (pooled difference 0.17 years [95% CI 0.03–0.31]; $P = 0.01$). The mean A1C, as a measurement of glycemic control in diabetes, did not differ in diabetic subjects with ASB compared with those without ASB (pooled difference 0.21 [−0.07 to 0.50]; $P = 0.14$).

The mean creatinine level did not differ in diabetic subjects with or without ASB in three cross-sectional surveys (pooled difference 0.21 μmol/l [95% CI −0.3 to 0.8]; $P = 0.36$) (7,11,19). Association of proteinuria and ASB was studied in three trials (10,19,20). Proteinuria, defined as ≥30 mg/24 h in two of the studies and as presence of macroalbuminuria in one study, was more common in patients with diabetes and ASB than those without ASB (OR 2.9 [95% CI 1.7–4.8]; $P < 0.0001$) (Fig. 5).

Renal function was measured with glomerulus filtration rate (GFR) in two studies, both of which included only women with diabetes. In the cross-sectional survey, there was no difference in GFR values between diabetic subjects with and without ASB, but in a 6-year follow-up study the GFR values decreased more in patients with diabetes and ASB than in those without ASB (14 vs. 9%, $P = 0.03$) (9,15). In multivariate analyses adjusted for age, length of follow-up, duration of diabetes, and microalbuminuria at baseline, the difference was no longer sta-

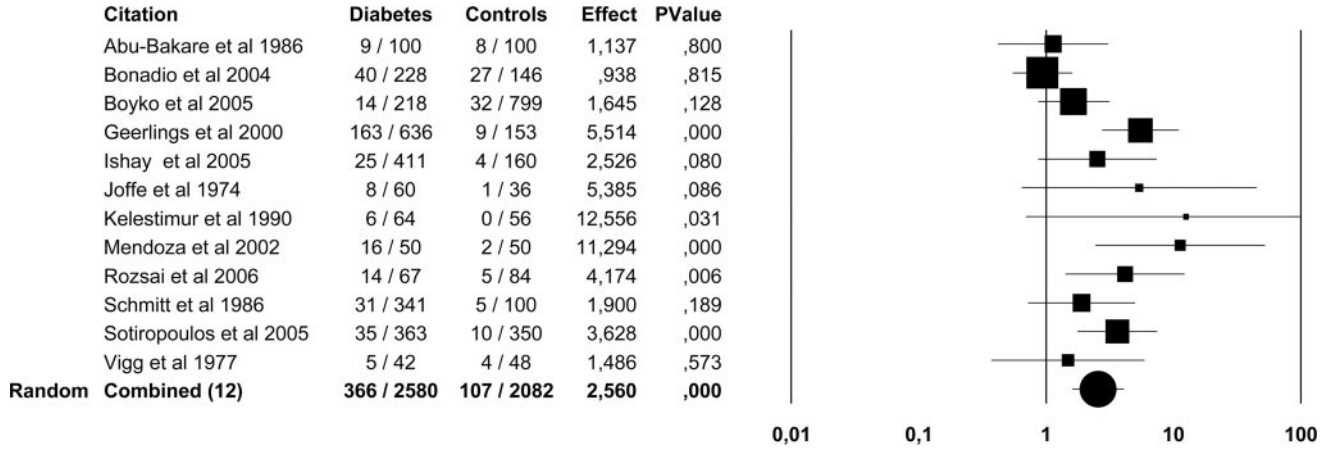


**Figure 2—***Forest plot of 12 studies on the prevalence of ASB in women with diabetes and healthy control subjects. Because of the heterogeneity of the studies (I2 63%,* $P < 0.001$*), the results of the random-effects model are presented.*

**Table 1—*Characteristics of the included studies***

| Reference | Study design | Number of patients (diabetic subjects/ control subjects) | Mean age (years) (diabetic subjects/control subjects) | Patient group and Source (diabetic subjects/control subjects) | Type of diabetes | Outcomes | Language | Quality score (1–5) |
|---|---|---|---|---|---|---|---|---|
| Ishay et al. 2005 (19) | Cross-sectional, controlled | 411/160 | 59.6/53.3 | Only women from a diabetes outpatient clinics | Type 2 diabetes | Prevalence, duration, urinary protein, creatinine, A1C | English | 4 |
| Bonadio et al. 2004 (9) | Cross-sectional, controlled | 228/146 | 57.7/59.0 | Only women from metabolic/cardiology outpatient clinics | Type 1 and type 2 diabetes | Prevalence, duration, A1C, GFR | English | 3 |
| Makuyana et al. 2002 (25) | Cross-sectional, controlled | 123/53 | 51.0/46.0 | Only black race from diabetes outpatient clinics/ outpatient clinics | Type 1 and type 2 diabetes | Prevalence | English | 2 |
| Geerlings et al. 2000 (10) | Cross-sectional, controlled | 636/153 | Not available/ 47.8 | Only women from diabetes outpatient clinics/eye and trauma outpatient clinics | Type 1 and type 2 diabetes | Prevalence, duration, urinary protein, A1C, UTI anamnesis | English | 3 |
| Kelestimur et al. 1990 (26) | Cross-sectional, controlled | 110/100 | Not available | Hospital patients | Type 1 and type 2 diabetes | Prevalence | Turkish | 1 |
| Schmitt et al. 1986 (27) | Cross-sectional, controlled | 752/200 | 55.0/54.0 | Outpatient clinics/outpatient clinics | Type 2 diabetes | Prevalence | English | 4 |
| Abu-Bakare et al. 1986 (28) | Cross-sectional, controlled | 190/190 | Not available | Only black race from diabetes outpatient clinics/ outpatient clinics | Type 1 and type 2 diabetes | Prevalence | English | 4 |
| Rozsai et al. 2006 (18) | Cross-sectional, controlled | 133/178 | 15.6/14.1 | Children and adolescents from diabetes outpatient clinics/medical students | Type 1 diabetes | Prevalence | English | 4 |
| Mendoza et al. 2002 (29) | Cross-sectional, controlled | 50/50 | Not available | Only women from Diabetes outpatient clinic/ outpatient clinic | Type 2 diabetes | Prevalence | Spanish | 1 |
| Vigg et al. 1977 (30) | Cross-sectional, controlled | 87/93 | 18–60/18–60 (range) | Diabetes outpatient clinics/outpatient clinics | Type 1 and type 2 diabetes | Prevalence | English | 1 |
| Joffe et al. 1974 (31) | Cross-sectional, controlled | 100/36 | 57.0/72.0 | Diabetes outpatient clinics/outpatient clinics | Type 1 and type 2 diabetes | Prevalence | English | 1 |
| Rozsai et al. 2003 (12) | Cross-sectional, controlled | 178/194 | 15.1/14.4 | Children and adolescents | Type 1 diabetes | Prevalence | English | 3 |
| Boroumand et al. 2006 (20) | Cross-sectional | 202 | 56.0 | Only women from diabetes outpatient clinics/ outpatient clinics | Type 2 diabetes | Urinary protein | English | 1 |
| Zhanel et al. 1995 (11) | Cross-sectional | 1,072 | >16 | Only women from diabetes outpatient clinics/ outpatient clinics | Type 1 and type 2 diabetes | Creatinine, A1C, UTI anamnesis | English | 1 |
| Boyko et al. 2005 (32) | Controlled follow-up (2 years) | 218/799 | Not available | Postmenopausal women from an epidemiological cohort study | Type 1 and type 2 diabetes | Prevalence | English | 2 |
| Sotiropoulos et al. 2005 (13) | Controlled follow-up (12 months) | 363/350 | 61.3/63.0 | Only women from diabetes outpatient clinics/ outpatient clinics | Type 2 diabetes | Prevalence, duration, A1C | English | 3 |
| Ribera-Montes et al. 2006 (21) | Follow-up (12 months) | 457 | 68.3 | Diabetes outpatient clinics/health center | Type 2 diabetes | UTI during follow-up | Spanish | 3 |
| Karunajeewa et al. 2005 (7) | Follow-up (2.9 years) | 496 | Not available | Diabetes outpatient clinics/outpatient clinics | Type 1 and type 2 diabetes | Creatinine, UTI during follow-up | English | 3 |
| Geerlings et al. 2001 (14) | Follow-up (18 months) | 378 | 59.4 | Only women from diabetes outpatient clinics/ health center | Type 1 and type 2 diabetes | UTI during follow-up | English | 3 |
| Semetkowska-Jurk 1995 (22) | Follow-up (14 years) | 49 | Not available | Diabetes outpatient clinics/outpatient clinics | Type 1 and type 2 diabetes | UTI during follow-up | English | 3 |
| Meiland et al. 2,006 (15) | Follow-up (6 years) | 348 | 51.1 | Only women from diabetes outpatient clinics/ outpatient clinics | Type 1 and type 2 diabetes | GFR, hypertension | English | 4 |
| Harding et al. 2002 (8) | Intervention | 105 | Antibiotics 57.0/ placebo 53.7 | Only women from diabetes outpatient clinics/ outpatient clinics | Type 1 and type 2 diabetes | UTI | English | 5 |

Of the non-English articles, only abstracts in English were reviewed.

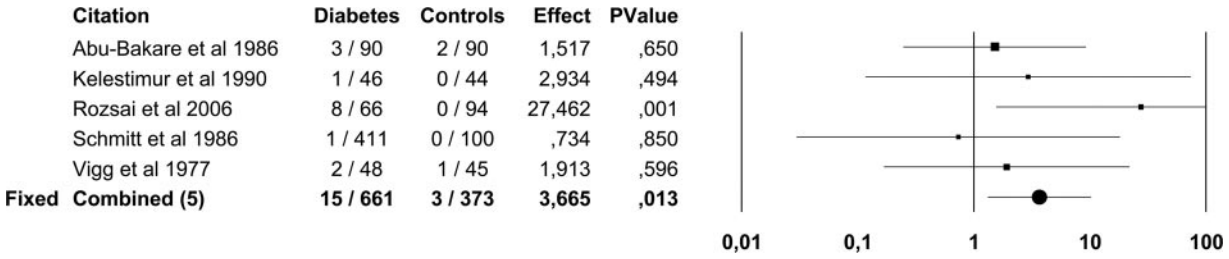


**Figure 3—***Forest plot of five studies on the prevalence of ASB in men with diabetes and healthy control subjects. Because the heterogeneity test was not significant (I2 25.6%,* P = *0.24) the results of the fixed-effects model are presented.*

tistically significant (15). Hypertension was more common in women with diabetes and ASB (54%) than without ASB (37%), but this difference was not statistically significant when adjusting for confounding variables in logistic modeling (15).

In two cross-sectional surveys (10,11) in which the history of having had a urinary tract infection (UTI) ever in the past was compared in diabetic subjects with and without ASB, positive UTI anamnesis was associated with ASB (OR 1.6 [95% CI 1.1–2.3]). In follow-up studies that included both women and men, symptomatic UTIs tended to be more common in diabetic subjects with ASB than in those without ASB (2.8 [0.8–9.8]) (7,14,21,22).

**CONCLUSIONS** — In this meta-analysis of observational studies, we were able to show that the prevalence of ASB was three times higher in all patients with diabetes compared with control subjects. We also found that diabetic subjects with ASB more often had albuminuria and symptomatic UTIs than those without ASB. Only one randomized controlled trial on the effect of active treatment of ASB on occurrence of symptomatic UTIs has been performed (8).

Whether glucosuria, as such, could increase the rate of ASB is unclear. Even though adding glucose to urine enhances the growth of bacteria in vitro, the association has not been verified in vivo (23). In this meta-analysis, A1C was slightly higher in diabetic subjects with ASB than in those without ASB, but the difference was neither statistically nor clinically significant. Thus, it seems unlikely that ASB would be just a consequence of a poor metabolic control of diabetes.

Urinary albumin is an important marker of diabetic nephropathy. We found that albuminuria was more common in diabetic subjects with than without ASB. The presence of bacteriuria, as such, does not seem to interfere with urinary albumin measurements. Kramer et al. (24) measured urine albumin concentrations in the same 81 diabetic individuals during ASB and with sterile urine, and no statistically significant differences were found.

Systematic reviews and meta-analyses of observational studies are very sensitive to biases atrributed to confounding factors. Meta-analyses of observational studies are good in developing new hypotheses that then have to be tested in intervention studies. In our meta-analysis, we were able to verify the higher incidence of ASB in diabetic compared with control subjects. Associations between ASB and important clinical outcomes, such as occurrence of symptomatic UTIs and complications of diabetes, have been evaluated in several surveys (10,11,13–15), but the conclusion has been that screening of ASB in diabetes is not beneficial. Lack of association has been interpreted as an evidence for equality (6). In this case, ASB does not cause any clinical consequences, and most of the research findings would show this. However, by chance alone, there would also be findings showing both negative and positive associations with ASB and clinical end points. Yet there are reports of no association and reports showing positive associations between ASB and clinical outcomes but no real contradictory reports. This was seen also in our meta-analysis, in which because a small number of studies and patients were included, only the association between albuminuria and ASB reached statistical significance. The lack of contradictory reports may well be because of publication bias, but we suggest that the associations of ASB and clinical outcomes should be further tested in prospective trials to better define the questions raised in this meta-analysis.

ASB is not a stable phenomenon but fluctuates over time even without any interventions. The pathophysiology of UTIs is unclear, but it is probable that the biologic reasons for asymptomatic and symptomatic urinary infections are similar. In the randomized controlled trial, routine screening and treatment of ASB in diabetic women did not change the occurrence of symptomatic UTsI or hospitalization because of UTIs (8). Harding et al.'s (8) trial is a landmark study in this field, but only women were included, mostly with type 2 diabetes. It is important to repeat these results and also include men and adolescents in the material. Altogether, the only way to thoroughly clarify the significance of ASB in patients with diabetes is to perform high-quality prospective studies on screening and treating ASB, with UTIs, metabolic control, and

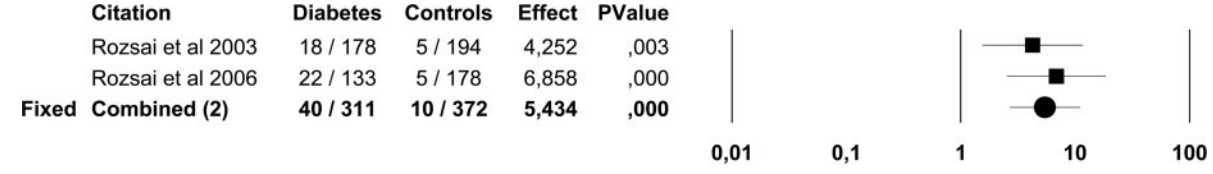


**Figure 4—***Forest plot of two studies on the prevalence of ASB in children and adolescents with diabetes and healthy control subjects. Because the heterogeneity test was not significant* ($I^2$, **P = 0.51) the results of the fixed-effects model are presented.*

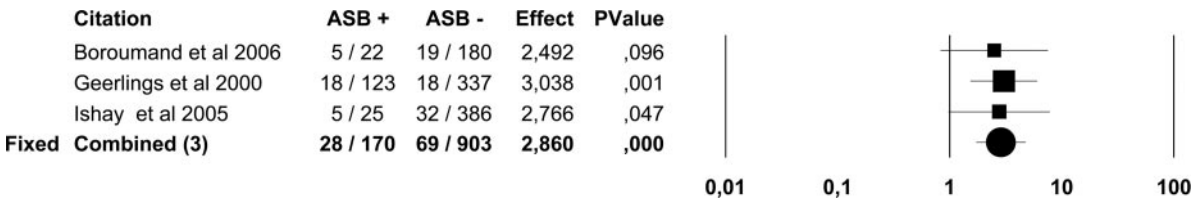


**Figure 5—***Forest plot of three studies on albuminuria in patients with diabetes with and without ASB. Because the heterogeneity test was not significant ($I^2$ 0%, P = 0.96) the results of the fixed-effects model are presented.*

occurrence of long-term complications of diabetes as outcomes.

The limitations of this meta-analysis arise mainly from the difficulties in obtaining detailed information from the articles included. We were not able to perform all analyses separately for the age-groups, sexes, or diabetes types. Also, the methodological quality of the majority of the studies included in this meta-analysis was poor. Almost all studies were performed among elderly women with type 2 diabetes, and whenever there were men, adolescents, or young adults included, the data for the different patient groups were not possible to separate. Yet this meta-analysis supports previous observations, verifies the incidence of ASB in the more seldom–investigated patient groups, and found significant association between albuminuria and ASB in patients with diabetes.

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M.R. participated in designing and planning the study, made the literature searches, read and reviewed the articles, made the analyses, and wrote the first version of the manuscript. P.Ta. participated in designing and planning the study, read and reviewed the articles, and edited the manuscript. P.To. participated in designing and planning the study, read and reviewed the articles, and edited the manuscript. T.P. participated in designing and planning the study, helped with the analyses, and edited the manuscript. M.U. participated in designing and planning the study, read and reviewed the articles, and edited the manuscript.

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