FEATURE ARTICLE

Association Between Diabetes and the Risk of Kidney Cancer: Systematic Review and Meta-Analysis

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Diabetes is a risk factor for several types of cancer, but the specific relationship between diabetes and kidney cancer is not well understood. We conducted a search strategy in scientific databases for case-control and cohort studies on this topic. We analyzed 17 studies and found that diabetes was significantly associated with the risk of developing kidney cancer and that this risk was slightly stronger for women and for people living in Asia. These findings were not influenced by obesity, cigarette smoking, or hypertension. We conclude that diabetes is an independent risk factor for the development of kidney cancer.

Diabetes and cancer are two diseases with the highest epidemiological surveillance worldwide because of their associated morbidity and mortality, as well as the presence of common risk factors that may promote the onset of both entities, including age, obesity, metabolic syndrome, smoking, and others (1,2). According to the World Health Organization, as of 2014, 422 million people had diabetes worldwide, and by 2012, diabetes was the eighth leading cause of mortality worldwide, accounting for 1.5 million deaths (2). Meanwhile, according to the Global Cancer Observatory, in 2018, 18.1 million new cases of all cancers occurred, of which 2.23% were kidney cancer. The documented incidence of kidney cancer has increased over time, in part because of the increased frequency of abdominal diagnostic imaging, which has improved case detection (3). In 2018, there were 9.5 million deaths from cancer, and of these, the raw mortality rate for kidney cancer was 2.3 per 100,000 (1).

Epidemiological studies have identified diabetes as an essential risk factor for the development of malignancies in different organs such as the liver, biliary tract, pancreas, colon, uterus, bladder, and kidneys (4). Biological events that might explain the association between diabetes and kidney cancer include hyperinsulinism, hyperglycemia, and the inflammatory activity that diabetes generates in the body, with different expressions and dysregulation of cytokines that can promote oxidative stress, angiogenesis, and uncontrolled cell proliferation (5–7). Two systematic reviews and meta-analyses have been conducted (8,9), the most recent in 2013, suggesting a positive association between these two diseases. Nevertheless, new data continue to emerge related to this association. Therefore, this study aimed to determine the association between diabetes and risk of kidney cancer based on the latest available data.

Research Design and Methods

We accomplished the recommendations described by the Cochrane Collaboration and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) for conducting and writing systematic reviews.

Eligibility Criteria

The inclusion criteria for our study were: *1*) articles describing case-control and cohort studies, *2*) with the exposure variable type 1 and/or type 2 diabetes, and *3*) with information available with which to calculate odds ratios (ORs), relative risks (RRs), or hazard ratio (HRs) with 95% CIs. We excluded studies that included the diagnosis of gestational diabetes, those with participants <18 years of age, and those not calculating OR, RR, or HR as an association measure.

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Information Sources

We performed a search in the MEDLINE, Embase, LILACS (Latin American and Caribbean Health Sciences Literature), and CENTRAL (Cochrane Central Register of Controlled Trials) indexes from inception to the present (Supplementary Material). To ensure literature saturation, we scanned references from relevant articles identified through the search, conferences, thesis databases, and the Open Gray, Google Scholar, and ClinicalTrials.gov websites, among others. There were no language or setting limits.

Study Selection

All the authors independently screened the results for a relevant title/abstracts and then full-text articles according to the inclusion and exclusion criteria. We then manually searched for references listed in the selected articles.

Data Extraction

We extracted the following information: first author's last name, year of publication, country, and continent of origin; duration of follow-up; cases in exposed and unexposed groups by sex; diabetes type, method of exposure determination, diagnostic criteria for diabetes, and time of exposure for diabetes; association measure estimates and their corresponding 95% CIs controlling for the significant potential confounders; and covariates controlled for in the analysis.

Assessment of Bias Risk Within Studies

We assessed the risk of bias based on the New Castle–Ottawa Scale (NOS). This scale evaluates three categories within each study: study design, comparability, and event, using a numeric grading scale from 0 to 9. Studies graded 0–3 were determined to be of low quality, those graded 4–6 were considered to be of intermediate quality, and those graded 7–9 were deemed high-quality studies (10).

Statistical Analysis

For meta-analysis calculation purposes, we selected HRs with 95% CIs as the summary measure for results of all included studies. This ratio was calculated using the method described by DerSimonian and Laird (11), assuming a random effect model. Statistical heterogeneity between studies was calculated using the I^2 statistic (12), considering 25, 50, and 75% as cutoffs for low, intermediate, and high heterogeneity, respectively. All statistical analyses were performed using Review Manager, v. 5.3, software.

Specific Analyses

Publication bias was evaluated using the funnel plot graphical method. Sensitivity analyses were conducted by type of study, with adjustment for the covariates of obesity, hypertension, and cigarette smoking because these factors are strongly related to kidney cancer occurrence (13–15). Subgroup analyses were performed to investigate the possible origin of heterogeneity between studies considering the variables of continent of origin, sex, and time of exposure.

Results

Study Selection

Through our search of databases, we found 42 potential articles for full-text analysis. We included 17 studies for the final analysis (Figure 1) (16–32).

Characteristics of Included Studies

Of the included studies, 12 were cohort studies (16–19,25–32) and five were case-control studies (20–24) (Tables 1 and 2). In total, we analyzed 2,296,993 people diagnosed with diabetes and 5,425,793 people without diabetes from the cohort studies. Also, we included for analysis 3,037 patients diagnosed with renal cancer, and 7,309 control subjects without kidney cancer.

With regard to the geographical distribution of the populations analyzed, one of the studies included populations from different regions (24); five included populations from Europe, including Italy (22,25), Iceland (26), Greece (21), and Sweden (23); six were conducted in Asia, including China (32), Israel (31), Japan (18), and Taiwan (20,27,28), and five were from North America, all of which were conducted in the United States (16,17,19,29,30).

With regard to type of diabetes included in the studies, six studies did not report type of diabetes (16,21,22,24,30,31), four included people with type 1 or type 2 diabetes (20,23,25,28), and seven included only people with type 2 diabetes (17–19,26,27,29,32). None of the studies were conducted in a population that was exclusively diagnosed with type 1 diabetes (Tables 1 and 2).

With regard to covariate adjustments for hypertension, obesity, and cigarette smoking, five studies adjusted by

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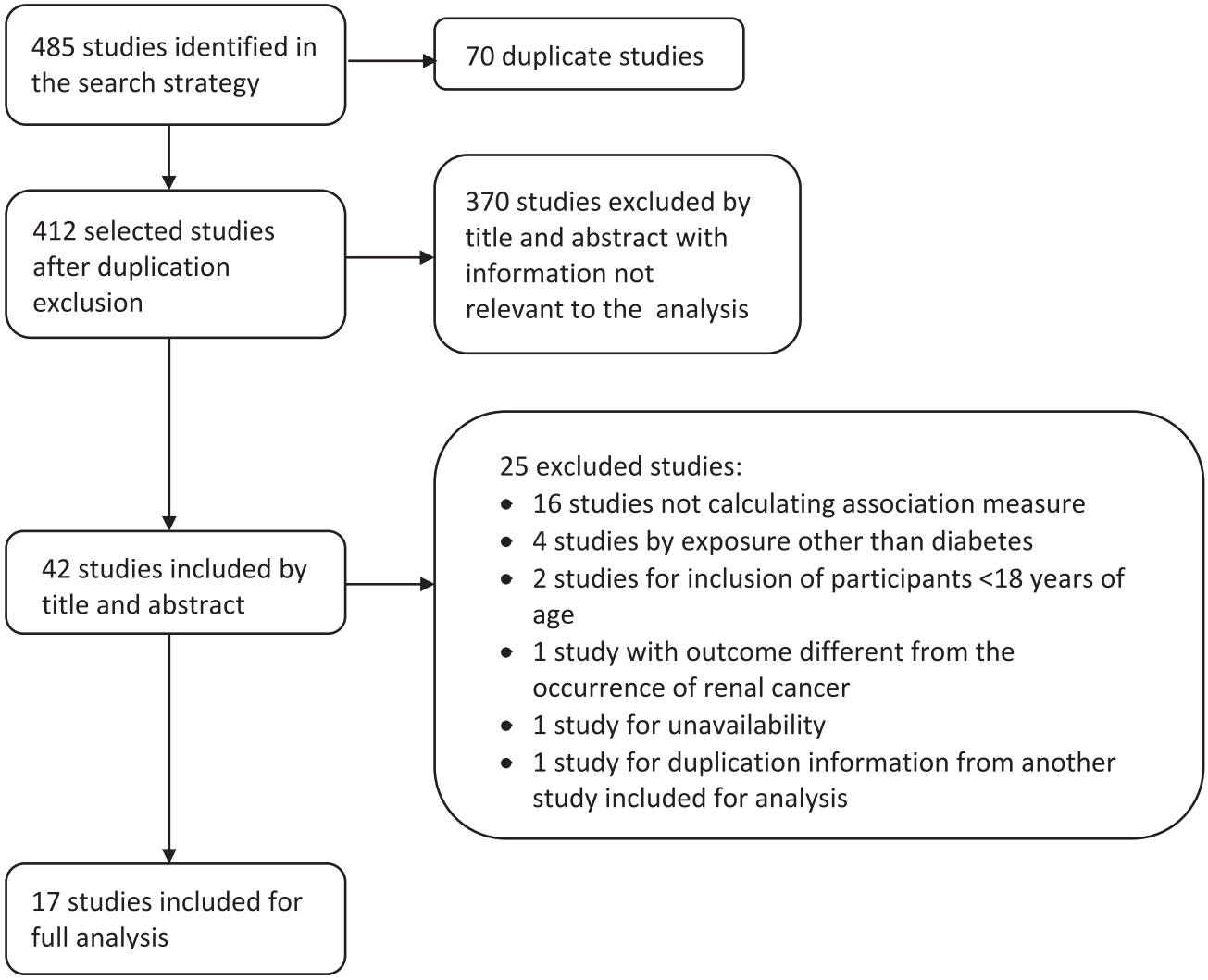

FIGURE 1 Flowchart of the study selection process.

the three variables simultaneously (29%), of which one was a case-control study (20) and four were cohort studies (15,25,26,29); nine adjusted based on at least one of the three variables (53.9%), of which three were case-control studies (22–24) and six were cohort studies (17–19,28,29,32); two adjusted by other covariates (11.7%), both of which were cohort studies (25,31); and one case-control study did not have any adjustments (21) (Tables 1 and 2).

Risk of Bias Within Studies

Among the studies included, we assessed 13 as being of high quality based on the NOS (16–19,21,23,26–32). We rated the remaining studies as being of intermediate quality (20,22,24,25). None of the studies included were deemed to be of low quality (Tables 1 and 2).

Diabetes as a Risk Factor for Kidney Cancer

We found an association between diabetes and kidney cancer (HR 1.36, 95% CI 1.25–1.48, $I^2 = 60\%$) (Figure 2).

Sensitivity Analyses

In the cohort study subgroup, we included 12 studies (16–19,25–32), and in the case-control subgroup, we included five studies (20–24). The cohort studies yielded an HR of 1.38 (95% CI 1.25–1.52, $I^2 = 71\%$), whereas the case-control subgroup yielded an HR of 1.29 (95% CI 1.08–1.53, $I^2 = 0\%$). There were no statistically significant differences between the groups.

Adjustment for Covariates

We divided the included studies into two subgroups: those with adjustment for the covariates of obesity, hypertension,

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TABLE 1 Characteristics of Included Cohort Studies

Study (Country)	Continent	Follow-Up Duration, years	Cases, *n*	Sample Size, *n*	Diabetes Type	Method of Exposure Determination	Diabetes Diagnostic Criteria	Adjusted OR, RR, or HR (95% CI)	Adjustment Covariates*	NOS Score
Gelfond et al. (16) (United States)	North America	13	73	11,497	NR	Self-report	NR	General HR: 1.07 (0.83–1.38)	5, 6, 7	8
Graff et al. (17) (United States)	North America	Study of women: 38; study of men: 28	Women: 418 (59 with diabetes); men: 302 (21 with diabetes)	Total: 166,436; women: 117,570 (5,265 with diabetes); men: 48,866 (1,594 with diabetes	Type 2	Self-report	ADA	General HR: 1.20 (0.71–2.03); HR women: 2.15 (1.62–2.84); HR men: 1.20 (0.76–1.88)	1, 5, 7	7
Inoue et al. (18) (Japan)	Asia	10.7	134 (99 men; 35 women)	97,771	Type 2	Self-report	NR	HR women: 1.36 (0.32–5.78); HR men: 1.92 (1.06–3.64)	2, 6, 7, 16, 17, 18	8
Joh et al. (19) (United States)	North America	32	330	Total: 118 (6, with diabetes)	Type 2	Self-report	NR	General HR: 1.60 (1.19–2.17)	1, 2, 4, 5, 6, 19	8
Ballotari et al. (25) (Italy)	Europe	4	Total: 437; women: 130 (19 with diabetes); men 307 (41 with diabetes)	407,157 (23,358 with diabetes)	Type 1 and type 2	Clinical records or external sources	WHO	General RR: 1.20 (0.67–2.14); RR women: 1.55 (0.94–2.54); RR men: 1.02 (0.74–1.44)	2, 3, 12	6
Mariusdottir et al. (26) (Iceland)	Europe	25	3 with diabetes	748 (3 with kidney cancer)	Type 2	Self-report	NR	General HR: 0.72 (0.29–1.76)	5, 6, 7	8
Tseng (27) (Taiwan)	Asia	3	Total: 485 (193 with diabetes, 129 with exposure >5 years)	Women: 503,614 (63,257 with diabetes); men: 495,114 (52,398 with diabetes)	Type 2	Clinical records or external sources	NR	General OR: 1.7 (1.3–2.1)	1, 5, 6, 7	8

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TABLE 1 Characteristics of Included Cohort Studies (Continued)

Study (Country)	Continent	Follow-Up Duration, years	Cases, *n*	Sample Size, *n*	Diabetes Type	Method of Exposure Determination	Diabetes Diagnostic Criteria	Adjusted OR, RR, or HR (95% CI)	Adjustment Covariates*	NOS Score
Chen et al. (28) (Taiwan)	Asia	9	Women: 1,906 (1,049 with diabetes); men: 1,507 (849 with diabetes)	Total: 1,229,747; women: 638,618 (319,310 with diabetes); men: 591,129 (295,566 with diabetes)	Type 1 and type 2	Clinical records or external sources	NR	General HR: 1.22 (1.13–1.31); HR women: 1.14 (1.04–1.26); HR men: 1.31 (1.18–1.46)	2, 5, 11	9
Lai et al. (29) (United States)	North America	10	Total: 2,111; women: 552 (65 with diabetes); men: 1,559 (206 with diabetes)	Total: 494,867; women: 199,591 (14,710 with diabetes); men: 295,276 (30,016 with diabetes)	Type 2	Self-report	NR	General HR: 1.18 (1.03–1.35); HR women: 1.21 (0.91–1.60); HR men: 1.17 (1.00–1.36)	3, 7	7
Macleod et al. (30) (United States)	North America	8	Total: 247 (32 with diabetes)	Total: 77,258 (32 with diabetes and kidney cancer; 5,369 with diabetes but no kidney cancer; 215 with kidney cancer but no diabetes; 71,642 with no diabetes and no kidney cancer)	NR	Self-report	NR	General HR: 1.39 (0.92–2.09)	5, 6, 7, 9, 10	7

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TABLE 1 Characteristics of Included Cohort Studies (Continued)

Study (Country)	Continent	Follow-Up Duration, years	Cases, *n*	Sample Size, *n*	Diabetes Type	Method of Exposure Determination	Diabetes Diagnostic Criteria	Adjusted OR, RR, or HR (95% CI)	Adjustment Covariates*	NOS Score
Dankner et al. (31) (Israel)	Asia	11	Total: 4,030: women: 1,456; men: 2,485	Total: 2,186,196; women: 1,152,122 (84,348 with prevalent diabetes, 214,408 with incident diabetes); men: 1,034,074 (74,756 with prevalent diabetes, 193,835 with incident diabetes)	NR	Clinical records or external sources	ADA	HR women: 1.85 (1.60–2.16); HR men: 1.51 (1.34–1.71)	2, 13, 14	9
Lo et al. (32) (China)	Asia	3.5	3,457 (1,915 with diabetes)	1,790,868 (895,434 with diabetes)	Type 2	Clinical records or external sources	NR	General HR: 1.28 (1.19–1.37)	1, 2, 3, 5, 8, 15	8

*Adjustment covariates: 1, duration of diabetes; 2, age; 3, sex; 4, BMI; 5, hypertension; 6, cigarette smoking; 7, obesity; 8, dyslipidemia; 9, chronic kidney disease; 10, alcohol consumption; 11, cystic renal disease; 12, immigration status; 13, socioeconomic status; 14, ethnic group; 15, area of residence; 16, history of stroke; 17, ischemic heart disease; 18, study area; 19, parity. ADA, American Diabetes Association; NR, not reported; WHO, World Health Organization.

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TABLE 2 Characteristics of Included Case Control Studies

Study (Country)	Continent	Follow-Up Duration, years	Cases, *n*	Sample Size, *n*	Diabetes Type	Method of Exposure Determination	Diabetes Diagnostic Criteria	Adjusted OR, RR, or HR (95% CI)	Adjustment Covariates*	NOS Score
Lai et al. (20) (Taiwan)	Asia	10	116 (48 women, 68 men)	464 (192 women, 272 men)	Type 1 and type 2	Clinical records or external sources	NR	General: OR 1.06 (0.58–1.94)	1, 6, 7, 8, 10, 12	6
Spyridopoulos et al. (21) (Greece)	Europe	NR	60 (21 with diabetes)	236 (39 with diabetes)	NR	Self-report	NR	General: OR 2.32 (0.95–5.66)	None	7
Bosetti et al. (22) (Italy)	Europe	19	767 (70 with diabetes); 273 women, 494 men	Total: 1,534 (111 with diabetes); 546 women, 988 men	NR	Self-report	NR	General: OR 1.26 (0.91–1.75)	2, 3, 4, 5, 7, 11	6
Attner et al. (23) (Sweden)	Europe	10	379 with exposure to diabetes from 3 months to 4 years; 362 with exposure to diabetes from 4 to 10 years	2,888 with exposure to diabetes from 3 months to 4 years; 2,766 with exposure to diabetes from 4 to 10 years	Type 1 and type 2	Clinical records or external sources	NR	Exposure to diabetes from 3 months to 4 years: RR 1.10 (0.67–1.79); exposure to diabetes from 4 to 10 years: RR 1.19 (0.76–1.91)	2, 3, 8, 9	7
Schlehofer et al. (24) (Australia, Denmark, Germany, Sweden, United States)	Multiple continents	NR	1,732	2,309	NR	Clinical records or external sources	NR	General: RR 1.4 (1.0–1.8) RR women: 1.3 (0.9–2.1) RR men: 1.4 (1.0–1.9)	2, 3, 5, 6, 7, 13	7

*Adjustment covariates: 1, duration of diabetes; 2, age; 3, sex; 4, education level; 5, BMI; 6, hypertension; 7, cigarette smoking; 8, obesity; 9, dyslipidemia; 10, chronic kidney disease; 11, alcohol consumption; 12, cystic renal disease; 13, reference center. NR, not reported.

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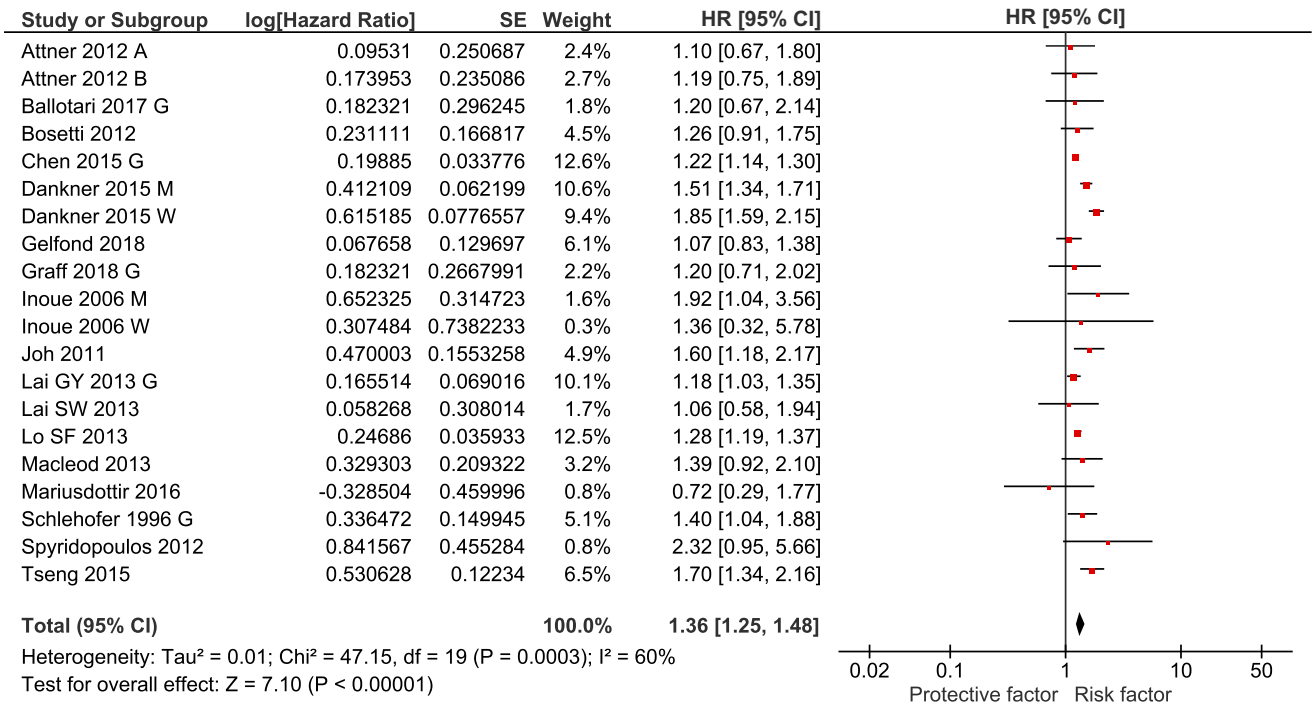

FIGURE 2 Meta-analysis of association between diabetes and kidney cancer. A, result for the time interval 90–1,460 days before kidney cancer diagnosis; B, result for the time interval 1,461–3,650 days before kidney cancer diagnosis; G, general result; M, result for men; W, result for women.

and/or cigarette smoking (16–24,26–30,32) and those with no adjustment (25,31). We found an HR of 1.26 (95% CI 1.20–1.33, $I^2 = 10\%$) in the covariate adjustment group and an HR of 1.64 (95% CI 1.38–1.95, $I^2 = 49\%$) in the group with no adjustment. There were no significant differences between groups.

Publication Bias Analyses

We performed a publication bias analysis using the visual exploration of a funnel plot. It resulted in a symmetrical graph, which indicates no publication bias (Figure 3).

Subgroup Analyses

Sex

We included seven studies for meta-analysis (17,18,24,25,28,29,31), as the remaining 10 studies did not included results by sex. We found an HR of 1.41 (95% CI 1.13–1.75, $I^2 = 80\%$) in women and an HR of 1.29 (95% CI 1.14–1.46, $I^2 = 56\%$) in men. There were no significant differences between groups ($\chi^2 = 0.44$, $df = 1$, $P = 0.51$, $I^2 = 0\%$) (Figure 4).

Geographical Location

Sixteen studies were grouped in three categories according to their continent of origin: five from Europe (21–23,25,26), six from Asia (18,20,27,28,31,32), and five from North America (16,17,19,29,30). One study was from multiple countries and therefore was not included in this analysis. We found an HR of 1.21 (95% CI 0.99–1.19, $I^2 = 0\%$) in studies from Europe, an HR of 1.46 (95% CI 1.28–1.66, $I^2 = 80\%$) in studies from Asia, and an HR of 1.23 (95% CI 1.08–1.39, $I^2 = 16\%$) in studies from North America. There were no significant differences between groups ($\chi^2 = 3.98$, $df = 2$, ($P = 0.14$, $I^2 = 49.8\%$) (Figure 5).

Exposure Time

We created two subgroups: five studies with <5 years of diabetes exposure (17,19,23,31,32), for which we found an HR of 1.93 (95% CI 1.13–3.31, $I^2 = 98\%$), and six studies with >5 years of diabetes exposure (17,19,23,25,31,32), for which we found an HR of 1.38 (95% CI 1.26–1.52, $I^2 = 16\%$). Six studies were not included, as they did not report exposure time. Nevertheless, there were no statistically significant differences between groups ($\chi^2 = 1.42$, $df = 1$, $P = 0.23$, $I^2 = 29.5\%$) (Figure 6).

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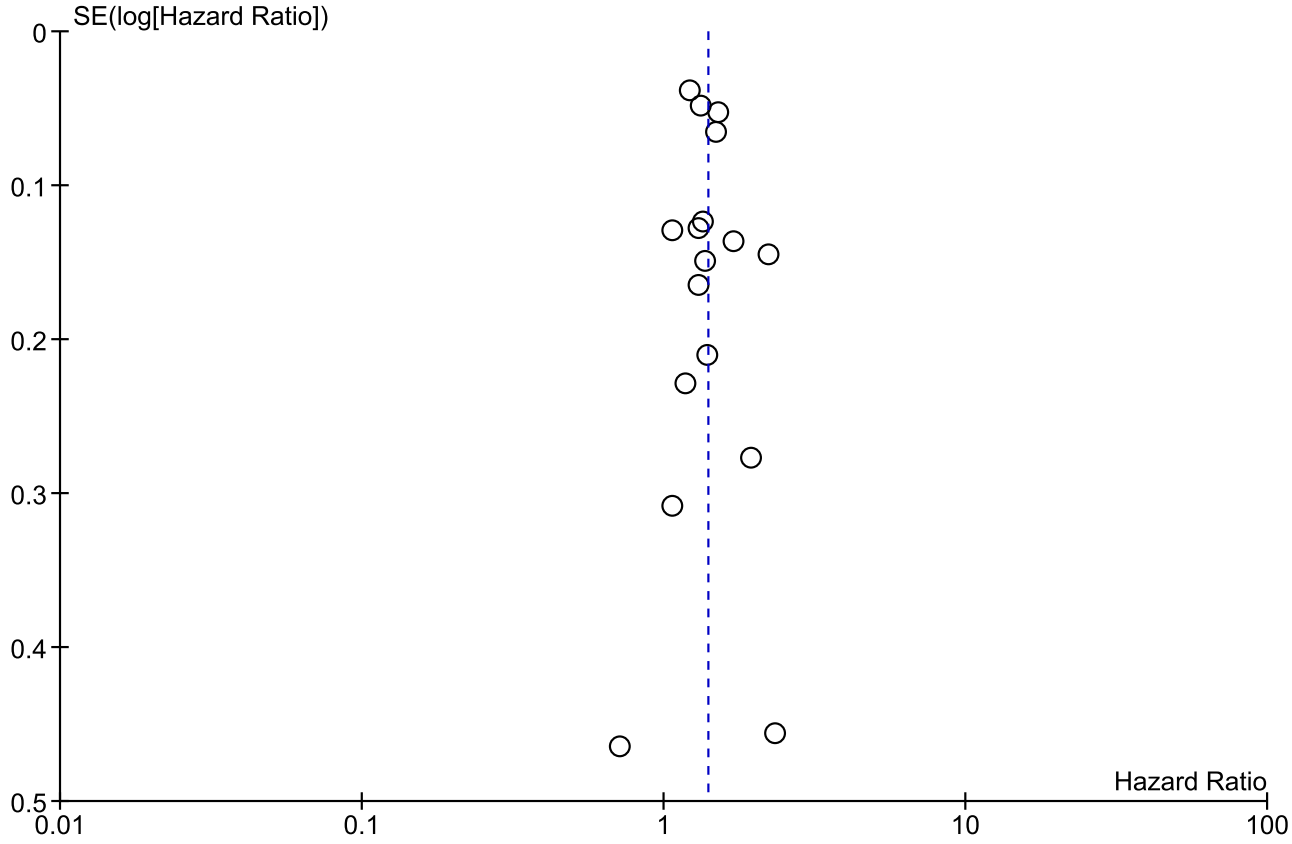

FIGURE 3 Funnel plot of publication bias analysis.

Discussion

Summary of Main Findings

The main finding of this systematic review and meta-analysis, which included cohort and case-control studies from different geographical areas of the world, suggests that diabetes increases the risk of kidney cancer. This association seems to be higher in women than in men, in Asia and North America than in Europe, and in people with <5 years of diabetes exposure, although these differences were not statistically significant. The sensitivity analysis showed that the main result was slightly attenuated by studies that adjusted for obesity, hypertension, and cigarette smoking, but it remained statistically significant after adjustment. This finding suggests that diabetes is an independent risk factor for the incidence of kidney cancer.

Association Between Diabetes and Kidney Cancer

Our results are consistent with those described in the systematic reviews of Bao et al. (8), which showed an increased 40% risk of kidney cancer in people with diabetes, and Larsson and Wolk (9), which showed an increased risk of 42% in this population.

Elevated blood glucose levels can trigger metabolic processes such as increased insulin and IGF-1 levels and promote the presence of proinflammatory cytokines in tissues that activate signaling pathways involved in cell growth and thus the development of tumors. Therefore, diabetes may increase the risk of cancer in a biologically plausible manner (5–7). None of the included studies evaluated the dose-response relationship between A1C in people with diabetes and the risk of renal cancer. Future research on this topic is needed.

The covariate adjustments could explain the high heterogeneity observed within the meta-analysis. However, this finding should be taken cautiously because there were few studies included in the no-adjustment subgroup. Nevertheless, adjustment for covariates did not affect the association between diabetes and kidney cancer risk.

The subgroup analysis did not reveal any statistically significant differences. Therefore, the heterogeneity might

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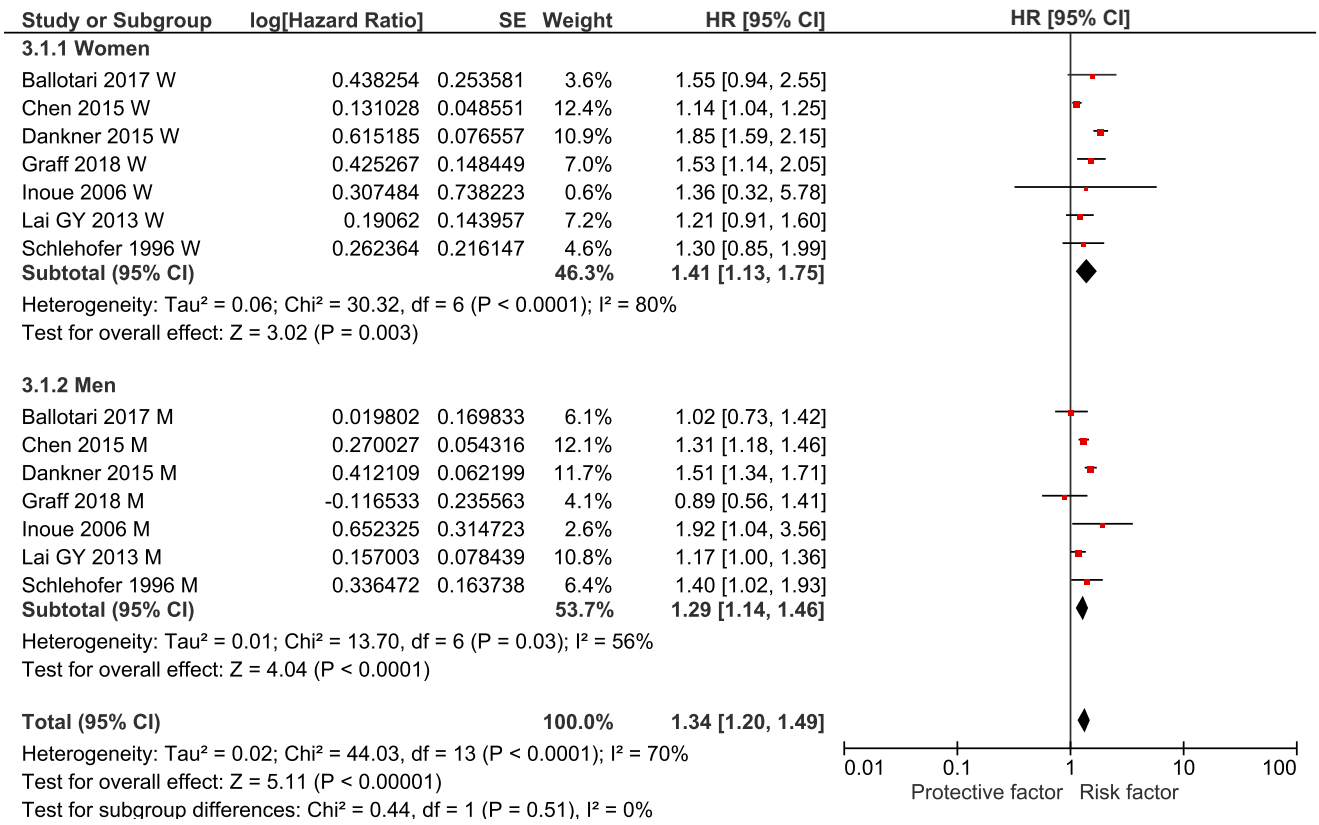

FIGURE 4 Subgroup analysis of diabetes and risk of kidney cancer by sex. M, result for men; W, result for women.

have resulted from the type of diabetes, which authors did not describe in six of the 17 included studies; in the other studies, participants were described as having type 2 diabetes, diabetes, or either type 1 or type 2 diabetes. Similarly, other variables such as the diagnostic criteria for diabetes used in the included studies or the sources of the data collected in these studies may have influenced the results. In addition, other variables such as the use of metformin in the populations with diabetes, which has demonstrated a possible protective effect for the development of various cancers (33), may have mitigated the real effect of diabetes on the risk of kidney cancer.

With regard to sex, this systematic review and meta-analysis showed an increased risk of kidney cancer in both sexes, but a slightly higher risk among women. This finding can be explained by differences in glucose homeostasis and the prevalence of metabolic syndrome, as women tend to have higher glucose intolerance and a higher prevalence of metabolic syndrome than men (31). This occurrence accounts for the possible biological plausibility that exists between glucotoxicity and oncogenesis (34).

This study also found a statistically significant association between diabetes and the risk of kidney cancer in populations from Asia and North America, with a higher risk in Asian populations. However, no association was found for European populations. These findings are consistent with those previously described in the study by Bao et al. (8). Genetic differences between these populations could account for these results. Nevertheless, further investigation is needed.

Finally, this systematic review and meta-analysis found a more significant association between diabetes and kidney cancer in people with a lower exposure to diabetes. In this regard, there is a high probability of detection bias in this association because there was more active surveillance (more imaging diagnostic techniques used) in patients with chronic kidney disease in the population recently diagnosed with diabetes (9).

Strengths and Limitations

This review has several strengths. First, the studies included in the analysis were of high or intermediate quality based

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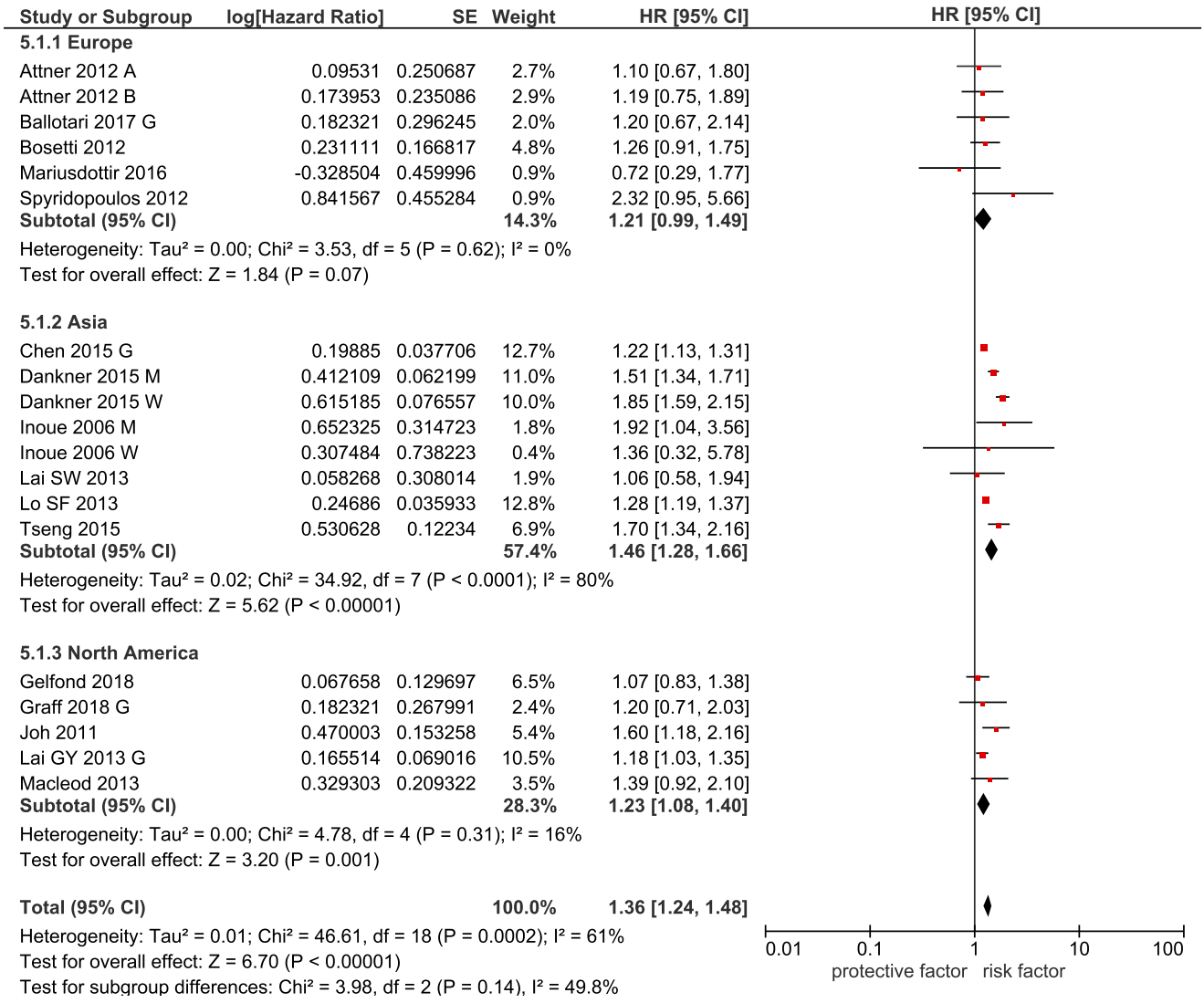

FIGURE 5 Subgroup analysis of diabetes and risk of kidney cancer by geographical location. A, result for the time interval 90–1,460 days before kidney cancer diagnosis; B, result for the time interval 1,461–3,650 days before kidney cancer diagnosis; G, general result; M, result for men; W, result for women.

on NOS assessment. Second, the subgroup analyses included potential cofounders in the summary association measure between diabetes and risk of kidney cancer, making the study result reliable. Third, the included studies accounted for different populations around the world, ensuring adequate external validity for the results.

This study also has limitations. First, there was a high degree of statistical heterogeneity. There were also covariates present in studies other than obesity, hypertension, and cigarette smoking. The studies included were observational in design and thus could have had various types of bias, as well as under-registration of variables that may have interfered with the outcomes they measured. Additionally, data on diagnoses of diabetes and kidney cancer were obtained from clinical records or external sources such as cancer or population registries. This strategy may have introduced selection and information biases. Also, type 2 diabetes is the form of the disease most consistently associated with kidney cancer in epidemiological studies. Thus, inclusion of individuals with type 1 diabetes in some of the studies could have led to attenuation of the real association between diabetes and kidney cancer. Finally, as stated in the meta-analysis summary, diabetes is an underdiagnosed disease, which may have resulted in bias due to misclassification of exposure.

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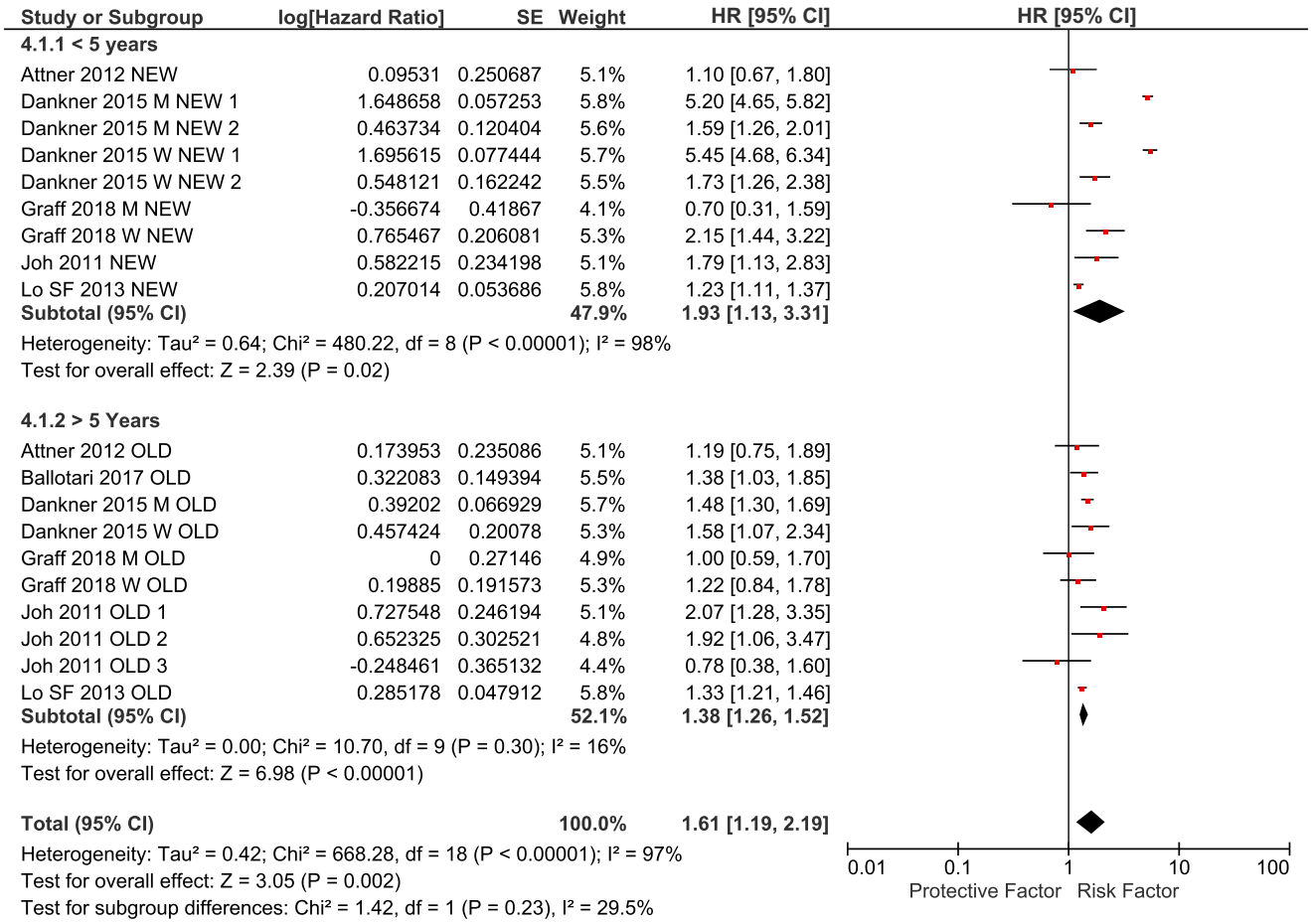

FIGURE 6 Subgroup analysis of diabetes and risk of kidney cancer by diabetes exposure time. M, result for men; W, result for women.

Practical Implications and Future Research

Based on the results of this study, diabetes may be considered an independent risk factor for kidney cancer. Additionally, we suggest incorporating a renal ultrasound into the regular follow-up care of patients with diabetes in primary care.

Conclusion

Diabetes is an independent risk factor for the development of kidney cancer. Future studies are needed to evaluate a possible dose-response interaction of A1C and kidney cancer risk and to assess kidney cancer risk in people with diabetes from other geographical locations such as Latin America, Africa, and Oceania.

DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

A.B.-S. and J.R.-M. researched data, wrote the manuscript, and contributed to the discussion. H.A.G.-P. researched data, reviewed and edited the manuscript, and contributed to the discussion. A.B.-S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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