

SYSTEMATIC REVIEW AND META-ANALYSIS

Solar Ultraviolet Radiation Exposure, Vitamin D Status, and Risk of Renal Cell Carcinoma: A Systematic Review and Meta-Analysis of Observational Studies

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ABSTRACT

Background: The incidence of renal cell carcinoma (RCC) continues to rise. Solar ultraviolet (UV) radiation is the main source of vitamin D, which is activated in the kidney, but individual-level evidence linking sunlight with RCC has not been pooled.

Objective: To quantify the associations of solar UV exposure and of vitamin D status with the incidence of RCC.

Methods: PubMed/MEDLINE, Europe PMC and OpenAlex were searched. Cohort and case-control studies reporting adjusted estimates for occupational, ambient or personal solar UV exposure, or for circulating or predicted 25-hydroxyvitamin D, were eligible. Adjusted relative risks (RR) for the highest versus lowest exposure were pooled separately for each domain with random-effects models (Hartung-Knapp intervals). Risk of bias was rated with the Newcastle-Ottawa Scale and certainty with GRADE.

Results: Eleven studies with 1,045,226 participants were included. In five UV studies (64,648 cases), the highest exposure carried a lower RCC risk: RR 0.84 (95% CI 0.75–0.95), I² 18.2%, prediction interval 0.72–0.99. Occupational studies alone gave 0.84 (0.67–1.06). Vitamin D results came from six studies. Four categorical studies gave 0.55 (0.31–0.98) and two per-doubling studies 0.79 (0.45–1.41); combined, 0.67 (0.48–0.92), yet the prediction interval (0.38–1.18) crossed unity and the largest consortium found no association. Certainty: low for UV, very low for vitamin D.

Conclusion: Individuals with more solar UV exposure had a modestly lower RCC risk, and vitamin D status pointed the same way, though inconsistently. With low certainty, and with UV a cause of skin cancer, the results call for research and do not change sun-protection advice.

1. Introduction

Renal cell carcinoma (RCC) accounts for most primary kidney cancers in recent registry series and is managed largely by urologists and surgical oncologists. Registry analyses showed wide international variation in incidence, with the highest rates in North America and Eastern Europe,¹ and rising or stable incidence in most European countries, North America and Asia over the past 15 years.² Incidence increased in 32 of the 37 countries studied, including among young men in 24 countries and young women in 18,³ and the global burden of kidney cancer was projected to grow further.⁴ In a single-center surgical series, more than four-fifths of clear cell tumors were detected incidentally on imaging,⁵ but population-based data also showed persistent sociodemographic gradients that detection practices alone did not explain.⁶ Surgery remains the cornerstone of curative treatment,⁷ so primary prevention depends on identifying modifiable causes, and most patients with RCC are first characterized in surgical services.

Smoking, excess body weight and hypertension are established risk factors,² and smoking and high body mass index account for a substantial share of the burden.^{8,9} Metabolically unhealthy obesity,¹⁰ certain antihypertensive drug classes¹¹ and physical inactivity^{12,13} were also associated with risk. Occupational and environmental agents, including trichloroethylene and other chlorinated solvents,^{14,15} pesticide-related agricultural tasks¹⁶ and petroleum-industry

exposures,¹⁷ have been investigated as causes, and systematic occupational screening of patients with kidney cancer identified exposures eligible for compensation.¹⁸ Many patients, however, have none of these exposures, and potentially protective environmental factors have received far less attention.

Solar ultraviolet B (UVB) radiation has long been recognized as the principal source of vitamin D in most populations. Its availability varies several-fold with latitude and season across Europe, with a “vitamin D winter” of several months at higher latitudes,^{19,20} and the kidney is the main site at which 25-hydroxyvitamin D [25(OH)D] is hydroxylated to calcitriol. Components of the vitamin D pathway were dysregulated in clear cell RCC,²¹ low renal expression of the vitamin D receptor was associated with shorter survival,²² and patients with urological cancers had lower circulating 25(OH)D than healthy individuals.²³ Beyond the kidney, occupational solar ultraviolet (UV) exposure was inversely associated with colon and prostate cancer in Danish registry studies,^{24,25} and residential UV with estrogen receptor-negative breast cancer²⁶ and lifetime sunlight with breast cancer,²⁷ whereas associations with lymphoma and with prostate cancer in other cohorts were null.^{28,29} Occupational UV exposure, in contrast, increased the risk of melanoma and basal cell carcinoma, with a similar but non-significant pattern for squamous cell carcinoma,^{30–32} so any benefit for internal cancers has to be weighed against a known harm.

Measuring lifetime sunlight exposure is difficult. Job-exposure matrices estimated that only about 2% of salaried French workers were occupationally exposed in their most recent job,³³ personal dosimetry showed large differences in daily dose between outdoor occupations,³⁴ and skin biomarkers distinguished chronically exposed outdoor workers from indoor workers.³⁵ Population 25(OH)D concentrations tracked cumulative vitamin D-effective UVB closely,¹⁹ and in UK Biobank serum 25(OH)D and time spent outdoors were each associated with kidney outcomes when analyzed as separate exposures,³⁶ but personal factors such as adiposity, skin type and sun-protective behavior strongly modified how much vitamin D a given exposure produced.³⁷ Exposure and biomarker therefore capture overlapping but different aspects of the same hypothesized pathway. They were treated in this review as two separate questions, and agreement in the direction of their associations was not taken as evidence of mediation.

For RCC, individual-level studies of occupational and ambient UV exposure and of circulating 25(OH)D reported inverse, null and sex-specific associations, and their combined evidence has not been quantified. A meta-analysis of vitamin D intake and circulating vitamin D³⁸ did not consider sunlight itself, and the large D-Health trial of vitamin D supplementation was designed around all-cause mortality and did not report kidney cancer separately.^{39,40} To our knowledge, this study is the first to pool the individual-level evidence on solar UV exposure and RCC, with occupational exposure examined as a subgroup, and to analyze the evidence on vitamin D status alongside it as a separate domain that represents the proposed biological pathway. The aim of this study was to quantify the association of solar UV exposure (occupational, ambient residential or personal) and, separately, of vitamin D status with the incidence of RCC in adults, and to rate the certainty of each body of evidence.

2. Methods

Protocol and registration

This systematic review and meta-analysis of observational studies was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.⁴¹ The review question, the two exposure domains, eligibility criteria, data items and the analysis plan were defined before the searches were run and are summarized in the Supplementary Material, together with the completed PRISMA checklist.

Eligibility criteria

Eligibility was defined by population, exposure, comparator, outcome and study design, as detailed in Table 1. Two exposure domains were defined in advance. Domain A comprised solar UV radiation assessed at the individual level: occupational exposure assigned from job histories or job-exposure matrices, ambient UV dose at the place of residence, or personal sun exposure reported by questionnaire. Domain B comprised vitamin D status, measured as circulating 25(OH)D or estimated with a validated predicted 25(OH)D score. Artificial UV sources, occupational titles without a UV metric, vitamin D intake alone, vitamin D-binding protein alone and genetic instruments were not eligible exposures.

The outcome was incident RCC or kidney cancer. Because most registries code kidney cancer as ICD-10 C64 and some report C64 together with renal pelvis (C65), both definitions were accepted and the definition used by each study was recorded. Cohort, nested case-control, case-cohort and case-control studies reporting an adjusted ratio estimate with its 95% confidence interval (CI), or data from which it could be derived, were eligible. Ecological and cross-sectional studies were excluded because they could not link exposure and outcome in the same individuals. When several reports described the same population, the most informative report was retained and the others were excluded as overlapping.

Table 1. Eligibility criteria (population, exposures, comparator, outcome and study design).

Element	Inclusion	Exclusion
Population	Adults in general-population, occupational or hospital-based samples; cohorts free of kidney cancer at baseline; case-control studies of newly diagnosed cases with controls	Children; populations defined by kidney transplantation, dialysis or chronic kidney disease
Exposure A	Solar ultraviolet radiation: occupational (job-exposure matrix or expert-coded job history), ambient residential (satellite or ground-based dose at the residence) or personal sun exposure (questionnaire)	Artificial ultraviolet sources (tanning devices, phototherapy, PUVA); occupation titles without an ultraviolet metric
Exposure B	Vitamin D status: circulating 25(OH)D measured in blood, or a validated predicted 25(OH)D score	Dietary or supplemental vitamin D intake alone; vitamin D-binding protein alone; genetic instruments; supplementation trials
Comparator	Lowest category of the same exposure, or a log-linear contrast when categories were not reported	—
Outcome	Incident renal cell carcinoma or kidney cancer (ICD-10 C64, or C64–C65 when reported as kidney cancer)	Kidney cancer survival or mortality only; urothelial or composite genitourinary outcomes
Design	Cohort, nested case-control, case-cohort and case-control studies reporting an adjusted ratio estimate with its 95% CI, or data from which it could be derived	Ecological, cross-sectional and laboratory studies; reviews, case reports, conference abstracts; overlapping reports of the same population (most informative retained)

25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; ICD-10, International Classification of Diseases, 10th revision; PUVA, psoralen plus ultraviolet A.

Information sources and search strategy

PubMed/MEDLINE, Europe PMC (which indexes MEDLINE, PubMed Central, Agricola and Chinese Biological Abstracts records) and OpenAlex were searched without date, language or design limits. OpenAlex was used as a multidisciplinary index that aggregated Crossref, institutional repository and journal metadata, and therefore covered much of the occupational and

environmental health literature indexed outside MEDLINE. Embase, Scopus and Web of Science were not searched. To reduce the risk of missing studies, the reference lists of the included studies and of previous reviews were screened, and related-article links of each included cohort were checked.

The search combined a solar UV block or a vitamin D block with a kidney cancer block and an etiological design block, using

controlled vocabulary and free-text terms. The full PubMed strategy was as follows.

("Sunlight"[Mesh] OR "Ultraviolet Rays"[Mesh] OR sunlight[tiab] OR "sun exposure"[tiab] OR "sun-exposure"[tiab] OR "solar radiation"[tiab] OR "solar UV"[tiab] OR "solar UVB"[tiab] OR ultraviolet[tiab] OR UVB[tiab] OR UVR[tiab] OR "UV radiation"[tiab] OR "UV exposure"[tiab] OR "outdoor work"[tiab] OR "outdoor occupation"[tiab] OR sunbath[tiab] OR "time outdoors"[tiab] OR "time spent outdoors"[tiab]) OR ("Vitamin D"[Mesh] OR "vitamin D"[tiab] OR "25-hydroxyvitamin D"[tiab] OR "25(OH)D"[tiab] OR 25OHD[tiab] OR calcidiol[tiab] OR calcifediol[tiab] OR cholecalciferol[tiab])) AND ("Kidney Neoplasms"[Mesh] OR "Carcinoma, Renal Cell"[Mesh] OR "renal cell carcinoma"[tiab] OR "renal cell cancer"[tiab] OR "kidney cancer"[tiab] OR "renal cancer"[tiab] OR "kidney neoplasm"[tiab] OR "renal neoplasm"[tiab] OR "kidney tumor"[tiab] OR "kidney tumour"[tiab] OR "renal tumor"[tiab] OR "renal tumour"[tiab] OR "renal carcinoma"[tiab] OR ((kidney[tiab] OR renal[tiab]) AND (cancer*[tiab] OR carcinoma*[tiab] OR neoplasm*[tiab] OR malignan*[tiab]))) AND ("Cohort Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Risk Factors"[Mesh] OR "Incidence"[Mesh] OR cohort*[tiab] OR "case-control"[tiab] OR "case control"[tiab] OR prospective[tiab] OR nested[tiab] OR risk[tiab] OR incidence[tiab] OR "odds ratio"[tiab] OR "hazard ratio"[tiab] OR "relative risk"[tiab]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])

The equivalent Europe PMC and OpenAlex strategies, with the number of records retrieved from each source, are given in Supplementary Table S1.

Study selection and data collection

Records were merged and de-duplicated on PubMed identifier, digital object identifier and normalized title. A prespecified keyword rule set marked records that were clearly ineligible (reviews, case reports, editorials, conference abstracts, laboratory studies, non-cancer kidney conditions, or records naming neither kidney cancer nor an eligible exposure); the rules were checked against all records retrieved by scoping searches before use, and every remaining record was screened on title and abstract. Potentially eligible reports were assessed in full against the criteria in Table 1.

Data were extracted into a piloted 23-item form covering study design, country, period, numbers of cases and participants, age, sex, exposure assessment, exposure contrast, outcome definition, the adjusted estimate with its 95% CI, covariates, follow-up and risk-of-bias items. Values that were not reported were recorded as not reported and were never imputed. Screening and extraction were performed by one reviewer. To limit errors, every exclusion at full-text stage was re-read against the eligibility criteria, and every extracted estimate, confidence limit and case count was checked a second time against the source table before analysis; the extraction workbook records the table from which each value was taken.

Overlap between studies was examined explicitly. The pooled vitamin D consortium included the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, the Cancer Prevention Study II Nutrition Cohort and the Prostate, Lung, Colorectal and Ovarian (PLCO) trial; separate reports from these cohorts were therefore excluded if they described the same nested case-control set or reported only vitamin D-binding protein. The Nurses' Health Study and Health Professionals Follow-up Study, the European Prospective Investigation into Cancer and Nutrition (EPIC), the Copenhagen City Heart Study and UK Biobank were not part of the consortium. In domain A, the US Kidney Cancer Study and the National Institutes of Health-AARP Diet and Health Study (NIH-AARP) drew on separate recruitment frames, so any overlap of individuals was unlikely and, if present, negligible.

Effect measures

The effect measure was the most fully adjusted relative risk (RR) for the highest versus the lowest exposure category. Odds ratios and hazard ratios were treated as estimates of the same RR because kidney cancer was rare: cumulative incidence was 0.43% over a mean of 9.1 years in the NIH-AARP cohort and 0.34% over 22 years in the predicted-score cohorts, and odds ratios from nested case-control studies with incidence-density sampling estimate rate ratios directly. For occupational studies with several exposure metrics, cumulative exposure was preferred; when several lag periods or models were reported, the authors' main lag and the model with the most complete adjustment for confounders were used, except when an added covariate was a component of the exposure itself (for example body mass index [BMI] in a predicted 25(OH)D score), in which case the authors' primary model was used and the more adjusted model was examined in a sensitivity analysis. Estimates for all participants were preferred to sex-specific estimates, which were extracted separately for the sex-stratified analysis. Log RRs and their standard errors were derived from the published 95% CIs (Equation 1).

$$\begin{aligned} y_i &= \ln(RR_i), \\ SE_i &= \frac{\ln(U_i) - \ln(L_i)}{2 \times 1.96}, \\ v_i &= SE_i^2 \end{aligned} \quad (1)$$

Reference categories differed between studies. The case-control studies compared the highest with the lowest quantile of cumulative exposure among all participants, so their reference group contained both unexposed and minimally exposed workers, whereas the Nordic registry study compared the highest exposure with never-exposed workers. Both contrasts compare high with low or no occupational exposure, and the difference was examined in the leave-one-out analysis.

When a study reported category-specific odds ratios against a middle reference category, the contrast between the highest and lowest categories was re-expressed from the published estimates and the numbers of cases and controls in each category. Pseudo-numbers of cases (a) and controls (b) were fitted, as described by Hamling et al.,⁴² so that they reproduced every published odds ratio and its variance exactly while staying as close as possible to the observed counts; the contrast between categories j and k and its variance then followed from Equation 2. The method preserved the published estimates and the correlation induced by the shared reference category, but it could not recover additional covariance from multivariable adjustment.

$$\begin{aligned} \ln(OR_{jk}) &= \ln\left(\frac{a_j b_k}{a_k b_j}\right), \\ \text{Var}\left(\ln(OR_{jk})\right) &= \frac{1}{a_j} + \frac{1}{b_j} + \frac{1}{a_k} + \frac{1}{b_k} \end{aligned} \quad (2)$$

An estimate reported per 50% reduction in 25(OH)D was inverted to express the association per doubling. Two studies reported the association of 25(OH)D only on a log-linear scale and contributed their per-doubling estimate. Because a doubling of 25(OH)D usually spans a smaller contrast than the difference between extreme categories, including these estimates was expected to bias the pooled vitamin D estimate toward the null; the analysis restricted to categorical estimates was therefore reported alongside the primary estimate.

Statistical synthesis

The two exposure domains were analyzed separately because they represent different points on the hypothesized pathway and were measured in different populations. Log RRs were pooled with inverse-variance random-effects models. The

between-study variance τ^2 was estimated with the DerSimonian–Laird method (Equation 3), and the pooled estimate was the weighted mean of the study estimates (Equation 4).

$$\tau^2 = \max \left\{ 0, \frac{Q - (k-1)}{\sum_i w_i - \frac{\sum_i w_i^2}{\sum_i w_i}} \right\}, \quad (3)$$

$$w_i = \frac{1}{v_i}$$

$$\hat{\mu} = \frac{\sum_i w_i^* y_i}{\sum_i w_i^*}, \quad (4)$$

$$w_i^* = \frac{1}{v_i + \tau^2}$$

Its 95% CI used the Hartung–Knapp adjustment with a t distribution on $k-1$ degrees of freedom (Equation 5), because intervals for small numbers of studies need to allow for uncertainty in τ^2 . Wald-type intervals were reported as a sensitivity analysis; newer approaches may perform better still.⁴³

$$\hat{\mu} \pm t_{k-1, 0.975} \sqrt{\frac{\sum_i w_i^* (y_i - \hat{\mu})^2}{(k-1) \sum_i w_i^*}} \quad (5)$$

Heterogeneity was quantified with Cochran's Q , τ , τ^2 and I^2 (Equation 6), and a 95% prediction interval was calculated to describe the range of associations expected in a new comparable population (Equation 7); because its coverage was imperfect with few studies, it was interpreted descriptively.⁴⁴

$$Q = \sum_i w_i (y_i - \hat{\mu}_{FE})^2,$$

$$I^2 = \max \left\{ 0, \frac{Q - (k-1)}{Q} \right\} \times 100\% \quad (6)$$

$$\hat{\mu} \pm t_{k-2, 0.975} \sqrt{\tau^2 + SE^2(\hat{\mu})} \quad (7)$$

Planned subgroup analyses examined exposure source (occupational or ambient), study design, adjustment for both smoking and BMI, risk of bias and sex for domain A, and exposure measure (measured or predicted 25(OH)D), design, risk of bias and sex for domain B. Two further groupings were added after the study characteristics had been tabulated but before any subgroup model was fitted: latitude, with a threshold of 44°N corresponding to the southernmost center of the European case-control study so that all European and Nordic studies formed one group, and the type of vitamin D contrast (categorical or per doubling). Because each domain contained five or six studies, all subgroup analyses were regarded as exploratory; Hartung–Knapp intervals were used within subgroups, which made intervals based on two studies very wide, and sex-specific estimates from two studies per stratum were pooled with Wald-type intervals.

Sensitivity analyses omitted each study in turn and used restricted maximum likelihood and Paule–Mandel estimators of τ^2 , Wald-type intervals and a common-effect model. Further analyses restricted domain A to occupational studies, to studies adjusted for smoking and BMI and to each design, and restricted domain B to categorical estimates, to measured 25(OH)D and to studies reported in full, and replaced the predicted-score estimate with its BMI-adjusted version. Small-study effects were explored with funnel plots; Egger's regression test was not

performed because each domain contained fewer than ten studies. Analyses used R 4.5.3 with the meta (version 8.2.1)⁴⁵ and metafor (version 4.8.0)⁴⁶ packages; figures were drawn with Python 3.14 and matplotlib 3.10. A two-sided $p < 0.05$ was considered statistically significant.

Risk of bias and certainty of evidence

Risk of bias was assessed with the Newcastle–Ottawa Scale, using the cohort or case-control version as appropriate, across selection (maximum four stars), comparability (two stars) and exposure or outcome ascertainment (three stars). The first comparability star required matching on or adjustment for age and sex, and the second required adjustment for both smoking and BMI, the two strongest established risk factors. Exposure ascertainment was rated higher for registry-linked or objectively assigned exposure blinded to case status and lower for exposure borrowed from another population or measured after diagnosis. Studies with 7–9 stars were judged at low, 5–6 at moderate and 4 or fewer at high risk of bias, and the judgement was used in a subgroup analysis. The scale was retained because it was prespecified and allowed comparison with earlier syntheses; the more detailed ROBINS-E tool,⁴⁷ designed for follow-up studies of exposures, was less readily applied to the case-control designs that formed half of the evidence.

Certainty of evidence for each domain was rated with Core GRADE.^{48–51} Observational evidence started at low certainty and was rated down for risk of bias, inconsistency, indirectness, imprecision or publication bias. Rating up for an exposure-response gradient was considered only when the gradient was observed within individual studies, so that it could not be explained by between-study differences in exposure assessment. The rating applied to each domain as a whole; subgroup estimates were not rated separately.

3. Results

Study selection

The database searches identified 3,165 records (PubMed/MEDLINE 726, Europe PMC 593, OpenAlex 1,846). After removal of 1,429 duplicates and 1,371 records marked ineligible by the keyword rules, 365 records were screened on title and abstract and 348 were excluded, mainly because they concerned skin cancer in transplant recipients, non-cancer kidney or mineral disorders, vitamin D treatment or metabolism without a kidney cancer outcome, or other cancers. Seventeen reports were sought in full, and two could not be retrieved. Of the 15 reports assessed, four were excluded: two measured vitamin D-binding protein without an eligible 25(OH)D estimate, one reported the same nested case-control set as the pooled consortium, and one reported estimates only for benign and malignant kidney neoplasms combined. Citation searching identified three further reports; one could not be retrieved and two were ineligible because kidney cancer was combined with other genitourinary cancers or no UV metric was used. Eleven studies were included, five on solar UV radiation and six on vitamin D status (Figure 1).

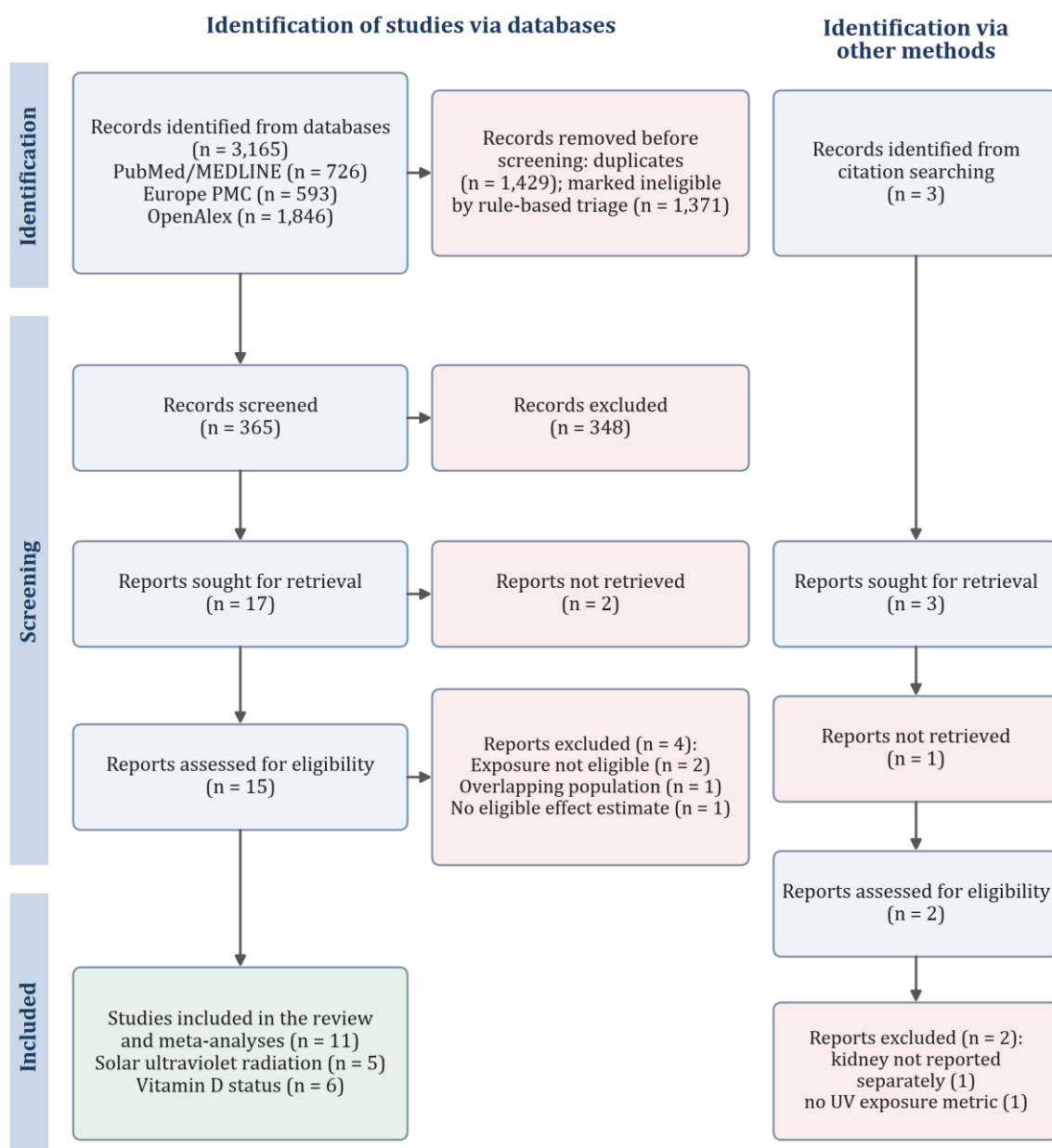


Figure 1. PRISMA 2020 flow diagram of the identification, screening and inclusion of studies.

Characteristics of the included studies

The characteristics of the included studies, which together comprised 1,045,226 participants, are detailed in Table 2. The five UV studies included 815,893 participants and 64,648 cases of kidney cancer. Four assessed occupational exposure: hospital- and population-based case-control studies from Central and Eastern Europe, the USA and South Korea,⁵²⁻⁵⁴ and a nested case-control study within the census cohorts of Finland, Iceland and Sweden that used the Nordic Occupational Cancer Study (NOCCA) job-exposure matrix.⁵⁵ Exposure was assigned from coded lifetime job histories, coded blind to case status and reviewed by industrial hygienists, in two studies, and from satellite-derived occupational doses of French workers matched by occupational group in the Korean study. One prospective cohort, the NIH-AARP study, assessed ambient erythemal UV at the residence from the satellite-based Total Ozone Mapping Spectrometer (TOMS).⁵⁶

Sample sizes and exposure contrasts differed widely. The Central and Eastern European study compared the highest with the lowest tertile of cumulative exposure among 1,097 cases and 1,476 hospital controls, and stratified results by study center as

a proxy for latitude. The US Kidney Cancer Study compared quartiles of cumulative exposure among 1,217 cases and 1,235 population controls and adjusted additionally for dietary vitamin D intake. In the Korean study, cases had a lower mean daily erythemal dose of their occupation than matched controls (0.728 ± 0.153 versus 0.757 ± 0.173 kJ/m²). The Nordic study compared 1,348 cases and 7,504 controls in the highest cumulative exposure category, lagged by ten years, with never-exposed workers, and the NIH-AARP cohort recorded 1,923 kidney cancers, including renal pelvis tumors, over a mean follow-up of 9.1 years.

The six vitamin D studies included 229,333 participants and at least 1,878 cases; two did not report the number of kidney cancers. Four used blood collected before diagnosis: a pooled analysis of eight cohorts from the USA, Finland and China,⁵⁷ the Copenhagen City Heart Study,⁵⁸ EPIC⁵⁹ and UK Biobank participants with metabolic syndrome.⁶⁰ One combined two US cohorts and used a validated predicted 25(OH)D score,⁶¹ and one Chinese hospital-based case-control study measured 25(OH)D at admission before surgery.⁶² Median 25(OH)D in the consortium was similar in cases and controls (44.4 and 45.4 nmol/L), and blood had been drawn a median of 5.5 years before

diagnosis, but only about two years in three of the eight cohorts. In the Chinese study, mean plasma 25(OH)D was 21.5 ± 7.4 ng/mL (53.7 ± 18.5 nmol/L) in cases and 24.1 ± 6.6 ng/mL (60.2 ± 16.5 nmol/L) in controls. Follow-up was 22 years in the

predicted-score cohorts, up to 28 years in the Copenhagen cohort and a median of 10.9 years in UK Biobank. No participant contributed to more than one included estimate.

Table 2. Characteristics of the included studies.

Study	Country	Design	Cases / participants	Exposure assessment	Contrast	Adjusted estimate (95% CI)	Adjusted for smoking / BMI / hypertension
A. Solar ultraviolet radiation							
Karami 2010 ⁵²	Czech Republic, Poland, Romania, Russia	Hospital-based case-control	1,097 / 2,573	Occupational; JEM (ISCO-68/NACE), hygienist-reviewed	Highest vs lowest tertile, cumulative	OR 1.01 (0.81 to 1.26)	Yes / Yes / Yes
Karami 2016 ⁵³	USA	Population-based case-control	1,217 / 2,452	Occupational; coded job histories, hygienist-reviewed	Highest vs lowest quartile, cumulative	OR 0.74 (0.56 to 0.99)	Yes / Yes / Yes
Jang 2019 ⁵⁴	South Korea	Matched case-control	633 / 1,266	Occupational; satellite-derived dose by ISCO-08 group	Highest vs lowest quartile	OR 0.66 (0.45 to 0.98)	Yes / No / Yes
Michalek 2019 ⁵⁵	Finland, Iceland, Sweden	Nested case-control (census cohorts)	59,778 / 358,668	Occupational; NOCCA job-exposure matrix	Highest cumulative vs unexposed (10-year lag)	OR 0.85 (0.79 to 0.92)	No / No / No§
Lin 2012 ⁵⁶	USA	Prospective cohort (NIH-AARP)	1,923 / 450,934	Ambient residential; satellite (TOMS)	Highest vs lowest quartile of July erythemal dose	HR 0.83 (0.73 to 0.94)	Yes / Yes / No
B. Vitamin D status							
Gallicchio 2010 ⁵⁷	USA, Finland, China	Pooled nested case-control (8 cohorts)	775 / 1,550	Measured 25(OH)D, central laboratory	≥100 vs <25 nmol/L†	OR 0.98 (0.46 to 2.09)	Yes / Yes / Yes
Joh 2013 ⁶¹	USA	Two prospective cohorts (NHS, HPFS)	408 / 118,431	Predicted 25(OH)D score	Highest vs lowest quintile	HR 0.54 (0.39 to 0.75)	Yes / No / Yes¶
Afzal 2013 ⁵⁸	Denmark	Prospective cohort (CCHS)	NR / 9,791	Measured plasma 25(OH)D	Per doubling‡	HR 0.75 (0.58 to 0.96)	NR (multivariable)
Muller 2014 ⁵⁹	10 European countries	Nested case-control (EPIC)	560 / 1,670	Measured 25(OH)D3 (LC-MS/MS)	Per doubling	OR 0.82 (0.68 to 0.99)	Yes / Yes / No
Li 2019 ⁶²	China	Hospital-based case-control	135 / 270	Measured plasma 25(OH)D at admission	≥30 vs <20 ng/mL	OR 0.30 (0.13 to 0.72)	Yes / Yes / Yes
Wu 2023 ⁶⁰	United Kingdom	Prospective cohort (UK Biobank, metabolic syndrome)	NR / 97,621	Measured serum 25(OH)D	≥75 vs <25 nmol/L	HR 0.54 (0.31 to 0.95)	NR (multivariable)

Cases / participants: number of kidney cancer cases and total participants (cases plus controls in case-control designs; cohort size in cohorts). All estimates were adjusted for or matched on age and sex. †Re-expressed from published category-specific estimates against the 50–<75 nmol/L reference (published ≥100 vs 50–<75 nmol/L: OR 0.92, 0.44–1.92). ‡Inverse of the published hazard ratio per 50% reduction in 25(OH)D (1.34, 1.04–1.73). §Mutually adjusted for 12 occupational agents including perceived physical workload. ¶BMI is a component of the predicted 25(OH)D score; the BMI-adjusted model was used in a sensitivity analysis. BMI, body mass index; CCHS, Copenhagen City Heart Study; EPIC, European Prospective Investigation into Cancer and Nutrition; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; ISCO, International Standard Classification of Occupations; JEM, job-exposure matrix; LC-MS/MS, liquid chromatography-tandem mass spectrometry; NACE, Statistical Classification of Economic Activities; NHS, Nurses' Health Study; NIH-AARP, National Institutes of Health-AARP Diet and Health Study; NOCCA, Nordic Occupational Cancer Study; NR, not reported; OR, odds ratio; TOMS, Total Ozone Mapping Spectrometer.

Risk of bias

Risk of bias is summarized in Table 3 and Figure 2. Nine studies were at low and two at moderate risk of bias. The main concerns were the absence of individual smoking and BMI data in the Nordic registry study, which received no comparability stars;

exposure assigned from a foreign occupational dose survey and no adjustment for BMI in the Korean study; and blood sampling at diagnosis in hospital-recruited participants in the Chinese case-control study. Two vitamin D reports gave limited detail on covariates, which reduced their comparability ratings, and a third did not report the length of follow-up.

Table 3. Risk of bias of the included studies (Newcastle–Ottawa Scale).

Study	Selection	Comparability	Exposure / outcome	Total	Risk of bias	Main concern
A. Solar ultraviolet radiation						
Karami 2010	3/4	2/2	2/3	7/9	Low	Hospital controls; JEM with blinded coding; adjusted for smoking and BMI; high response
Karami 2016	4/4	2/2	2/3	8/9	Low	Population controls; blinded expert coding; full confounder set
Jang 2019	3/4	1/2	1/3	5/9	Moderate	Population controls but exposure borrowed from French occupational UV doses; no BMI
Michalek 2019	4/4	0/2	3/3	7/9	Low	Registry-based; JEM exposure; no smoking or BMI adjustment
Lin 2012	4/4	2/2	3/3	9/9	Low	Large cohort; objective satellite exposure; registry outcome; complete adjustment except hypertension
B. Vitamin D status						
Gallicchio 2010	4/4	2/2	3/3	9/9	Low	Prospective blood; central laboratory; matched and adjusted
Joh 2013	4/4	1/2	3/3	8/9	Low	Predicted (not measured) exposure; long follow-up; BMI not in primary model

Study	Selection	Comparability	Exposure / outcome	Total	Risk of bias	Main concern
Afzal 2013	4/4	1/2	3/3	8/9	Low	General-population cohort; complete follow-up; covariates not itemised in the report
Muller 2014	4/4	2/2	2/3	8/9	Low	Prospective blood; mass spectrometry; follow-up length not reported
Li 2019	2/4	2/2	1/3	5/9	Moderate	Hospital-based; blood drawn at diagnosis (reverse causation possible); controls selected as healthy
Wu 2023	3/4	1/2	3/3	7/9	Low	Restricted to metabolic syndrome; covariates not itemised in the report

Newcastle–Ottawa Scale, case-control or cohort version as appropriate. Overall risk of bias: low, 7–9 stars; moderate, 5–6 stars; high, ≤ 4 stars. BMI, body mass index.

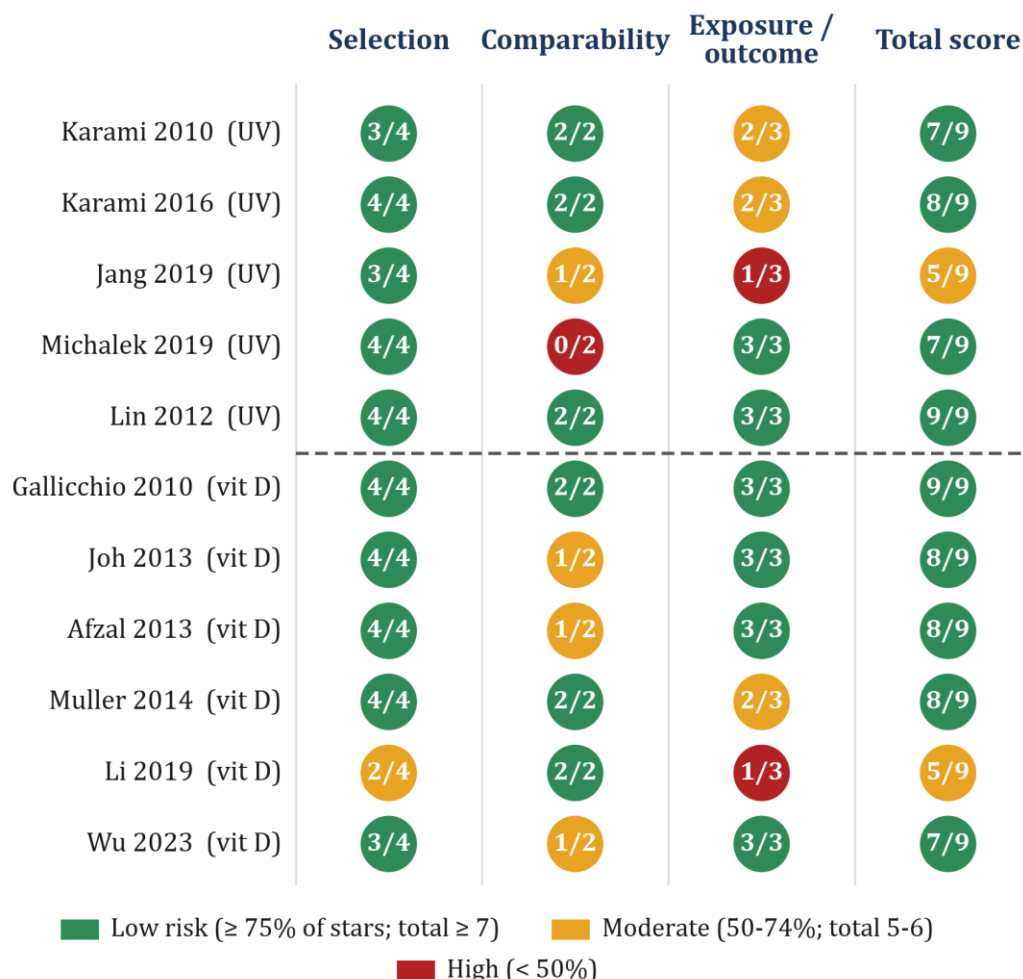


Figure 2. Newcastle–Ottawa Scale ratings of the included studies by domain. Numbers are stars awarded out of the domain maximum; colors indicate the proportion of available stars (green $\geq 75\%$, amber 50–74%, red $< 50\%$) and, for the total score, low (7–9), moderate (5–6) or high (≤ 4) risk of bias. UV, solar ultraviolet radiation domain; vit D, vitamin D status domain.

Solar ultraviolet radiation and RCC

Higher solar UV exposure was associated with a lower incidence of RCC (pooled RR 0.84 [95% CI 0.75 to 0.95]; $p = 0.016$; Figure 3). Heterogeneity was low (I^2 18.2%, 95% CI 0.0% to 83.0%; $\tau = 0.040$, $\tau^2 = 0.0016$; $Q = 4.89$ on 4 degrees of freedom, $p = 0.30$), and the 95% prediction interval (0.72 to 0.99) lay below unity. The Nordic and NIH-AARP studies carried 51.0% and 27.4% of the weight. Study estimates ranged from 0.66 in Korea⁵⁴ to 1.01 in Central and Eastern Europe.⁵²

For occupational exposure alone, the pooled RR was 0.84 (95% CI 0.67 to 1.06) with the Hartung–Knapp interval and 0.84

(95% CI 0.74 to 0.96) with a Wald-type interval; the ambient UV estimate from the NIH-AARP cohort was 0.83 (0.73 to 0.94). Tests for trend across exposure categories were statistically significant in four of the five studies (p for trend 0.03 in the US study, 0.028 in the Korean study, below 0.001 in the Nordic study and 0.030 in the NIH-AARP cohort). In the Central and Eastern European study the inverse association was confined to men (RR 0.76, 95% CI 0.58 to 1.00) and was strongest among men in Moscow, the most northerly center, whereas in the US study it was stronger in women (RR 0.48, 95% CI 0.21 to 1.00).

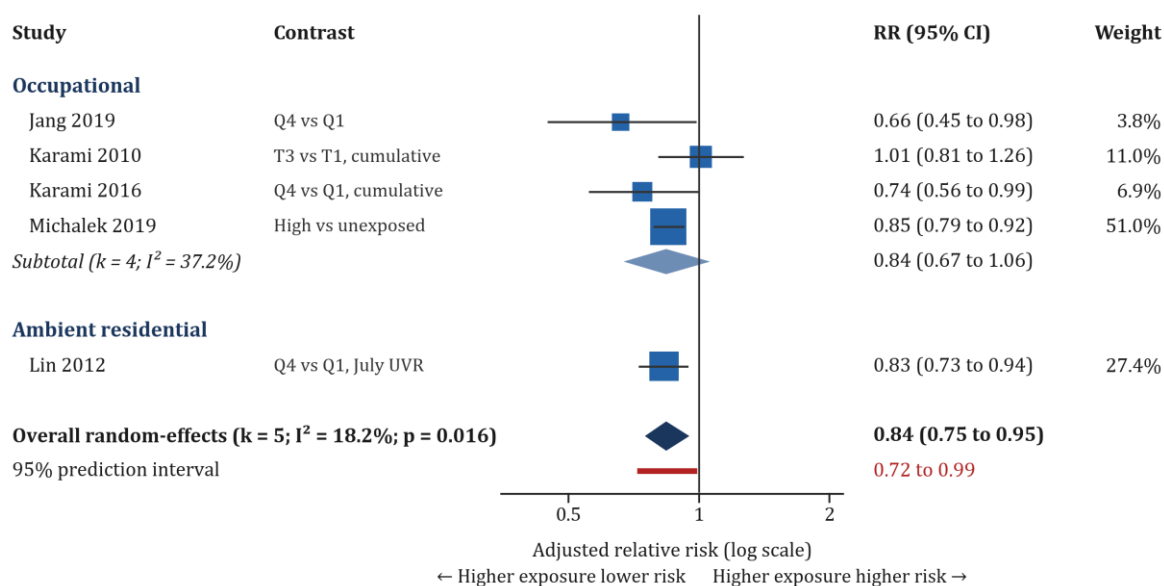


Figure 3. Forest plot of adjusted relative risks of renal cell carcinoma for the highest versus the lowest solar ultraviolet radiation exposure, grouped by exposure source. Squares are study estimates (size proportional to random-effects weight) with 95% confidence intervals; diamonds are random-effects pooled estimates (DerSimonian-Laird, Hartung-Knapp) and the red bar is the 95% prediction interval. Q, quartile; T, tertile; UVR, ultraviolet radiation.

Vitamin D status and RCC

Higher vitamin D status was associated with a lower incidence of RCC (pooled RR 0.67 [95% CI 0.48 to 0.92]; $p = 0.023$; Figure 4); because this summary combines highest-versus-lowest and per-doubling contrasts, it indicates the direction rather than the size of the association. Heterogeneity was moderate (I^2 52.6%, 95% CI 0.0% to 81.1%; $\tau = 0.190$, $\tau^2 = 0.0360$; $Q = 10.56$ on 5 degrees of freedom, $p = 0.061$), and the 95% prediction interval (0.38 to 1.18) included unity. The pooled consortium estimate was null (0.98 [0.46 to 2.09] for 100 nmol/L or more versus less than 25 nmol/L; the published estimate against the 50 to less than 75 nmol/L reference was 0.92, 95% CI 0.44 to 1.92).⁵⁷ The predicted-score cohorts and the UK Biobank analysis both

reported RRs of 0.54,^{60,61} and the Chinese hospital-based study reported the strongest association (0.30 [0.13 to 0.72]).⁶²

Restricted to the four studies that reported highest-versus-lowest categories, the pooled RR was 0.55 (95% CI 0.31 to 0.98), whereas the two log-linear studies gave 0.79 (95% CI 0.45 to 1.41) per doubling of 25(OH)D (p for difference 0.051). The cohort and nested case-control studies alone gave 0.71 (95% CI 0.54 to 0.93). In the EPIC study, the per-doubling estimate weakened from 0.72 (95% CI 0.60 to 0.86) to 0.82 (0.68 to 0.99) after adjustment for smoking, cotinine, BMI and alcohol, and in the predicted-score cohorts further adjustment for BMI attenuated the sex-specific estimates to 0.60 (0.35 to 1.02) in women and 0.66 (0.40 to 1.09) in men.

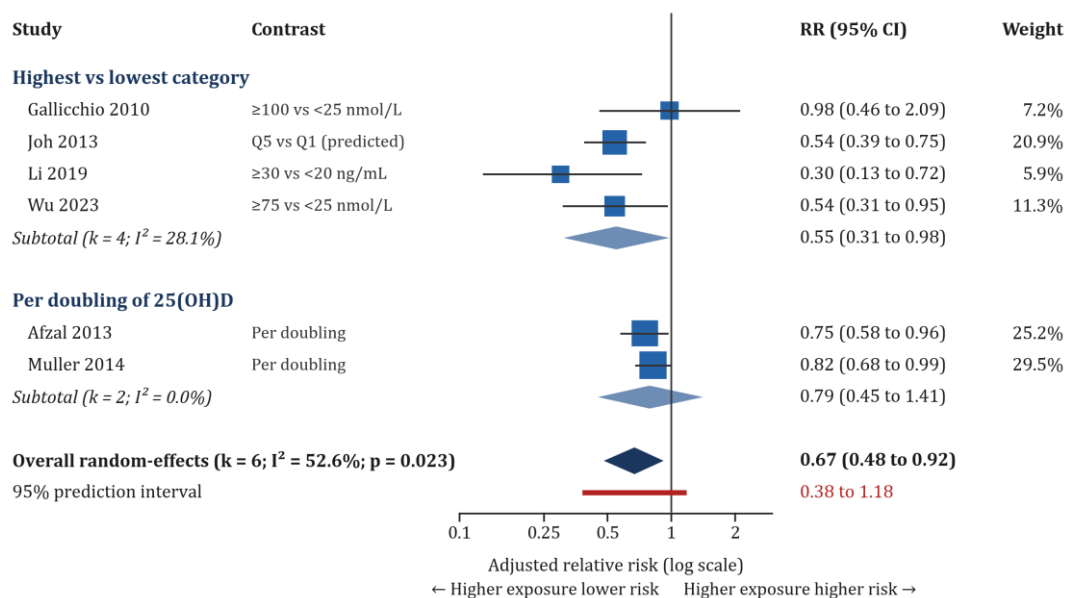


Figure 4. Forest plot of adjusted relative risks of renal cell carcinoma for higher versus lower vitamin D status, grouped by the reported contrast (highest versus lowest category or per doubling of 25-hydroxyvitamin D). Layout as in Figure 3. Q, quintile; 25(OH)D, 25-hydroxyvitamin D.

Exploratory subgroup analyses

Subgroup and sex-specific estimates are detailed in Table 4; all were exploratory and several strata contained a single study. In domain A, no subgroup difference was statistically significant:

estimates were similar for case-control and cohort or nested designs ($p = 0.80$), for studies above and below 44°N ($p = 0.23$) and for studies with and without adjustment for both smoking and BMI ($p = 0.66$). The two cohort or nested studies gave 0.84

(0.74 to 0.97). Sex-specific estimates, available from the two case-control studies with job histories, were 0.79 (0.63 to 0.99) for men and 0.82 (0.33 to 2.03) for women, with marked heterogeneity among women (I^2 78.4%; Figure 5).

In domain B, the estimate was 0.50 (0.32 to 0.76) in women and 0.93 (0.38 to 2.25) in men (p for difference 0.21), and the association was weaker for measured than for predicted 25(OH)D (0.71 [0.49 to 1.05] versus 0.54 [0.39 to 0.75]; p = 0.20).

Table 4. Pooled, subgroup and sex-specific relative risks of renal cell carcinoma.

Analysis	k	RR (95% CI)	I^2 (%)	p for difference
A. Solar ultraviolet radiation				
Overall (primary analysis)	5	0.84 (0.75 to 0.95)	18.2	
95% prediction interval		0.72 to 0.99		
Exposure source: Occupational	4	0.84 (0.67 to 1.06)	37.2	0.85
Exposure source: Ambient residential	1	0.83 (0.73 to 0.94)	—	
Study design: Case-control	3	0.82 (0.47 to 1.41)	58.1	0.80
Study design: Cohort or nested case-control	2	0.84 (0.74 to 0.97)	0.0	
Latitude: Higher latitude ($\geq 44^\circ\text{N}$)	2	0.90 (0.33 to 2.48)	52.2	0.23
Latitude: Lower latitude ($< 44^\circ\text{N}$)	3	0.80 (0.65 to 0.99)	0.0	
Confounder adjustment: Adjusted for smoking and BMI	3	0.86 (0.61 to 1.21)	40.9	0.66
Confounder adjustment: Not adjusted for both	2	0.81 (0.24 to 2.74)	32.0	
Risk of bias: Low (NOS ≥ 7)	4	0.85 (0.76 to 0.96)	11.4	0.22
Risk of bias: Moderate (NOS 5–6)	1	0.66 (0.45 to 0.98)	—	
Sex: men†	2	0.79 (0.63 to 0.99)	0.0	0.94
Sex: women†	2	0.82 (0.33 to 2.03)	78.4	
B. Vitamin D status				
Overall (primary analysis)	6	0.67 (0.48 to 0.92)	52.6	
95% prediction interval		0.38 to 1.18		
Exposure measure: Measured 25(OH)D	5	0.71 (0.49 to 1.05)	43.2	0.20
Exposure measure: Predicted 25(OH)D	1	0.54 (0.39 to 0.75)	—	
Study design: Cohort or nested case-control	5	0.71 (0.54 to 0.93)	38.0	0.054
Study design: Case-control	1	0.30 (0.13 to 0.72)	—	
Effect metric: Highest vs lowest category	4	0.55 (0.31 to 0.98)	28.1	0.051
Effect metric: Per doubling of 25(OH)D	2	0.79 (0.45 to 1.41)	0.0	
Risk of bias: Low (NOS ≥ 7)	5	0.71 (0.54 to 0.93)	38.0	0.054
Risk of bias: Moderate (NOS 5–6)	1	0.30 (0.13 to 0.72)	—	
Sex: men†	2	0.93 (0.38 to 2.25)	85.7	0.21
Sex: women†	2	0.50 (0.32 to 0.76)	0.0	

All subgroup and sex-specific analyses were exploratory. Relative risks (RR) are from random-effects models (DerSimonian–Laird τ^2 , Hartung–Knapp 95% CI) fitted separately within each subgroup; rows with $k = 1$ show the single study estimate, and Hartung–Knapp intervals with $k = 2$ are wide by construction. p values test the difference between subgroups. †Sex-specific estimates were available from two studies per domain and were pooled with Wald-type intervals. BMI, body mass index; CI, confidence interval; NOS, Newcastle–Ottawa Scale; 25(OH)D, 25-hydroxyvitamin D.

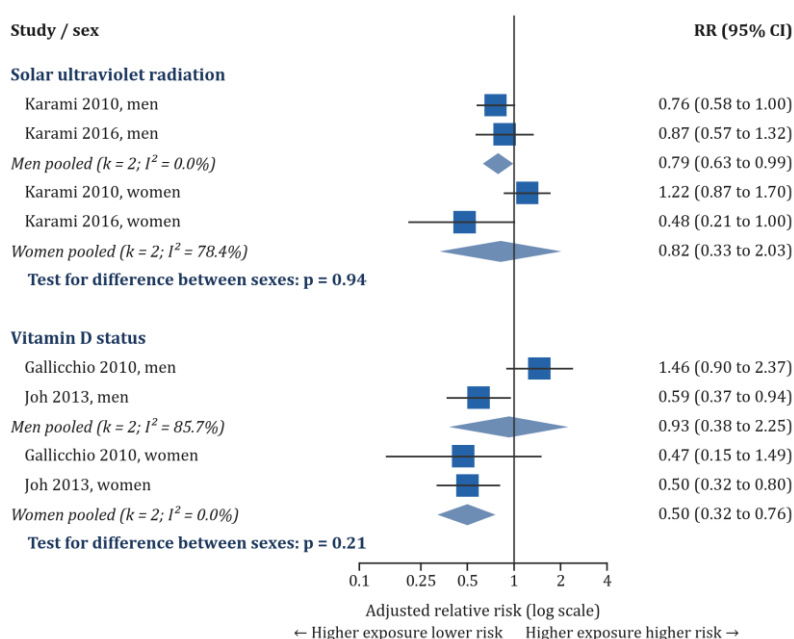


Figure 5. Sex-specific adjusted relative risks for solar ultraviolet radiation and vitamin D status. Diamonds are random-effects pooled estimates with Wald-type 95% confidence intervals (two studies per stratum); p values test the difference between men and women.

Sensitivity analyses

Sensitivity analyses are illustrated in Figure 6. Omitting each UV study in turn gave RRs between 0.83 and 0.85; the Hartung–Knapp interval included unity only when the Nordic study (0.83 [0.65 to 1.07]) or the NIH-AARP cohort (0.84 [0.67 to 1.06]) was omitted. The restricted maximum likelihood (0.85 [0.77 to 0.93]), Paule–Mandel (0.84 [0.74 to 0.96]) and common-effect (0.85 [0.80 to 0.90]) models gave nearly identical results. Restriction to the three studies adjusted for both smoking and BMI gave 0.86 (0.61 to 1.21).

For vitamin D status, the leave-one-out estimates ranged from 0.61 (omitting Muller 2014) to 0.71 (omitting Joh 2013); omitting the consortium gave 0.65 (0.44 to 0.94) and omitting the Chinese case-control study 0.71 (0.54 to 0.93). Restriction to measured 25(OH)D gave 0.71 (0.49 to 1.05), restriction to the three studies with full covariate and case information gave 0.55 (0.16 to 1.97), and replacing the predicted-score estimate with its BMI-adjusted version gave 0.70 (0.53 to 0.93).

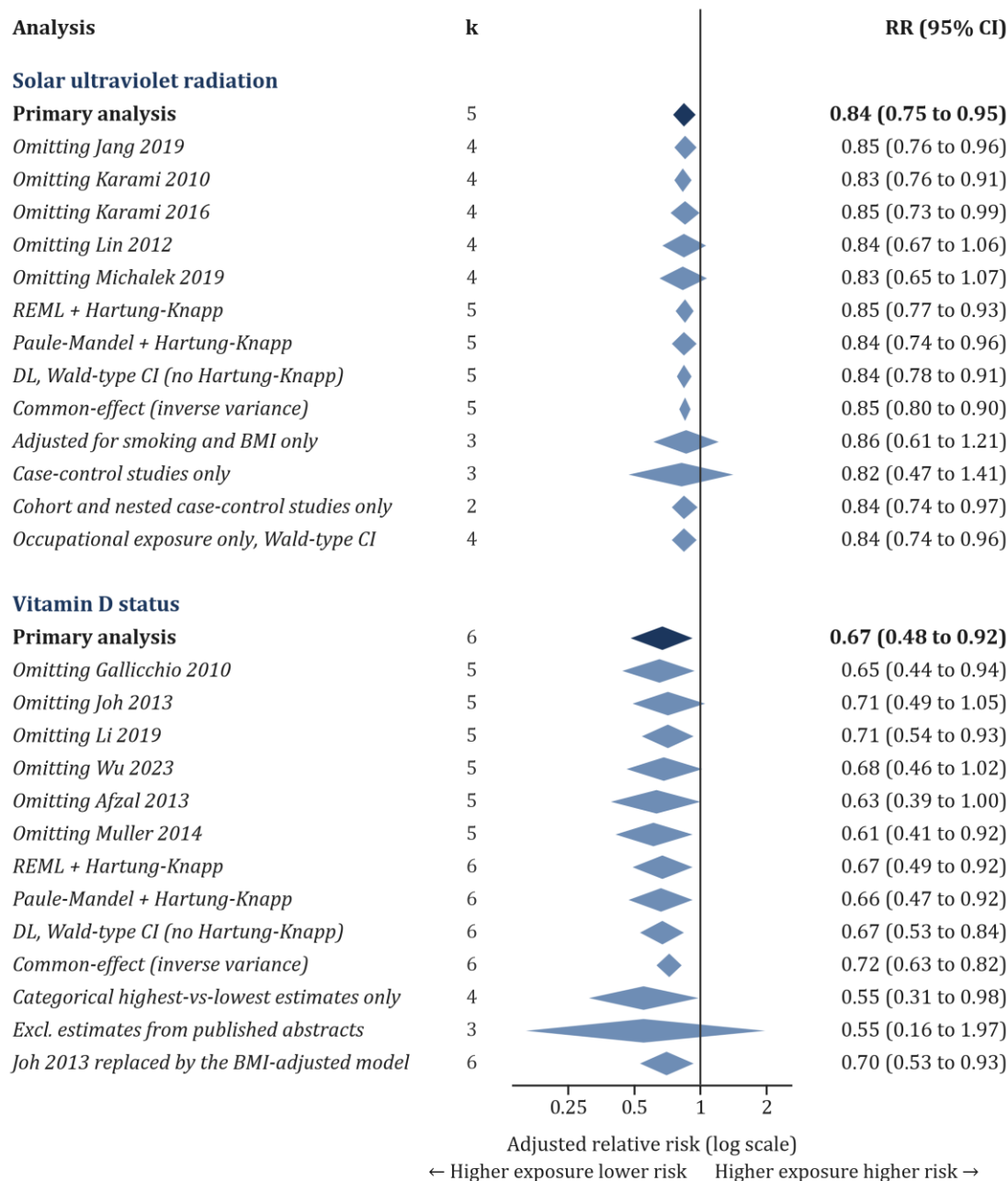


Figure 6. Sensitivity analyses: pooled relative risks after omitting each study in turn and under alternative estimators and study sets. Diamonds show point estimates with 95% confidence intervals; the dark diamond is the primary analysis of each domain. BMI, body mass index; DL, DerSimonian–Laird; REML, restricted maximum likelihood.

Small-study effects and certainty of evidence

The funnel plots (Figure 7) showed no obvious asymmetry, although with five and six studies they had little power to detect it. The certainty of evidence is summarized in Table 5. For solar

UV exposure it was low: it was rated down for indirect exposure assessment and up for the exposure-response gradients observed within four of the five studies. For vitamin D status it was very low because of inconsistency and indirectness.

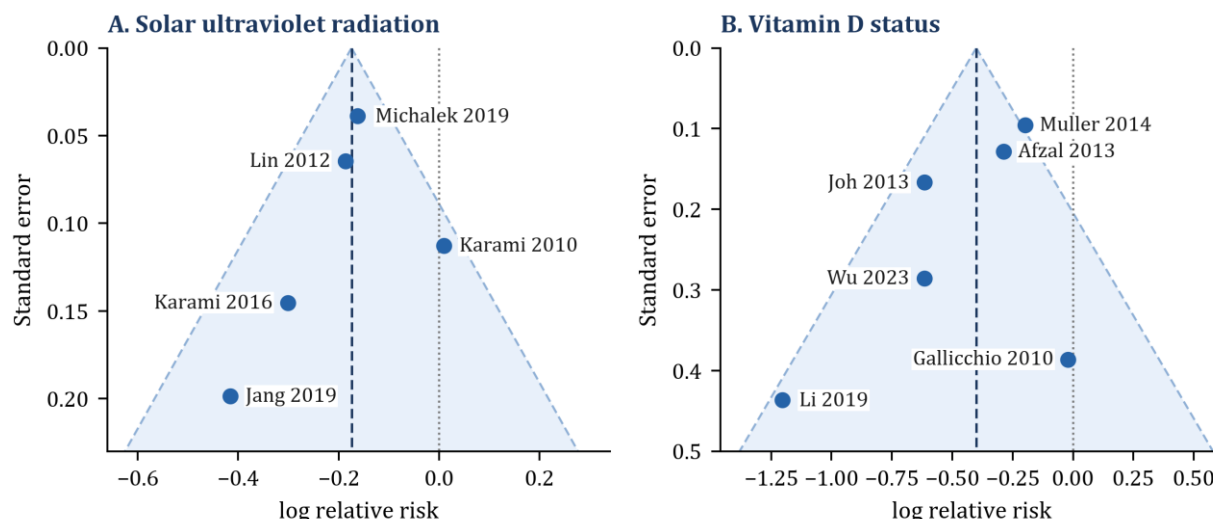


Figure 7. Funnel plots of the log relative risks against their standard errors for (A) solar ultraviolet radiation and (B) vitamin D status. The dashed line marks the pooled estimate, the dotted line no association and the shaded triangle the pseudo 95% confidence region.

Table 5. Summary of findings and certainty of evidence (GRADE).

Outcome	Studies (participants; cases)	Relative effect (95% CI)	Certainty	Assessment
Incident RCC/kidney cancer, highest vs lowest solar UV exposure	5 (815,893 participants; 64,648 cases)	RR 0.84 (0.75 to 0.95)	⊕⊕○○ Low	Risk of bias: Not serious (four of five studies at low risk; excluding the moderate-risk study did not change the estimate). Inconsistency: Not serious (I^2 18.2%; prediction interval 0.72 to 0.99). Indirectness: Serious (exposure assigned from job-exposure matrices or residential ambient UV rather than personal dose; one study included renal pelvis tumors). Imprecision: Not serious (95% CI 0.75 to 0.95). Publication bias: Not assessable (fewer than 10 studies); funnel plot without obvious gap. Rating up: Exposure-response gradient (p for trend <0.05 in four of five studies); +1.
Incident RCC/kidney cancer, highest vs lowest vitamin D status	6 (229,333 participants; ≥1,878 cases)	RR 0.67 (0.48 to 0.92)	⊕○○○ Very low	Risk of bias: Not serious (five of six studies at low risk). Inconsistency: Serious (I^2 52.6%; prediction interval 0.38 to 1.18; null consortium estimate). Indirectness: Serious (two estimates per doubling of 25(OH)D, one predicted score, one cohort restricted to metabolic syndrome). Imprecision: Not serious (95% CI 0.48 to 0.92). Publication bias: Not assessable (fewer than 10 studies). Rating up: None.

Observational evidence started at low certainty and was rated down or up according to Core GRADE. CI, confidence interval; RCC, renal cell carcinoma; RR, relative risk (pooled odds, risk and hazard ratios); UV, ultraviolet.

4. Discussion

Principal findings

To our knowledge, this is the first review to pool the individual-level evidence on solar UV exposure and RCC. Across five studies, the highest exposure was associated with a 16% lower risk, with little heterogeneity, a prediction interval below unity and exposure-response gradients within four of the five studies. The occupational studies gave the same point estimate, but with the primary interval method their pooled estimate was compatible with no association. Vitamin D status pointed in the same direction (highest versus lowest category, RR 0.55 [95% CI 0.31 to 0.98]; per doubling of 25(OH)D, 0.79 [0.45 to 1.41]), but the estimates were heterogeneous, the prediction interval included unity, and the largest consortium found no association. The certainty of evidence was low and very low, respectively.

Comparison with previous evidence

Earlier evidence on sunlight and kidney cancer came mainly from ecological comparisons of regional UV and incidence or mortality rates, as reviewed by the authors of the included occupational studies;^{52,54} such comparisons cannot separate individual exposure from regional confounding. The individual-level studies pooled here reduce that problem. The magnitude of the association resembled that reported for occupational UV and prostate or colon cancer in Danish men and women^{24,25} and for residential UV and estrogen receptor-negative breast cancer.²⁶ Higher residential UV was also associated with lower all-cause and cancer mortality in UK Biobank,⁶³ whereas null results for lymphoma and for prostate cancer in a Canadian

cohort showed that the pattern is not universal across cancer sites.^{28,29}

For vitamin D status, the present estimate agreed in direction with an earlier meta-analysis of circulating vitamin D,³⁸ which did not include the UK Biobank cohort or consider sunlight itself. Lower 25(OH)D was associated with higher mortality from several common cancers in UK Biobank,⁶⁴ whereas Mendelian randomization studies did not support causal effects of genetically predicted 25(OH)D on overall or colorectal cancer⁶⁵ or of genetically predicted time outdoors on colorectal cancer,⁶⁶ and no such analysis has yet focused on RCC. Large supplementation trials did not reduce overall cancer incidence.⁴⁰

Interpreting the two exposure domains

The two domains answered different questions in different populations, and their results were not combined into a single causal argument. Agreement in direction was compatible with a vitamin D-mediated effect, but it did not demonstrate mediation, because no study measured both exposures in the same participants. Two features nevertheless deserve comment. First, the UV estimate was more precise and more consistent than the vitamin D estimate, even though vitamin D status was closer to the proposed mechanism. A single 25(OH)D measurement reflects recent months, whereas occupational histories integrated exposure over decades, which may be the relevant window for a cancer with a long latency. Second, sunlight might act through pathways other than vitamin D, such as effects on systemic immunity or circadian biology, so an association with

UV exposure does not require a matching association with a single 25(OH)D measurement.

The null consortium result had specific explanations. Male smokers from the ATBC trial made up 36.9% of the consortium sample, and after their exclusion the authors reported more inverse estimates at both extremes of 25(OH)D (0.57, 95% CI 0.27 to 1.17, for 100 nmol/L or more versus the middle reference).⁵⁷ In three of the eight cohorts blood had been drawn only about two years before diagnosis, and the reference category lay in the middle of the distribution. At the other extreme, the strongest estimate came from a hospital-based study in which 25(OH)D was measured at diagnosis, when illness, reduced outdoor activity and the tumor itself may have lowered concentrations; reverse causation cannot be excluded there.⁶² The UK Biobank estimate came from participants with metabolic syndrome,⁶⁰ in whom adiposity, which lowers 25(OH)D³⁷ and raises RCC risk,^{9,10} may confound the association. The vitamin D results are therefore best read as weak, inconsistent support rather than as confirmation.

Confounding and bias

Outdoor work entailed more physical activity, which was itself associated with a lower RCC risk in large cohorts,^{12,13} and manual outdoor workers might be leaner, while the healthy-worker effect selected fitter people into physically demanding jobs. All three biases acted in the same direction as the hypothesized UV effect. In the Nordic study, perceived physical workload was itself inversely associated with kidney cancer, and the UV estimate was mutually adjusted for it but not for smoking or BMI.⁵⁵ The two job-history studies adjusted for smoking, BMI and hypertension,^{52,53} and the NIH-AARP cohort for BMI, smoking and routine and vigorous physical activity,⁵⁶ and their pooled estimate (0.86 [95% CI 0.61 to 1.21]; Table 4) was similar to that of the Nordic study. Residual confounding of the size needed to explain a 16% lower risk could not be excluded, but it would have to be similar across settings with very different adjustment sets.

Two observations argue partly against confounding by outdoor physical work alone. In the European study the inverse association was confined to men in low-intensity occupations (the study classed agricultural and rural outdoor jobs as high intensity) and was strongest at the most northerly center, and in the US study it was confined to jobs with low-intensity exposure.^{52,53} Cutaneous vitamin D synthesis reaches a plateau with prolonged exposure, so short or low-intensity exposures may be more efficient,⁵³ and at high latitudes, where vitamin D status reflects UVB accumulated over the summer, sustained low-intensity exposure may matter more than peak intensity;^{19,20} this pattern is more consistent with a vitamin D-related effect than with a simple marker of heavy outdoor labor. Occupational co-exposures such as chlorinated solvents, pesticide-related agricultural tasks and welding fumes were more common in outdoor and industrial jobs and were, if anything, associated with higher kidney cancer risk,^{14,16,55} so

they were more likely to have masked than to have produced an inverse association. Non-differential misclassification from job-exposure matrices would usually bias estimates toward the null.

Heterogeneity, latitude and sex

Heterogeneity was low among the UV studies, but the Korean and US estimates were stronger than the European ones. The exploratory latitude grouping suggested a slightly stronger association below 44°N, the opposite of the pattern within the European study, so no consistent latitude gradient could be inferred from five studies. Some genetic determinants of vitamin D status differ by ancestry and interact with ambient UVB,⁶⁷ whereas genetic isoforms of vitamin D-binding protein rarely modified associations between 25(OH)D and cancer, with a possible exception for bladder cancer;⁶⁸ the available studies could not examine either source of variation.

The sex-specific analyses were exploratory and underpowered. In domain A, the two case-control studies with sex-specific estimates pointed in opposite directions for women, and their pooled estimates for men and women did not differ. In domain B, the association appeared stronger in women, consistent with the female-specific estimate in the consortium⁵⁷ and, for dietary vitamin D intake, with the earlier meta-analysis,³⁸ but the difference was not statistically significant. Differences between men and women in occupational exposure patterns, clothing, skin type and adiposity could all produce such patterns, and larger studies with sex-specific reporting are needed to resolve them.

Biological plausibility

Kidney-specific evidence for a role of vitamin D was limited but consistent with the hypothesis. The vitamin D receptor and CYP27B1 are expressed along the developing nephron, and vitamin D pathway genes are dysregulated in renal tumors,²¹ as summarized conceptually in Figure 8. In clear cell RCC, low receptor expression was associated with shorter survival, and restoring receptor expression in tumor cells suppressed β -catenin/Smad3 signaling and DNA-damage pathways.²² Clear cell RCC is driven by pseudohypoxic hypoxia-inducible factor (HIF) signaling and angiogenesis, which shape treatment response,^{69,70} and is characterized by an immunosuppressive tumor microenvironment that includes CD39⁺CD8⁺ T cells.⁷¹

Evidence from other tumors was more extensive but less directly applicable. Vitamin D modulated microbiome-dependent cancer immunity in experimental models,⁷² increased memory CD8 T cells and reduced regulatory T cells in human colon tumors in a randomized trial,⁷³ and reduced M1 and M2 macrophage markers when added ex vivo to macrophages derived from patients with breast cancer.⁷⁴ Whether these effects occur in the renal tumor microenvironment remains unknown. The mechanistic evidence therefore makes an effect of chronic sunlight exposure on renal carcinogenesis plausible but does not establish it.

Exposure measured in domain A → status measured in domain B → putative anti-tumour actions in the kidney

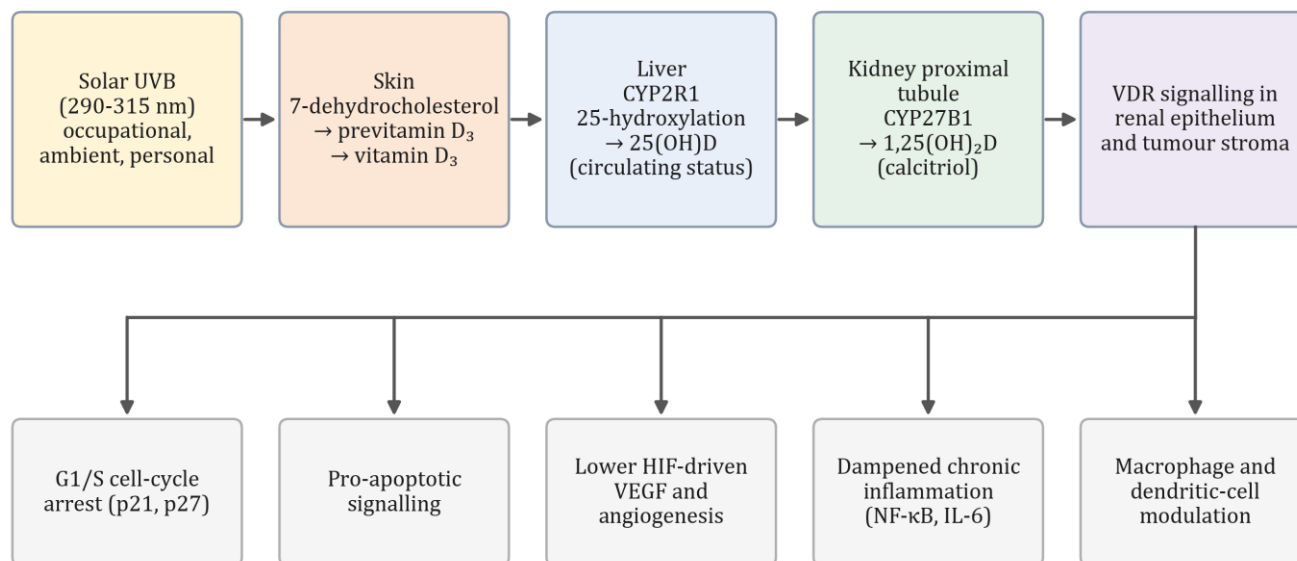


Figure 8. Conceptual diagram of hypothesized mechanisms (not findings of this review) linking the two exposure domains. Solar ultraviolet B radiation drives cutaneous vitamin D synthesis, circulating 25-hydroxyvitamin D [25(OH)D] reflects vitamin D status, and renal 1 α -hydroxylation (CYP27B1) produces calcitriol [1,25(OH)₂D], which acts through the vitamin D receptor (VDR) on processes relevant to renal carcinogenesis.

Relevance for urological and surgical practice

RCC remains a predominantly surgically treated disease, and surgeons and urologists see most patients at the point of diagnosis. The findings do not alter diagnostic or operative management, including the active surveillance of small renal masses.⁷⁵ They are relevant to surgical practice in three ways. First, a structured occupational history at presentation, already shown to identify compensable exposures such as trichloroethylene,¹⁸ could routinely record outdoor work and sun exposure at little extra cost. Second, surgical cohorts with stored pre-operative blood would be well placed to study 25(OH)D, vitamin D-binding protein and tumor receptor expression together, provided that blood taken at diagnosis is interpreted in the light of possible reverse causation. Third, the results should not be translated into advice to increase sun exposure, because occupational UV exposure is associated with a higher incidence of melanoma and basal cell carcinoma.^{30,32} Correcting vitamin D deficiency remains appropriate on its own merits, but supplementation has not reduced cancer incidence,⁴⁰ and low-dose UVB lighting used by indoor workers during working hours did not maintain 25(OH)D in winter.⁷⁶

Applicability to tropical settings

All included studies came from latitudes between about 23°N and 70°N, and only one domain A study came from Asia. In equatorial countries such as Indonesia, vitamin D-effective UVB is available throughout the year and a few minutes of midday exposure can maintain vitamin D status in people with light skin,²⁰ so the contrast between indoor and outdoor workers in vitamin D synthesis is likely to be smaller than at high latitudes and to depend more on clothing, skin type and indoor occupations. The present estimates should therefore not be transferred directly to tropical populations. Occupational cohorts in South-East Asia, where outdoor agricultural, construction and fishing work remains common, would provide a valuable test of the hypothesis under very different exposure conditions.

Strengths and limitations

The strengths of this review were the separation of exposure and biomarker into prespecified domains, the use of adjusted

estimates, the re-expression of category-specific estimates to a common contrast, Hartung–Knapp and prediction intervals suited to small numbers of studies, explicit checks of population overlap, sensitivity analyses that address each influential study, and a formal certainty assessment that distinguishes the two domains.

The limitations are important. First, few studies were available in each domain, so subgroup comparisons had little power and publication bias could not be tested formally; small negative occupational studies might remain unpublished. Second, Embase, Scopus and Web of Science were not searched; citation searching found no additional eligible study, but some studies may have been missed. Third, exposure was assessed indirectly, by job-exposure matrices or residential UV, without personal dosimetry, and recreational exposure was not captured. Fourth, residual confounding by physical activity, BMI and occupational co-exposures could not be excluded, and the largest UV study had no individual data on smoking or BMI. Fifth, the vitamin D estimates mixed categorical and log-linear contrasts, included a predicted score and a cohort restricted to metabolic syndrome, and three reports gave limited detail on covariates and case numbers. Sixth, three reports could not be obtained, one occupational case-control study, one recreational exposure study and one occupational cohort (two identified by database searching and one by citation searching; Figure 1), and all included studies came from temperate or high-latitude populations. Seventh, screening and extraction were performed by one reviewer, with a second verification of every exclusion and extracted value, which was less protective than independent duplicate assessment.

Implications for research

The research priorities identified were cohorts measuring personal UV dose with wearable dosimeters, repeated 25(OH)D concentrations and physical activity, with enough incident RCC cases to examine histological subtypes and sex; occupational studies in tropical and low-latitude countries, where outdoor work is common and UV exposure high all year; analyses in existing consortia that report kidney cancer separately from other genitourinary cancers; and Mendelian randomization analyses of 25(OH)D and RCC using large genetic consortia.

Studies of surgical cohorts should combine pre-operative 25(OH)D, vitamin D-binding protein and tumor vitamin D receptor expression with long-term outcomes.

5. Conclusion

In this systematic review and meta-analysis, higher solar UV exposure, assessed mainly through occupation, was associated with a 16% lower incidence of RCC, with consistent results across studies and exposure-response gradients within studies, although the occupational subset alone was compatible with no association under the primary interval method. Higher vitamin D status pointed in the same direction (categorical estimate RR 0.55 [95% CI 0.31 to 0.98]) but was heterogeneous, and the largest consortium found no association. The certainty of evidence was low for solar UV exposure and very low for vitamin D status, and confounding by outdoor physical work could not be excluded. The findings are compatible with the hypothesis that sunlight modestly lowers RCC risk, possibly in part through the renal vitamin D pathway, but they do not demonstrate it. They do not justify changes to sun-protection advice, because occupational UV exposure is a recognized risk factor for skin cancer. For urologists and surgical oncologists, a structured occupational and sun-exposure history and stored pre-operative blood in surgical cohorts would allow the hypothesis to be tested. Prospective studies with personal UV dosimetry, repeated 25(OH)D measurements and adjustment for physical activity, including studies in tropical populations, were identified as the main research need.

6. Declarations

Ethics Approval and Consent to Participate

Not applicable. This review analyzed published aggregate data only.

Consent for Publication

Not applicable. The review contains no individually identifiable participant data.

Availability of Data and Materials

The search strategies, the list of records excluded at each stage with reasons, the extraction workbook and the R and Python scripts that reproduce every analysis and figure are provided as Supplementary Material and are available from the corresponding author on reasonable request.

Artificial Intelligence Use Statement

None.

Author Contribution Statement

R.D.H.: Conceptualization, Methodology, Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. The author reviewed and approved the final manuscript.

Funding Statement

None.

Conflict of Interest / Competing Interests

The author declares no competing interests.

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