Antihypertensive Medications and Risk of Melanoma and Keratinocyte Carcinomas: A Systematic Review and Meta-Analysis

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Some antihypertensive medications are photosensitizing. The implications for skin cancer risk remain unclear because results from prior studies are inconsistent and as new evidence is published. We performed a systematic review and meta-analysis to evaluate the association between antihypertensives and common skin cancers (cutaneous squamous cell carcinoma, basal cell carcinoma, and melanoma) and to evaluate dose−response relationships. Forty-four articles met inclusion criteria, and 42 could be meta analyzed. Increased risks were seen for basal cell carcinoma with calcium channel blockers (relative risk [RR] = 1.17, 95% confidence interval [CI] = 1.11−1.22), diuretics (RR = 1.06, 95% CI = 1.03−1.10), and thiazides (RR = 1.10, 95% CI = 1.04−1.16); for squamous cell carcinoma with calcium channel blockers (RR = 1.08, 95% CI = 1.01−1.14), diuretics (RR = 1.29, 95% CI = 1.17−1.43), and thiazides (RR = 1.36, 95% CI = 1.15−1.61); and for melanoma in angiotensin-converting enzyme inhibitors (RR = 1.09, 95% CI = 1.03−1.14), calcium channel blockers (RR = 1.08, 95% CI = 1.03−1.12), and thiazides (RR = 1.09, 95% CI = 1.02−1.17). The quality of evidence was low or very low. We observed evidence for dose−response for thiazides with basal cell carcinoma; angiotensin-converting enzyme inhibitors, diuretics, and thiazides with squamous cell carcinoma; and angiotensin-converting enzyme inhibitors, diuretics, and thiazides with melanoma. Our meta-analysis supports a potential causal association between some antihypertensives, particularly diuretics, and skin cancer risk.

Keywords: Basal cell carcinoma, Epidemiology, Health services research, Melanoma, Squamous cell carcinoma

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INTRODUCTION

Despite dozens of primary papers and several meta-analyses, there is a significant knowledge gap in understanding the relationship between antihypertensive medications and skin cancers. Some antihypertensive medications are known to be photosensitizing: hydrochlorothiazide, for example, is a well-documented cause of phototoxic and photoallergic skin eruptions. When medications designed for chronic use (including many antihypertensives) are photosensitizing, this leads to concern for increased skin cancer risks. In fact, hydrochlorothiazide labeling requirements starting in 2020 in the United States require description of an increased risk of basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (SCC) (U. S. Food & Drug Administration, 2020). Although there have been many analyses of the association between antihypertensive medications and skin cancers, these have yielded conflicting results. This association is critically important to evaluate both from a public health perspective, given the frequency and chronicity of these prescriptions, and from a research perspective, owing to implications for important risk factors that should perhaps be collected and used in skin cancer research.

To address the conflicting results on antihypertensive medications and skin cancer in the literature, there have been several prior systematic reviews and meta-analyses (Gandini et al, 2018; Tang et al, 2018a, 2018b). However, not only do the primary papers on antihypertensive medications and skin cancer have conflicting results, but the 3 meta-analyses, all published in 2018, also have discordant conclusions. Prior meta-analyses have not been comprehensive in terms of the antihypertensive medications evaluated nor the outcomes included (ie, BCC, SCC, melanoma, and all skin cancers) and did not include rigorous assessment of dose−response

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Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; BCC, basal cell carcinoma; CCB, calcium channel blocker; CI, confidence interval; RR, relative risk; SCC, squamous cell carcinoma

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relationships. Finally, several large, high-quality papers (Pedersen et al, 2018; Pottegård et al, 2019, 2018; Su et al, 2018) have been published in the last several years, which were not included in the prior meta-analyses and which could significantly impact the conclusions. The aim of this systematic review and meta-analysis was to examine the most contemporary and complete evidence on the effect of antihypertensive medications on skin cancer, specifically the most common types (SCC, BCC, and melanoma), and to evaluate any dose–response relationships that may support a causal association.

RESULTS

Search results

The systematic literature search identified 8640 entries. After additional records were identified through review of reference lists, and duplicates were removed, there were 7898 unique articles to screen. Of these, 129 full-text articles were assessed for eligibility. After double independent review, 85 articles were excluded (flow diagram is shown in Figure 1). Notably, 3 studies (Friis et al, 2001; Jensen et al, 2008; Olsen et al, 1997) met inclusion criteria but had overlapping data with a larger and more recent study (Schmidt et al, 2015) and were thus excluded. Finally, 44 articles (Adalsteinsson et al, 2021; Beiderbeck-Noll et al, 2003; Bright et al, 2021; Chang et al, 2015; Christian et al, 2008; Daniels et al, 2020; de Vries et al, 2012; Drucker et al, 2021; Dyer et al, 2012; Eworuke et al, 2021; Fujimoto et al, 2017; Gallelli et al, 2022; Ghiasvand et al, 2023; Habel et al, 2021; Hole et al, 1998, 1993; Kaae et al, 2010; Kim et al, 2021; Koomen et al, 2009; Lecaros-Astorga et al, 2021; Lee et al, 2020; León-Muñoz et al, 2021; Lever et al, 1998; Lindholm et al, 2001; McDonald et al, 2014; Morales et al, 2020; Nardone et al, 2017; Pahor et al, 1996; Park et al, 2020; Pedersen et al, 2018; Pottegård et al, 2019, 2018; Robinson et al, 2013; Rosenberg et al, 1998; Rouette et al, 2021; Ruiter et al, 2010; Sajadieh et al, 1999; Schmidt et al, 2015; Schneider et al, 2021; Su et al, 2018; Tiba et al, 2022; VanWormer et al, 2022; Westerdahl et al, 1996; Xiong et al, 2013) were included in the qualitative synthesis of the available evidence (Table 1). Twenty were case controls, 19 were cohorts, and 5 were randomized trials. Individual papers reported on 1 or more skin cancer outcomes: 17 reported on BCC, 16 reported on SCC, 24 reported on melanoma, and 17 reported on a combination of skin cancer outcomes. The majority of studies (25 of 42) included in

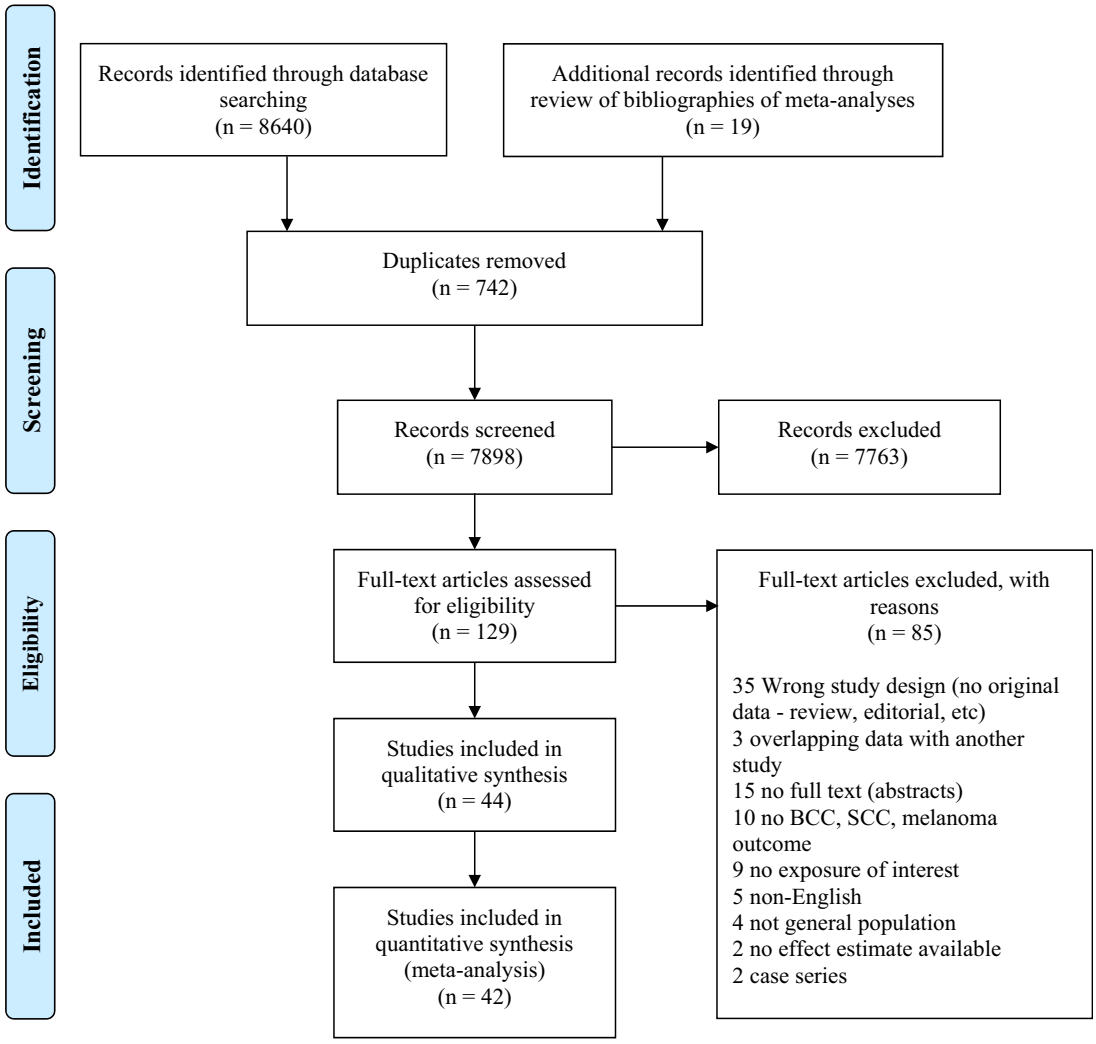

Figure 1. PRISMA flow diagram of included and excluded studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Characteristics of Included Studies

Study Characteristics					Outcomes				Adjusting Variables							Meta-Analysis
Study	Country	Data Source	n	Drug Categories	Melanoma	BCC	SCC	Skin Cancer	Age	Sex	Race	Phenotype[1]	Sun Exposure	Skin Cancer History	Other Medical Comorbidities	Included Studies
Case Control																
Adalsteinsson et al, 2021[2]	Iceland	Icelandic Prescription and Cancer Registries	6880	Thiazides (hydrochlorothiazide)		x	x		x	x					x	x
Bright et al, 2021	India	Large tertiary care hospital records	90	Thiazides (hydrochlorothiazide)				x								x
Daniels et al, 2020[3]	Australia	Australian Department of Veterans Affairs	13,105	ACEIs, ARBs, CCBs, diuretics, thiazides (hydrochlorothiazide)[4]	x				x	x			x		x	x
de Vries et al, 2012	Finland, Germany, Greece, Italy, Malta, Poland, Scotland, Spain	11 dermatology centers	2921	Thiazides (bendroflumethiazide)	x	x	x		x	x		x				x
Gallelli et al, 2022	Italy	Multicenter medical records	19,320	Thiazides (hydrochlorothiazide)				x	x	x						x
Ghiasvand et al, 2023[5]	Norway	The Cancer Registry of Norway, the National Registry, and the Norwegian Prescription Database	129,943	β-Blockers, CCBs, diuretics, renin-angiotensin system-acting agents	x								x			x
Habel et al, 2021[6]	US	Kaiser Permanente Northern California	273,957	Thiazides (hydrochlorothiazide)	x				x	x						x
Koomen et al, 2009	The Netherlands	PHARMO and PALGA databases	8104	ACEIs, ARBs	x				x	x					x	x
Lecaros-Astorga et al, 2021	Spain	Spanish Pharmacovigilance System for Medicinal Products of Human Use	13	Thiazides (hydrochlorothiazide)	x	x	x									x
León-Muñoz et al, 2021[7]	Spain	SIDIAP and BIFAP	12,048,410	Thiazides (hydrochlorothiazide)	x	x	x		x	x					x	x
Morales et al, 2020[8]	United Kingdom	The Health Improvement Network Database	2,415,633	Thiazides (hydrochlorothiazide)	x	x	x		x	x					x	x
Pedersen et al, 2018	Denmark	Danish cancer registry	1,683,507	Thiazides (hydrochlorothiazide)[9]		x	x		x	x					x	x
Pottegård et al, 2018[10]	Denmark	Danish cancer registry	212,003	ACEIs, ARBs, CCBs, thiazides[9]	x				x	x				x	x	x

(continued)

Table 1. Continued

Study Characteristics					Outcomes				Adjusting Variables							Meta-Analysis
Study	Country	Data Source	n	Drug Categories	Melanoma	BCC	SCC	Skin Cancer	Age	Sex	Race	Phenotype[1]	Sun Exposure	Skin Cancer History	Other Medical Comorbidities	Included Studies
Pottegård et al, 2019[11]	Taiwan	National Health Insurance Research Database	319,902	Thiazides (hydrochlorothiazide)	x			x	x	x					x	x
Robinson et al, 2013[12]	US	New Hampshire Health Study	5072	Cardiovascular drugs (thiazides, loop diuretics, CCBs, K- sparing diuretics, alpha, amiodarone, quinidine, sulfonylureas)		x	x		x	x			x			x
Rosenberg et al, 1998[13]	US	Hospitalized patients	11,005	ACEIs, β-blockers, CCBs	x				x	x	x				x	x
Schmidt et al, 2015	Denmark	Danish cancer registry	254,927	ACEIs, ARBs, β-blockers, CCBs, diuretics, thiazides[9]	x	x	x		x	x					x	x
Tiba et al, 2022[14]	Brazil	Brazilian Association of Dermatology survey	89	Thiazides (hydrochlorothiazide)				x	x	x		x		x	x	x
VanWormer et al, 2022	US	Marshfield Clinic Health System (MCHS)	999	Thiazides (hydrochlorothiazide)				x	x				x		x	x
Westerdahl et al, 1996	Sweden	South Swedish Health Care Region Regional Tumour Registry	1367	β-Blockers, diuretics, thiazides	x				x	x		x	x			x
Cohort																
Beiderbeck-Noll et al, 2003	The Netherlands	Rotterdam Study	3204	CCBs				x	x	x					x	x
Chang et al, 2015	Taiwan	Longitudinal Health Insurance Database 2000, subset of the Taiwan Nation Health Insurance Research Database	24,238	β-Blockers				x	x	x					x	x
Drucker et al, 2021[15]	Canada	Administrative dataset	907,902	ACEIs, ARBs, β-blockers, CCBs, thiazides	x			x	x	x					x	x
Eworuke et al, 2021[16]	US	US Food and Drug Administration's Sentinel System	10,422,642	Thiazides (hydrochlorothiazide)		x	x		x	x					x	x

(*continued*)

Table 1. Continued

Study Characteristics					Outcomes				Adjusting Variables							Meta-Analysis
Study	Country	Data Source	n	Drug Categories	Melanoma	BCC	SCC	Skin Cancer	Age	Sex	Race	Phenotype[1]	Sun Exposure	Skin Cancer History	Other Medical Comorbidities	Included Studies
Fujimoto et al, 2017	US; Japan	US Food and Drug Administration Adverse Event Reporting System; Japan Medical Data Center claims database	3,308,116 ;96,012	ARBs	x											x
Kim et al, 2021[17]	Korea	National Health Insurance Service National Sample Cohort	1,125,691	Thiazides (hydrochlorothiazide)				x	x	x					x	x
Rouette et al, 2021[18]	United Kingdom	United Kingdom Clinical Practice Research Datalink	20,513	Thiazides (hydrochlorothiazide)	x	x	x		x	x					x	x
Schneider et al, 2021	United Kingdom	UK primary-care database	546,417	Thiazides	x	x	x		x	x					x	x
Hole et al, 1993	Scotland	Glasgow Blood Pressure Clinic	6528	β-Blockers (atenolol)	x			x	x	x						x
Hole et al, 1998	Scotland	Glasgow Blood Pressure Clinic	5207	CCBs	x			x	x	x						x
Kaae et al, 2010[19]	Denmark	Danish cancer registry	4,761,749	Thiazides (bendroflumethiazide)[6], diuretics (loops), β-blockers (atenolol), ACEIs, alpha agonists (methyldopa), CCBs (verapamil)	x	x	x		x	x						x
Lee et al, 2020[20]	South Korea	Observational Medical Outcomes Partnership; (OMOP) Common Data Model Network	667,348	Thiazides (hydrochlorothiazide)	x			x	x	x					x	x
Lever et al, 1998	Scotland	Glasgow Blood Pressure Clinic	5207	ACEIs; diuretics or CCBs or β-blockers or other				x	x	x						x
McDonald et al, 2014[21]	US	United States Radiologic Technologists Study	58,213	Diuretics		x			x	x			x		x	x
Nardone et al, 2017[22]	US	Northwestern Medicine Enterprise Data Warehouse	224,469	ACEIs, ARBs, thiazides	x	x	x		x	x	x				x	x
	US		5052	CCBs				x	x	x					x	x

(*continued*)

Table 1. Continued

Study Characteristics					Outcomes				Adjusting Variables							Meta-Analysis
Study	Country	Data Source	n	Drug Categories	Melanoma	BCC	SCC	Skin Cancer	Age	Sex	Race	Phenotype[1]	Sun Exposure	Skin Cancer History	Other Medical Comorbidities	Included Studies
Pahor et al, 1996		Established Populations for Epidemiologic Studies of the Elderly														
Park et al, 2020[23]	South Korea	Health Insurance Review and Assessment Service	3,565,952	Thiazides (hydrochlorothiazide)	x			x	x	x					x	x
Ruiter et al, 2010[24]	The Netherlands	Rotterdam Study	10,994	Diuretics (loops), thiazides, diuretics (K+ sparing)		x			x	x						x
Su et al, 2018	US	KPNC's Research Program in Genes and Environmental Health	28,357	ACEIs, ARBs, β-blockers, CCBs, thiazides			x		x	x				x	x	x
Randomized controlled trials																
Christian et al, 2008[25]	US	Department of Veterans Affairs Topical Tretinoin Chemoprevention Trial	1051	ACEIs/ARBs, β-blockers, CCBs, diuretics		x	x		x	x	x	x		x	x	x
Dyer et al, 2012	US	Department of Veterans Affairs Topical Tretinoin Chemoprevention Trial	1131	ACEIs/ARBs		x			x	x		x	x	x		
Lindholm et al, 2001	Sweden	STOP-Hypertension-2 study population	6614	ACEIs; CCBs; β-blockers and diuretics (thiazides and K+ sparing)	x			x	x	x						x
Sajadieh et al, 1999[26]	Denmark	Danish Verapamil Infarction Trial II	1775	CCBs				x								x
Xiong et al, 2013	US	Department of Veterans Affairs Topical Tretinoin Chemoprevention Trial	1131	ACEIs/ARBs			x		x	x			x	x		

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BCC, basal cell carcinoma; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria; CCB, calcium channel blocker; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; KPNC, Kaiser Permanente Northern California; NMSC, nonmelanoma skin cancer; NSAID, nonsteroidal anti-inflammatory drug; PALGA, Pathological Anatomy National Automated Archive; SCC, squamous cell carcinoma; SIDIAP, The Information System for Research in Primary Care; US, United States.

PHARMO denotes PHARMO Database Network.

[1]Phenotype is any skin phototype, propensity to tan or burn, skin color, eye color, hair color, or related skin phenotype.

[2]Adalsteinsson et al (2021) matched on age and sex, adjusted for use of other photosensitizing medications, including tetracyclines and retinoids.

[3]Daniels et al (2020) matched on age and sex, adjusted for photosensitizing medications and possible anticancer effects, comorbidities by Charlson Comorbidity Index score, and UVR by residence latitude.

[4]In Australia, hydrochlorothiazide is often prescribed in combination with other antihypertensive drugs; ever use of any hydrochlorothiazide containing medication was analyzed, as was cumulative dose of hydrochlorothiazide.

[5]Ghiasvand et al (2022) adjusted for region of ambient UVR exposure and all CVD medications.

[6]Habel et al (2021) adjusted for age; sex; calendar time of follow-up; highest education achieved; socioeconomic level on the basis of the US Census block of residence; and number of ambulatory visits, including dermatology visits, internal medicine visits, and urgent care visits for the period from start of follow-up to 1 year prior to the index date.

[7]León-Muñoz et al (2021) adjusted for age, sex, time up to index date since first day registered in database, any use of photosensitizing drugs, any use of drugs with suggested antineoplastic effects, any use of glucocorticoids, comorbidity (diagnosis of diabetes, COPD, chronic kidney disease, myocardial infarct, heart failure, peripheral vascular disease, cerebrovascular accident, dementia or Alzheimer's disease, connective tissue disease, gastric ulcer, hemiplegia, liver disease), and smoking status.

[8]Morales et al (2020) matched on age and sex, adjusted for smoking and body mass index.

[9]In Denmark, hydrochlorothiazide is prescribed almost exclusively in combination with other antihypertensive drugs; cumulative dose of hydrochlorothiazide was analyzed.

[10]Pottegård et al (2018) reported on 2 separate thiazide groups; the larger group was chosen in primary analysis.

[11]Pottegård et al (2019) adjusted for age, sex, and calendar time (by risk-set matching and the conditional analysis); use of topical retinoids, oral retinoids, tetracycline, macrolides, aminoquinolines, or amiodarone; use of aspirin, nonaspirin, nonsteroidal anti-inflammatory drugs, or statins; history of diabetes or COPD; and Charlson Comorbidity Index score.

[12]Robinson et al (2013) adjusted for phenotype but found that it was not a significant confounder and thus did not include it in the final models (and not included in this study).

[13]Rosenberg et al (1998) adjusted for body mass index and number of visits to physician 2 years prior to admission, which was considered as other medical comorbidities.

[14]Tiba et al (2022) matched on age, sex, smoking status, and Fitzpatrick skin phototype and adjusted for age, sex, phototype, and personal or family history of skin cancer.

[15]Drucker et al (2021) adjusted for age, sex, location of residence (urban or rural), socioeconomic status on the basis of residential postal code, history of hypertension, Charlson Comorbidity Index, and time-varying cumulative dose of each of the other 4 nonindex antihypertensive classes.

[16]Eworuke et al (2021) adjusted for year of treatment initiation, age, sex, presence of high-risk skin conditions for NMSC, use of photosensitizing medications, use of drugs with potential chemoprotective effects, use of immunosuppressive medications, diabetes mellitus, human papilloma virus, arsenic exposure, and alcohol use or abuse; healthcare utilization metrics; a comorbidity score; and UV exposure.

[17]Kim et al (2021) matched on index date, sex, age group, and income level and adjusted for age, sex, Charlson Comorbidity Index, prior photosensitizing mediation use (doxycycline, piroxicam, naproxen, ibuprofen, amiodarone, and furosemide), and prevalence of common systemic comorbidities (hypertension, diabetes, dyslipidemia, and thyroid disorders).

[18]Rouette et al (2021) matched on calendar year of cohort entry, previous use of antihypertensive drugs, and propensity score with a caliper of 0.01. Rouette et al (2021) adjusted for age, sex, alcohol-related disorders, body mass index, smoking status, number of physician visits, comorbidities (including congestive heart failure, precancerous skin conditions, cancers other than skin cancer, organ transplantation), healthcare utilization, and drug use (statins, NSAIDs, antiparkinsonian drugs, immunosuppressive drugs, antidiabetic drugs, antihypertensive drugs).

[19]Kaae et al (2010) reported on 2 separate ACEI and diuretic groups; the larger group was chosen in primary analysis, unless the effect estimate overlapped completely with the 95% CI, and thus an SE was unable to be calculated, in which case the estimate was excluded from meta-analysis.

[20]Lee et al (2020) adjusted for age, sex, aspirin, statins, NSAIDs, history of diabetes or COPD, and Charlson Comorbidity Index score and also propensity score matched.

[21]McDonald et al (2014) adjusted for body mass index, which was considered as other medical comorbidities.

[22]Nardone et al (2017) adjusted for phenotype: hair color, eye color, propensity to burn, skin phototype (skin response to sun exposure).

[23]Park et al (2020) adjusted for age, sex, and Charlson Comorbidity Index score.

[24]Ruiter et al (2010) reported on 2 separate groups within diuretic users; the larger group (high ceiling loops) was used in primary analysis, and the smaller (K sparing) group was used in sensitivity analysis.

[25]Christian et al (2008) adjusted for sun sensitivity score, which was considered phenotype.

[26]Sajadieh et al (1999) reported on men and women separately; the larger group (males) was chosen for primary analysis.

Table 2. Risk of Bias Assessment within Individual Studies

Study	Country	Case Definition	Representativeness	Case Selection	Case Control Studies (Newcastle-Ottawa) Control Definition	Comparability	Exposure Ascertainment	Same Method of Ascertainment for Cases and Controls	Nonresponse Rate	Selection (of 4 Possible)	Comparability (of 2 Possible)	Exposure (of 3 Possible
Adalsteinsson et al, 2021	Iceland	1	1	1	1	1	1	1	na	4	1	2
Bright et al, 2021	India	1	1	1	1	1	1	1	na	3	1	2
Daniels et al, 2020	Australia	1	1	1	1	2	1	1	na	4	2	2
De Vries et al, 2012	Finland, Germany, Greece, Italy, Malta, Poland, Scotland and Spain	1	1	0	1	1	0	0	0	3	1	0
Gallelli et al, 2022	Italy	1	1	1	1	2	1	1	na	3	2	2
Ghiasvand et al, 2022	Norway	1	1	1	1	2	1	1	na	4	2	2
Habel et al, 2021	US, CA	1	1	1	1	2	1	1	na	4	2	3
Koomen et al, 2009	The Netherlands	1	1	1	1	1	1	1	na	4	1	2
Lecaros-Astorga et al, 2021	Spain	0	0	1	1	1	1	1	na	2	1	1
León-Muñoz et al, 2021	Spain	1	1	1	1	2	1	1	na	4	2	3
Morales et al, 2020	UK	1	1	1	1	1	1	1	na	4	1	2
Pedersen et al, 2018	Denmark	1	1	1	1	1	1	1	na	4	1	2
Pottegård et al, 2018	Denmark	1	1	1	1	2	1	1	na	4	2	2
Pottegård et al, 2019	Taiwan	0	1	1	1	2	1	1	na	3	2	2
Robinson et al, 2013	US, NH	1	0	1	0	2	1	1	1	2	2	3
Rosenberg et al, 1998	US	0	0	1	1	2	0	1	0	2	2	1
Schmidt et al, 2015	Denmark	1	1	1	1	1	1	1	na	4	1	2

(*continued*)

Table 2. Continued

Study	Country	Case Definition	Representativeness	Case Selection	Case Control Studies (Newcastle-Ottawa) Control Definition	Comparability	Exposure Ascertainment	Same Method of Ascertainment for Cases and Controls	Nonresponse Rate	Selection (of 4 Possible)	Comparability (of 2 Possible)	Exposure (of 3 Possible
Tiba et al, 2021	Brazil	1	1	1	1	1	1	1	1	2	1	2
VanWormer et al, 2022	US, north-central Wisconsin	1	1	1	1	1	1	1	na	3	2	2
Westerdahl et al, 1996	Sweden	1	1	1	1	2	0	1	1	4	2	2

Cohort Studies (Newcastle-Ottawa)

Study	Country	Representativeness of Exposed	Selection of Nonexposed	Ascertainment of Exposure	Outcome Not Present at Start	Comparability	Assessment of Outcome	Follow-Up Pong Enough	Adequacy of Follow-Up	Selection (of 4 Possible)	Comparability (of 2 Possible)	Outcome (of 3 Possible)
Beiderbeck-Noll et al, 2003	The Netherlands	1	1	1	1	1	1	1	1	4	1	3
Chang et al, 2015	Taiwan	1	1	1	1	2	1	1	1	4	2	3
Drucker et al, 2021	Canada	1	1	1	1	2	1	1	1	4	2	3
Eworuke et al, 2021	US	1	1	1	1	2	1	1	1	4	2	3
Fujimoto et al, 2017	US, Japan	0	0	1	0	0	1	0	0	1	0	1
Hole et al, 1993	Scotland	1	1	1	1	1	1	1	0	4	1	2
Hole et al, 1998	Scotland	1	1	1	1	1	1	1	0	4	1	2
Kaae et al, 2010	Denmark	1	1	1	1	1	1	1	1	4	1	3
Kim et al, 2021	Korea	1	1	1	1	2	1	1	1	3	2	3
Lee et al, 2020	Korea	1	1	1	1	2	1	1	1	4	2	3
Lever et al, 1998	Scotland	1	0	1	1	1	1	1	1	3	1	3
McDonald et al, 2014	US	0	1	0	1	2	1	1	1	2	2	3
Nardone et al, 2017	US, IL	1	1	1	1	2	1	1	1	4	2	3

(*continued*)

Table 2. Continued

Cohort Studies (Newcastle-Ottawa)

Study	Country	Representativeness of Exposed	Selection of Nonexposed	Ascertainment of Exposure	Outcome Not Present at Start	Comparability	Assessment of Outcome	Follow-Up Pong Enough	Adequacy of Follow-Up	Selection (of 4 Possible)	Comparability (of 2 Possible)	Outcome (of 3 Possible)
Pahor et al, 1996	US	1	1	1	1	1	1	1	1	4	1	3
Park et al, 2020	Korea	1	1	1	1	2	1	1	1	4	2	3
Rouette et al, 2021	UK	1	1	1	1	2	1	1	1	4	2	3
Ruiter et al, 2010	The Netherlands	1	1	1	1	1	1	1	1	4	1	3
Schneider et al, 2021	UK	1	1	1	1	2	1	1	1	4	2	3
Su et al, 2018	US, Northern CA	1	1	1	1	2	1	1	1	4	2	3
Christian et al, 2008[1]	US, IL CA AZ OK FL NC	0	1	1	1	2	1	1	1	3	2	3
Dyer et al, 2012[1]	US, IL CA AZ OK FL NC	0	1	1	1	2	1	1	1	3	2	3
Xiong et al, 2013[1]	US, IL CA AZ OK FL NC	0	1	1	1	2	1	1	1	3	2	3

RCT (RoB 2.0)

Study	Country	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Overall
Lindholm et al, 2001	Sweden	Low	Some	Low	Low	Low	Some
Sajadieh et al, 1999	Denmark	Low	Low	Low	Low	Low	Low

Abbreviations: AZ, Arizona; CA, California; FL, Florida; IL, Illinois; na, not applicable; NC, North Carolina; NH, New Hampshire; OK, Oklahoma; RCT, randomized controlled trial; RoS, risk of bias; UK, United Kingdom; US, United States.

The Newcastle-Ottawa Scale was used for nonrandomized studies, and the Cochrane RoB 2.0 tool was used for randomized trials. The Newcastle-Ottawa Scale quality instrument is scored by awarding points on the basis of a series of questions; possible total points are 4 points for selection, 2 points for comparability, and 3 points for outcomes. Details on Newcastle-Ottawa Scale can be found at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp, details on Cochrane RoB 2.0 can be found at https://www.riskofbias.info/welcome/rob-2-0-tool.

[1]Christian et al (2008), Dyer et al (2012), and Xiong et al (2013) are from an RCT (Department of Veterans Affairs Topical Tretinoin Chemoprevention Trial) but are presented in this study as a cohort because the intervention to which patients were randomized was a topical chemopreventive agent. The analyses presented used the patients enrolled in the trial as a cohort and evaluated antihypertensives and skin cancer risk.

Table 3. RR and 95% CI for Association between Antihypertensive Drugs and SCC

Study	Drug Name if Specified	RR	95% CI	Used in Main Analysis
α-Agonist				
Kaae et al, 2010	Methyldopa	1.3	0.8–2	
Aceis				
Kaae et al, 2010	Captopril	1.2	1–1.4	Used in sensitivity analysis (smaller n)
Kaae et al, 2010	Enalapril	1.1	1–1.2	—
Nardone et al, 2017		1.94	1.37–2.76	—
Schmidt et al, 2015		1.09	0.94–1.27	—
Su et al, 2018		1.10	1.01–1.19	—
ACEI/ARB				
Christian et al, 2008		0.61	0.48–0.78	
Xiong et al, 2013		0.65	0.51–0.84	
ARBs				
Nardone et al, 2017		2.22	1.37–3.61	—
Schmidt et al, 2015		1.16	0.95–1.41	—
Su et al, 2018		0.97	0.87–1.08	—
β-Blocker				
Christian et al, 2008		0.77	0.56–1.07	—
Kaae et al, 2010	Atenolol	1.0	0.9–1.1	—
Schmidt et al, 2015		1.08	0.95–1.24	—
Su et al, 2018		1.04	0.96–1.12	—
CCBs				
Christian et al, 2008		0.91	0.67–1.23	—
Kaae et al, 2010	Verapamil	1.1	1–1.3)	—
Schmidt et al, 2015		1.13	0.99–1.29	—
Su et al, 2018		1.06	0.98–1.15	—
Diuretics				
Christian et al, 2008		1.09	0.79–1.51	—
Kaae et al, 2010	Furosemide	1.4	1.3–1.4	—
Kaae et al, 2010	Bumetanide	1.2	1–1.4	Used in sensitivity analysis (smaller n)
Robinson et al, 2013		1.3	0.9–1.2	—
Schmidt et al, 2015		1.19	1.06–1.33	—
Thiazides				
Adalsteinsson et al, 2021	HCTZ	1.02	0.81–1.29	Used in sensitivity analysis (smaller n)
Adalsteinsson et al, 2021	HCTZ	1.24	1.01–1.52	—
de Vries et al, 2012	Bendroflumethiazide	1.66	1.16–2.37	—
Eworuke et al, 2021	HCTZ	1.15	1.12–1.17	—
Kaae et al, 2010[1]	Bendroflumethiazide	1.0	0.8–1.2	—
Lecaros-Astorga et a, 2021	HCTZ	3.22	0.98–10.564	—
León-Muñoz et al, 2021; BIFAP	HCTZ	1.32	1.23–1.41	—
Morales et al, 2020	HCTZ	1.22	0.99–1.50	Used in sensitivity analysis (5-year lag time)
Morales et al, 2020	HCTZ	1.25	1.05–1.48	—
Nardone et al, 2017		4.11	2.66–6.35	—
Pedersen et al, 2018[1]	HCTZ	1.75	1.66–1.85	—
Robinson et al, 2013		1.3	0.7–2.4	—
Rouette et al, 2021	HCTZ	1.5	1.06–2.11	—
Schmidt et al, 2015[1]		1.03	0.91–1.17	—
Schneider et al, 2021		1.15	1.12–1.18	—
Su et al, 2018		1.09	0.99–1.19	—
Cardiovascular/antihypertensive drugs (grouped)				
Su et al, 2018		1.06	0.98–1.15	
Robinson et al, 2013		1.30	1–1.7	

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria; CCB, calcium channel blocker; CI, confidence interval; HCTZ, hydrochlorothiazide; RR, relative risk; SCC, squamous cell carcinoma.

Meta-analysis was not performed for drug categories with <3 independent observations.

[1]In Denmark, HCTZ is prescribed almost exclusively in combination with K-sparing diuretic, amiloride, ACEI, or ARB; content of HCTZ was identified in all combination or single drugs dispensed to individuals in the study population, and on the basis of this information, the cumulative dose of HCTZ to which each individual had been exposed up to index date was calculated.

Table 4. RR and 95% CI for Association between Antihypertensive Drugs and BCC

Study	Drug Name if Specified	RR	95% CI	Used in Main Analysis
α-Agonist				
Kaae et al, 2010	Methyldopa	1.3	1–1.6	
ACEI				
Kaae et al, 2010	Captopril	1.0	1–1.1	—
Kaae et al, 2010	Enalapril	1.0	1–1	CI overlaps with estimate; no SE was able to be calculated, excluded from analysis
Nardone et al, 2017		2.23	1.78–2.81	—
Schmidt et al, 2015		1.02	0.96–1.08	—
ACEI/ARB				
Christian et al, 2008		0.61	0.5–0.74	
Dyer et al, 2012		0.72	0.6–0.86	
ARB				
Nardone et al, 2017		2.86	2.13–3.83	
Schmidt et al, 2015		1.09	1.01–1.17	
β-Blocker				
Christian et al, 2008		1.12	0.88–1.44	—
Kaae et al, 2010	Atenolol	1.0	(1–1.1	—
Schmidt et al, 2015		1.09	1.04–1.15	—
CCB				
Christian et al, 2008		1.16	0.92–1.46	—
Kaae et al, 2010	Verapamil	1.2	1.1–1.3	—
Schmidt et al, 2015		1.15	1.09–1.22	—
Diuretics				
Christian et al, 2008		0.99	0.76–1.29	—
Kaae et al, 2010	Furosemide	1.0	1–1	CI overlaps with estimate; no SE able to be calculated, excluded from analysis
Kaae et al, 2010	Bumetanide	1.0	0.9–1.1	—
McDonald et al, 2014		1.22	1.07–1.38	—
Schmidt et al, 2015		1.05	1–1.1	—
Ruiter et al, 2010	K-sparing	1.04	0.93–1.17	Used in sensitivity analysis (smaller n)
Ruiter et al, 2010	Loop	1.07	1.02–1.13	—
Thiazides				
Adalsteinsson et al, 2021	HCTZ	1.14	1.02–1.29	—
de Vries et al, 2012	Bendroflumethiazide	1.27	0.92–1.75	—
Eworuke et al, 2021	HCTZ	1.09	1.07–1.11	—
Kaae et al, 2010[1]	Bendroflumethiazide	1.0	1–1.1	—
Lecaros-Astorga et al, 2021	HCTZ	4.86	2.2–10.74	—
León-Muñoz et al, 2021; BIFAP	HCTZ	1.06	1.03–1.10	—
Morales et al, 2020	HCTZ	1.06	0.98–1.15	Used in sensitivity analysis (5-y lag time)
Morales et al, 2020	HCTZ	1.10	1.03–1.17	—
Nardone et al, 2017		2.11	1.6–2.79	—
Pedersen et al, 2018[1]	HCTZ	1.08	1.06–1.1	—
Rouette et al, 2021	HCTZ	1.01	0.91–1.13	—
Ruiter et al, 2010		1.00	0.95–1.05	—
Schmidt et al, 2015[1]		1.05	1–1.11	—
Schneider et al, 2021		1.17	1.1–1.24	—
Cardiovascular/antihypertensive drugs (grouped)				
Robinson et al, 2013		0.8	0.5–1.3	

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BCC, basal cell carcinoma; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria; CCB, calcium channel blocker; CI, confidence interval; HCTZ, hydrochlorothiazide; RR, relative risk.

Meta-analysis was not performed for drug categories with <3 independent observations.

[1]In Denmark, HCTZ is prescribed almost exclusively in combination with K-sparing diuretic, amiloride, ACEI, or ARB; content of HCTZ was identified in all combination or single drugs dispensed to individuals in the study population, and on the basis of this information, the cumulative dose of HCTZ to which each individual had been exposed up to the index date was calculated.

meta-analysis adjusted for age, sex, and other comorbidities. A minority (6 of 42) adjusted for race or skin phenotype (phototype, propensity to tan or burn, skin color, eye color, hair color, or related skin phenotype measure), and a minority (7 of 42) adjusted for sun exposure. Risk of bias in the comparability domain of Newcastle–Ottawa Scale (because

Table 5. RR and 95% CI for Association between Antihypertensive Drugs and MM

Study	Drug Name if Specified	RR	95% CI	Used in Main Analysis
α-Agonist				
Kaae et al, 2010	Methyldopa	1.5	1–2.3	
ACEI				
Daniels et al, 2020		1.14	0.97–1.34	—
Drucker et al, 2021		0.98	0.73–1.32	—
Kaae et al, 2010	Captopril	0.9	0.7–1.1	Used in sensitivity analysis (smaller n)
Kaae et al, 2010	Enalapril	1.1	1–1.2	—
Koomen et al, 2009		1.00	0.8–1.3	—
Lindholm et al, 2001		1.70	0.78–3.23	—
Nardone et al, 2017		1.71	0.97–3	—
Pottegard et al, 2018		1.07	0.99–1.16	—
Rosenberg et al, 1998		1.30	0.5–3.1	—
Schmidt et al, 2015		1.07	0.92–1.24	—
ARB				
Daniels et al, 2020		0.94	0.79–1.12	—
Drucker et al, 2021		1.73	0.63–4.75	—
Fujimoto et al, 2017; US		0.71	0.59–0.85	—
Fujimoto et al, 2017; Japan		1.70	0.73–4.29	—
Koomen et al, 2009		1.00	0.68–1.46	—
Nardone et al, 2017		1.24	0.54–2.85	—
Pottegard et al, 2018[1]		1.18	1.07–1.30	—
Schmidt et al, 2015		1.14	0.95–1.37	—
β-Blocker				
Drucker et al, 2021		0.76	0.55–1.05	—
Ghiasvand et al, 2022		0.97	0.92–1.03	—
Hole et al, 1993	Atenolol	1.43	0.36–3.89	—
Kaae et al, 2010	Atenolol	1.0	0.9–1.1	—
Rosenberg et al, 1998		1.20	0.87–1.65	—
Schmidt et al, 2015		1.15	1.01–1.3	—
Westerdahl et al, 1996		1.70	1.03–2.79	—
CCB				
Daniels et al, 2020		1.05	0.89–1.24	—
Drucker et al, 2021		0.86	0.55–1.35	—
Ghiasvand et al, 2022		1.10	1.03–1.17	—
Hole et al, 1998		0.52	0.026–2.57	—
Kaae et al, 2010	Verapamil	1.1	1–1.2	—
Lindholm et al, 2001		1.70	0.78–3.23	—
Pottegard et al, 2018		1.06	0.98–1.15	—
Rosenberg et al, 1998		1.60	0.8–3.1	—
Schmidt et al, 2015		0.97	0.84–1.12	—
Diuretics				
Daniels et al, 2020	Indapemide	1.22	0.88–1.68	Used in sensitivity analysis (smaller n)
Daniels et al, 2020	Furosemide	0.83	0.69–0.99	—
Ghiasvand et al, 2022		1.08	1.01–1.15	—
Kaae et al, 2010	Furosemide	2.0	1.36–2.98	—
Kaae et al, 2010	Bumetanide	0.9	0.7–1.1	Used in sensitivity analysis (smaller n)
Schmidt et al, 2015		1.04	0.93–1.17	—
Westerdahl et al, 1996		0.40	0.1–1.44	—
Thiazides				
Daniels et al, 2020	HCTZ	1.22	1.01–1.46	—
de Vries et al, 2012	Bendroflumethiazide	1.22	0.77–1.93	—
Drucker et al, 2021		1.34	1.01–1.78	—
Habel et al, 2021	HCTZ	1.09	1.03, 1.16	—
Kaae et al, 2010[1]	Bendroflumethiazide	1.3	1–1.6	—
Lecaros-Astorga et al, 2021	HCTZ	0.88	0.22–3.57	—
Lee et al, 2020	HCTZ	1.09	0.71–1.67	Used in sensitivity analysis (confounded by combination use)
Lee et al, 2020	HCTZ	1.19	0.33–4.32	—

(*continued*)

Table 5. Continued

Study	Drug Name if Specified	RR	95% CI	Used in Main Analysis
León-Muñoz et al, 2021; BIFAP	HCTZ	1.14	1.04−1.25	—
León-Muñoz et al, 2021; SIDIAP	HCTZ	1.19	1.12−1.27	—
Morales et al, 2019	HCTZ	1.18	0.91−1.53	Used in sensitivity analysis (5-y lag time)
Morales et al, 2019	HCTZ	1.09	0.88−1.36	—
Nardone et al, 2017		1.82	1.01−3.82	—
Park et al, 2020	HCTZ	0.85	0.75−0.97	—
Pottegard et al, 2018[1]	HCTZ	1.17	1.11−1.23	—
Pottegard et al, 2018[1]	Bendroflumethiazide	1.10	1.02−1.19	Used in sensitivity analysis (secondary analysis in original article)
Pottegard et al, 2019	HCTZ	0.90	0.82−0.99	—
Rouette et al, 2021	HCTZ	0.82	0.63−1.08	—
Schmidt et al, 2015[1]		1.11	0.97−1.25	—
Schneider et al, 2021		1.02	0.99−1.05	—
Westerdahl et al, 1996		1.40	0.7−2.8	—
Cardiovascular/antihypertensive drugs (grouped)				
Lindholm et al, 2001	Antihypertensives	1.39	0.87−2.1	
Lindholm et al, 2001	β-Blocker + diuretic (thiazide + K+ sparing)	0.76	0.21−1.93	
Westerdahl et al, 1996		1.30	1−1.9	

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria; CCB, calcium channel blocker; CI, confidence interval; HCTZ, hydrochlorothiazide; MM, melanoma; RR, relative risk; SIDIAP, The Information System for Research in Primary Care; US, United States.

Meta-analysis was not performed for drug categories with <3 independent observations.

[1]In Denmark, HCTZ is prescribed almost exclusively in combination with K-sparing diuretic, amiloride, ACEI, or ARB; content of HCTZ was identified in all combination or single drugs dispensed to individuals in the study population, and on the basis of this information, the cumulative dose of HCTZ to which each individual had been exposed up to the index date was calculated.

risk of confounding bias is particularly important in this research question) was assessed as low in approximately half of studies and high in the other half (low was full score [2] in comparability, high was 0 or 1 in comparability) (Table 2). Effect estimates for each included study by skin cancer outcome and by medication class are shown in Tables 3−6.

Meta-analysis

There were 21 medication class/skin cancer outcome combinations (eg, diuretics and SCC, thiazides and BCC) from 42 articles(Adalsteinsson et al, 2021; Beiderbeck-Noll et al, 2003; Bright et al, 2021; Christian et al, 2008; Daniels et al, 2020; de Vries et al, 2012; Drucker et al, 2021; Eworuke et al, 2021; Fujimoto et al, 2017; Gallelli et al, 2022; Ghiasvand et al, 2023; Habel et al, 2021; Hole et al, 1998, 1993; Kaae et al, 2010; Kim et al, 2021; Koomen et al, 2009; Lecaros-Astorga et al, 2021; Lee et al, 2020; León-Muñoz et al, 2021; Lindholm et al, 2001; McDonald et al, 2014; Morales et al, 2020; Nardone et al, 2017; Pahor et al, 1996; Park et al, 2020; Pottegård et al, 2019, 2018; Robinson et al, 2013; Rosenberg et al, 1998; Rouette et al, 2021; Ruiter et al, 2010; Sajadieh et al, 1999; Schmidt et al, 2015; Schneider et al, 2021; Su et al, 2018; Tiba et al, 2022; VanWormer et al, 2022; Westerdahl et al, 1996) that could be meta analyzed (if at least 3 independent studies were available), which included 43,210,409 participants.

BCC. For BCC, meta-analyses on angiotensin-converting enzyme inhibitors (ACEIs), β-blockers, calcium channel blockers (CCBs), diuretics, and thiazides were performed (Figure 2). Statistically significant increased risks were seen in CCBs (relative risk [RR] = 1.17, 95% confidence interval [CI] = 1.11−1.22, $I^2 < 1\%$) and diuretics (RR = 1.06, 95% CI = 1.03−1.10, $I^2 = 0\%$).

SCC. For SCC, meta-analyses on ACEIs, angiotensin receptor blockers, β-blockers, CCBs, diuretics, and thiazides were performed (Figure 3). Statistically significant increased risks were seen in CCBs (RR = 1.08, 95% CI = 1.01−1.14, $I^2 = 0\%$), diuretics (RR = 1.29, 95% CI = 1.17−1.43, $I^2 = 65\%$), and thiazides (RR = 1.36, 95% CI = 1.15−1.61, $I^2 = 99\%$).

Melanoma. For melanoma, meta-analyses on ACEIs, angiotensin receptor blockers, β-blockers, CCBs, diuretics, and thiazides were performed (Figure 4). Statistically significant increased risks were seen in ACEIs (RR = 1.09, 95% CI = 1.03−1.14, $I^2 = 0\%$), CCBs (RR = 1.08, 95% CI = 1.03−1.12, $I^2 < 1\%$), and thiazides (RR = 1.09, 95% CI = 1.02−1.17, $I^2 = 84\%$).

Combination skin cancer outcomes. For combination skin cancer outcomes, 3 studies on ACEIs, 3 studies on β-blockers, 6 studies on CCBs, and 11 studies on thiazides with combination nonmelanoma skin cancer outcomes (including BCC, SCC, and other nonmelanoma skin cancer types) were meta analyzed, with no statistically significant increased risks observed (Figure 5).

Sensitivity analyses. We conducted a number of sensitivity analyses. There were several included studies that reported results separately for >1 medication per medication class (eg, reported 2 thiazide medications separately and not

Table 6. RR and 95% CI for Association between Antihypertensive Drugs and Skin Cancer Overall

Study	Drug Name if Specified	RR	95% CI	Used in Main Analysis
ACEI				
Drucker et al, 2021		1.08	0.95–1.06	—
Lindholm et al, 2001		0.59	0.28–1.09	
Lever et al, 1998		0.65	0.28–1.283	
β-Blocker				
Chang et al, 2015	Propranolol	0.53	0.22–1.24	
Drucker et al, 2021		0.98	0.93–1.04	—
Hole et al, 1993	Atenolol	0.93	0.5165–1.548	
CCB				
Beiderbeck-Noll et al, 2003		2.83	1.1–7.5	—
Drucker et al, 2021		1.03	0.95–1.13	—
Hole et al, 1998		1.534	1.02–2.21	—
Pahor et al, 1996		1.11	0.14–8.62	—
Lindholm et al, 2001		0.84	0.46–1.42	—
Sajadieh et al, 1999	Verapamil, men	0.7	0.4–1.2	—
Sajadieh et al, 1999	Verapamil, women	0.7	0.2–2.2	Used in sensitivity analysis (smaller n)
Thiazides				
Bright et al, 2021		1.00	0.34–2.98	—
Drucker et al, 2021		1.08	1.03–1.14	—
Gallelli et al, 2022[1]	Hydrochlorothiazide	0.47	0.41–0.53	—
Kim et al, 2021		1.48	1.03–2.13	—
Lee et al, 2020	Hydrochlorothiazide	0.80	0.53–1.21	—
Lee et al, 2020	Hydrochlorothiazide	0.97	0.82–1.13	Used in sensitivity analysis (confounded by combination use)
León-Muñoz et al, 2021; BIFAP	Hydrochlorothiazide	1.10	1.07–1.14	—
León-Muñoz et al, 2021; SIDIAP	Hydrochlorothiazide	1.13	1.11–1.15	—
Park et al, 2020	Hydrochlorothiazide	0.96	0.91–1.02	—
Pottegard et al, 2019	Hydrochlorothiazide	1.10	1.06–1.14	—
Tiba et al, 2021	Hydrochlorothiazide	0.89	0.25–3.23	—
VanWormer et al, 2022	Hydrochlorothiazide	1.14	1.11–1.18	—
Cardiovascular/antihypertensive drugs (grouped)				
Lindholm et al, 2001	Antihypertensives	0.78	0.56–1.07	
Lindholm et al, 2001	β-Blocker + diuretic (thiazide + K+ sparing)	0.91	0.51–1.5	
Lever et al, 1998	Diuretics or CCB or β-blocker or other	1.37	0.9957–1.84	

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria; CCB, calcium channel blocker; CI, confidence interval; RR, relative risk; SIDIAP, The Information System for Research in Primary Care.

Meta-analysis was not performed for drug categories with <3 independent observations.

[1]ORs and 95% CIs were calculated for Gallelli et al (2022) for the total sample because the reported ORs were listed by men and women separately.

combined). We included the medication with larger sample size for the main analyses and performed sensitivity analyses for alternate medication(s). Results were similar (Figures 6–15).

Dose–response relationship. We collected information on dose–response analyses from each included paper, when present (22 studies) (Adalsteinsson et al, 2021; Daniels et al, 2020; Kaae et al, 2010; Koomen et al, 2009; Lee et al, 2020; McDonald et al, 2014; Morales et al, 2020; Park et al, 2020; Pedersen et al, 2018; Pottegård et al, 2019, 2018; Robinson et al, 2013; Rosenberg et al, 1998; Ruiter et al, 2010; Schmidt et al, 2015; Su et al, 2018). The measures used to evaluate dose–response relationship by different studies were too heterogenous to meta analyze because definitions varied (total cumulative dose per subject, years of use, etc). The dose–response analyses and results of each paper are shown in Table 7. In BCC, our meta-analysis results were statistically significant in thiazides. In diuretics, 1 of 5 dose–response analyses were statistically significant, and in thiazides, 7 of 18 dose–response analyses were statistically significant. In SCC, our meta-analysis results were statistically significant for ACEIs, diuretics, and thiazides. In ACEIs, 3 of 4 dose–response analyses were statistically significant; in diuretics, 3 of 4 dose–response analyses were statistically significant; and in thiazides, 7 of 14 dose–response analyses were statistically significant. In melanoma, our meta-analysis results were statistically significant in ACEIs, diuretics, and thiazides. In ACEIs, 0 of 9 dose–response analyses were statistically significant; in diuretics, 1 of 5 dose–response analyses were statistically significant; and in thiazides, 7 of 18 dose–response analyses were statistically significant. In

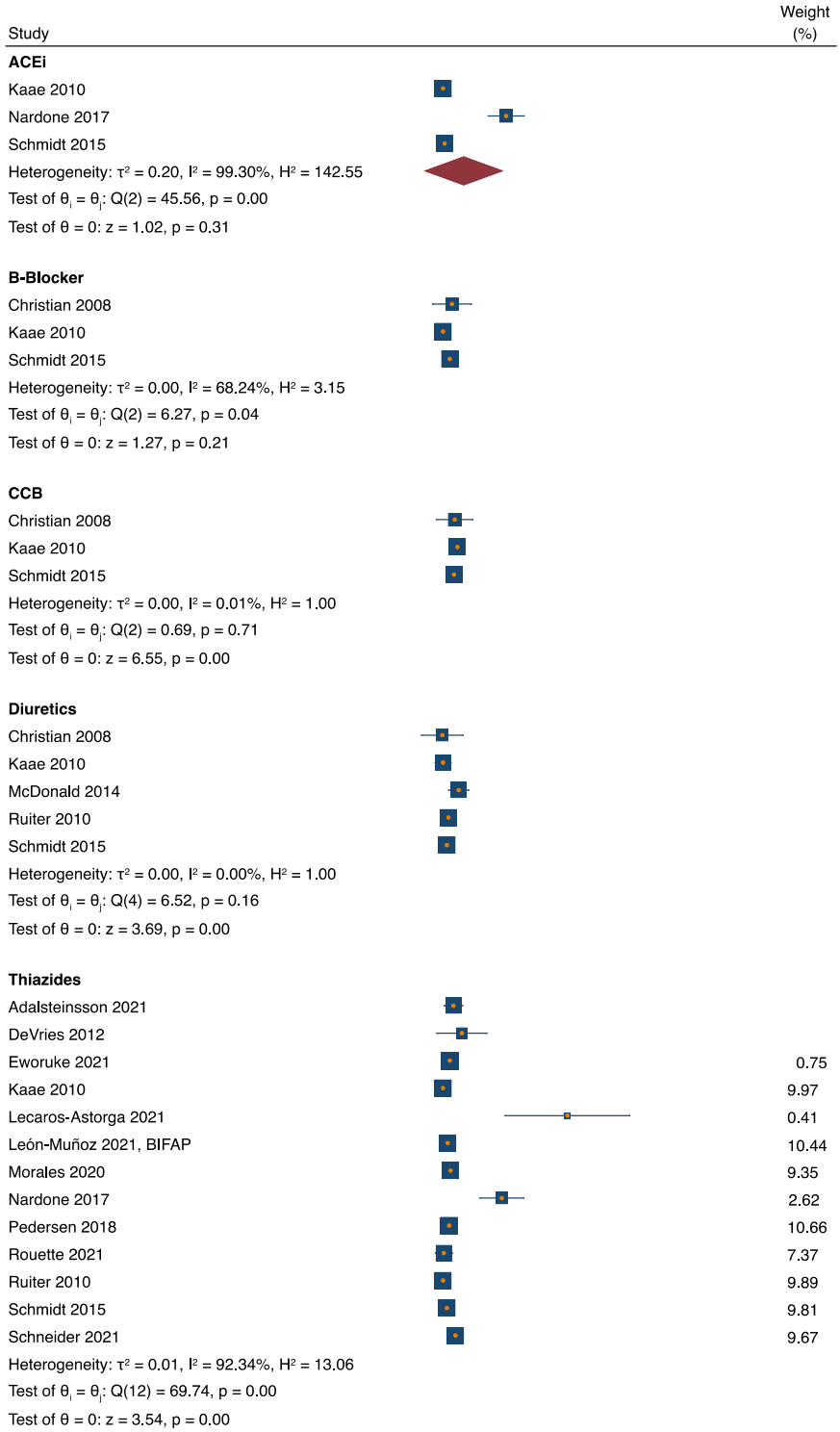

Figure 2. Results of meta-analyses: basal cell carcinoma outcome. Forest plots of the association between antihypertensive medication classes and basal cell carcinoma are shown. The square markers for each study indicate the effect estimate found in that study (also listed to the right of the markers). The size of the square marker indicates the weight of the study in the meta-analysis. The diamond marker indicates the result of the random-effects meta-analysis for that medication class, with the left and right corners showing the 95% confidence interval (also listed to the right of the marker).

combination skin cancer outcomes, no meta-analysis results were statistically significant. In CCBs, 2 of 6 dose–response analyses were statistically significant, and in thiazides, 6 of 11 dose–response analyses were statistically significant.

Quality of evidence. We used Grading of Recommendations, Assessment, Development and Evaluation to evaluate the quality of evidence for each outcome. For all statistically significant outcomes, the quality of evidence was low or very low. All outcomes had risk of bias, and the majority of outcomes had inconsistency of results and/or indirectness of evidence (Table 8 provides more detail).

DISCUSSION

In this study, we present results of a systematic review and meta-analyses of antihypertensive medications and skin

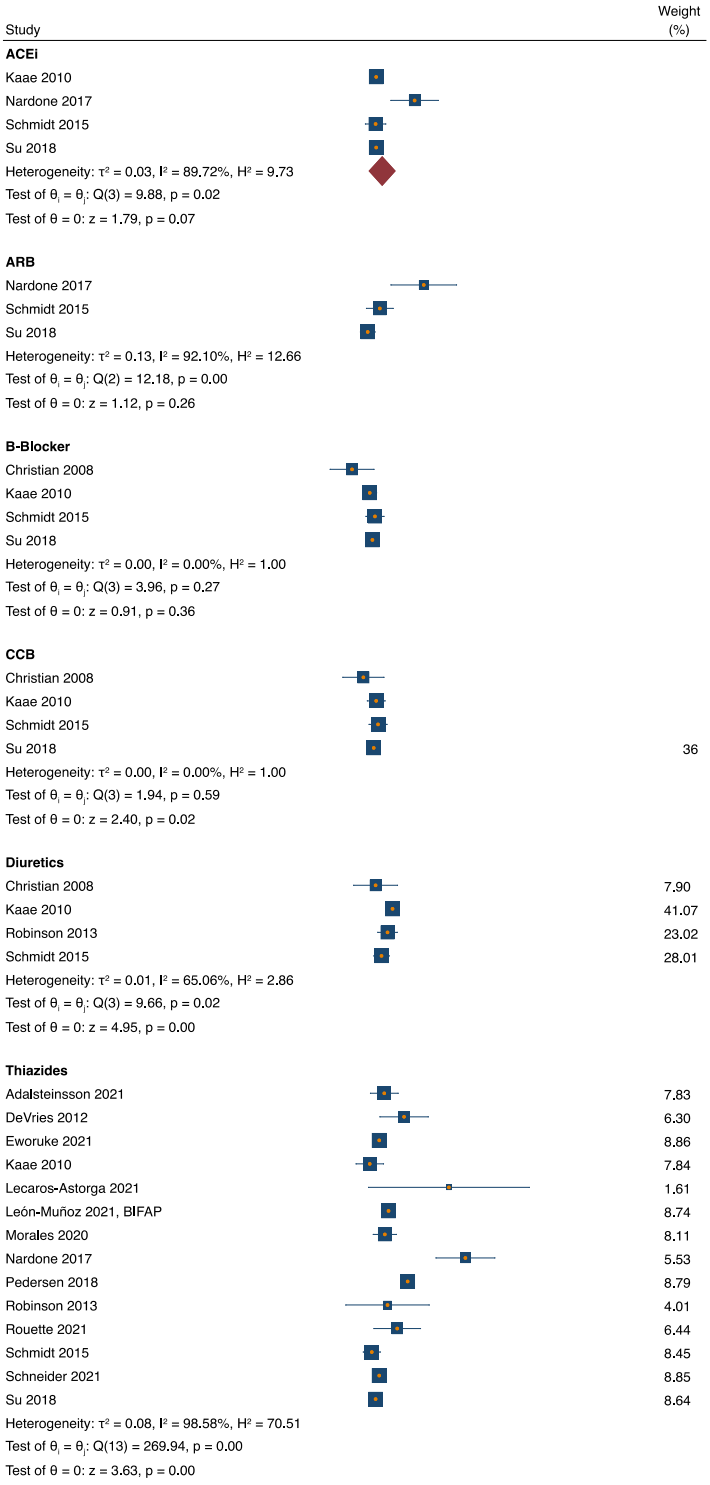

Figure 3. Results of meta-analyses: squamous cell carcinoma outcome. Forest plots of the association between antihypertensive medication classes and squamous cell carcinoma are shown. The square markers for each study indicate the effect estimate found in that study (also listed to the right of the markers). The size of the square marker indicates the weight of the study in the meta-analysis. The diamond marker indicates the result of the random-effects meta-analysis for that medication class, with the left and right corners showing the 95% confidence interval (also listed to the right of the marker).

cancer risk, specifically BCC, SCC, and melanoma. We used results from 42 studies including >43 million participants and performed 21 meta-analyses. We found statistically significant increased risks for (i) CCBs with BCC, SCC, and melanoma; (ii) diuretics with BCC and SCC; (iii) thiazides with BCC, SCC, and melanoma; and (iv) ACEIs with melanoma. Within these, we found larger, potentially clinically relevant effect sizes for thiazides with SCC (1.36, 95% CI = 1.15−1.61) and diuretics with SCC (1.29, 95% CI = 1.17−1.43). In addition, we observed evidence for a dose−response effect for thiazides with BCC; for ACEIs, diuretics, and thiazides with SCC; and for ACEIs, diuretics, and thiazides with melanoma. However, there was evidence for significant heterogeneity in thiazides and in diuretics with SCC, and the quality of evidence was low or very low for all these outcomes.

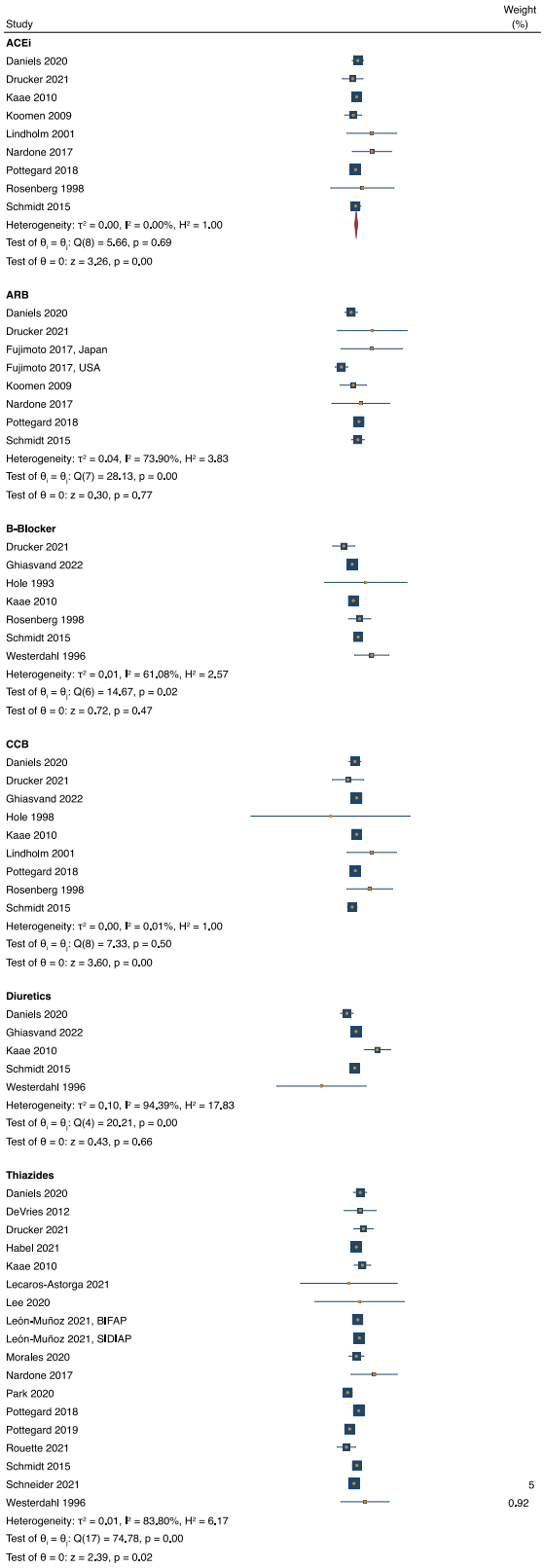

Figure 4. Results of meta-analyses: melanoma outcome. Forest plots of the association between antihypertensive medication classes and melanoma are shown. The square markers for each study indicate the effect estimate found in that study (also listed to the right of the markers). The size of the square marker indicates the weight of the study in the meta-analysis. The diamond marker indicates the result of the random-effects meta-analysis for that medication class, with the left and right corners showing the 95% confidence interval (also listed to the right of the marker).

These associations are also biologically plausible because there is evidence of medication-induced photosensitivity for several antihypertensive medication classes. Diuretics and thiazides in particular have fairly extensive support for causing photosensitivity (Drucker and Rosen, 2011; Frishman et al, 2002; Quintero and Miranda, 2000; Selvaag and Thune, 1997; Su et al, 2018). ACEIs have reports of photosensitivity, particularly enalapril (Drucker and Rosen, 2011; Frishman et al, 2002; Quintero and Miranda, 2000; Zammit, 2010), but are listed in some literature as unknown photosensitizing potential (Su et al, 2018). Angiotensin receptor blockers have a few reports (Drucker and Rosen, 2011; Quintero and Miranda, 2000; Zammit, 2010) but are often not considered photosensitizing (Su et al, 2018). CCBs, similar to ACEIs, have reports (Drucker and Rosen, 2011; Frishman et al, 2002; Quintero and Miranda, 2000; Zammit, 2010), but their photosensitization is unclear (Su et al, 2018). β-Blockers are often listed as nonphotosensitizing (Su et al, 2018), although there are reports of photosensitive eruptions (Drucker and Rosen, 2011; Frishman et al, 2002; Zammit, 2010). Our meta-analyses results with the larger effect sizes (thiazides and diuretics with SCC) fit well with the strongest evidence for biologic plausibility in the literature. Our statistically significant results in CCBs and ACEIs are less clear from a biologic plausibility standpoint and merit further investigation. In summary, our synthesis of existing studies supports a potential causal association between some antihypertensive medications, particularly diuretics overall as well as thiazides specifically, and skin cancer risk. We did not find statistically significant associations for 12 of the 21 meta-analyses we performed.

Our study has several strengths. We carefully evaluated overlapping study populations between individual papers to avoid including the same population more than once in meta-analysis, which was a limitation of prior meta-analyses (Gandini et al, 2018; Tang et al, 2018a, 2018b) because including nonindependent effect estimates in meta-analyses can skew the final results. We also included a thorough dose–response evaluation, which helps put our summative results in context when considering whether the associations we examined represent causal associations. Finally, we included several large, high-quality papers (Pedersen et al, 2018; Pottegård et al, 2019, 2018; Su et al, 2018) that have been published in the last several years, which were not available for prior meta-analyses on this topic.

Our study also has limitations. Most included studies were observational; thus, our findings could be the result of shared risk factors and residual confounding, particularly because factors such as skin type and immune status of study participants were not adjusted for in all included studies (Table 1). Particularly notable is that a minority of studies (7 of 42) had information on participants' sun exposure, which would likely be an important effect modifier if there is a causal as-

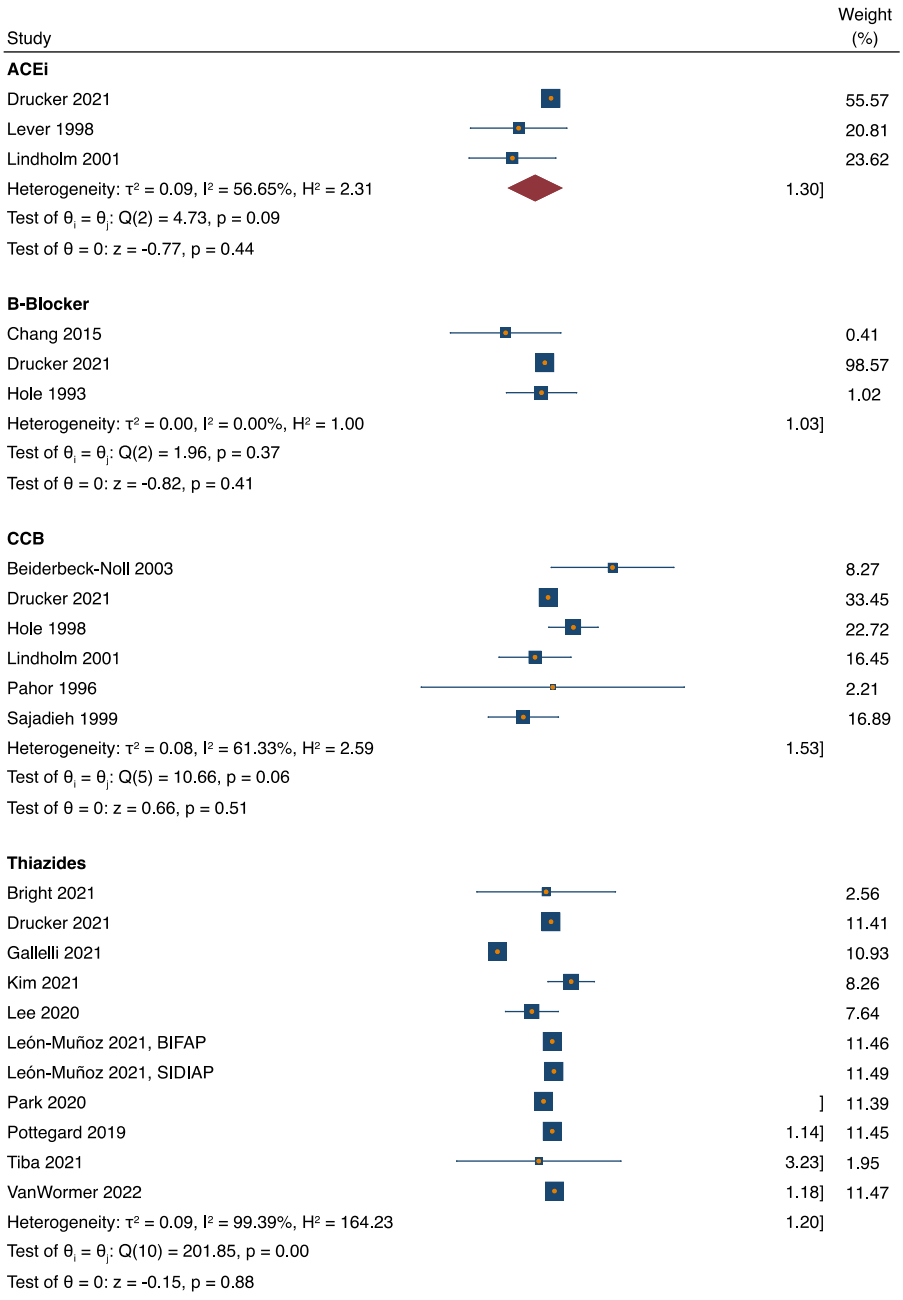

Figure 5. Results of meta-analyses: combined skin cancer outcome. Forest plots of the association between antihypertensive medication classes and combined skin cancer outcomes are shown. The square markers for each study indicate the effect estimate found in that study (also listed to the right of the markers). The size of the square marker indicates the weight of the study in the meta-analysis. The diamond marker indicates the result of the random-effects meta-analysis for that medication class, with the left and right corners showing the 95% confidence interval (also listed to the right of the marker).

sociation between antihypertensive medications and skin cancer. Second, all studies required the antihypertensive exposure to start before the skin cancer diagnosis, but a limited number of studies accounted for a latency period that is likely required between taking the antihypertensive medication and a causal impact on skin cancer risk. Third, although we used random-effects meta-analysis, several of our meta-analyses had considerable heterogeneity, such as the SCC and thiazide and diuretic analyses (those with the largest effect estimates and the most biologic plausibility). Finally, many patients use >1 antihypertensive over time, and most papers did not require users of a particular antihypertensive to be antihypertensive naïve prior to starting. Some studies also ignored the presence of other antihypertensive medication types rather than the one being studied: for example, in Denmark, thiazides are almost always prescribed as a combination medication that includes another antihypertensive. Several studies on thiazides from Denmark thus focus just on the thiazide and do not consider the other antihypertensives that are being given concurrently (Kaae et al, 2010; Pedersen et al, 2018; Pottegård et al, 2018; Sajadieh et al, 1999; Schmidt et al, 2015). This unfortunately makes analyses of different antihypertensives and skin cancer outcomes difficult. Future studies on antihypertensives and

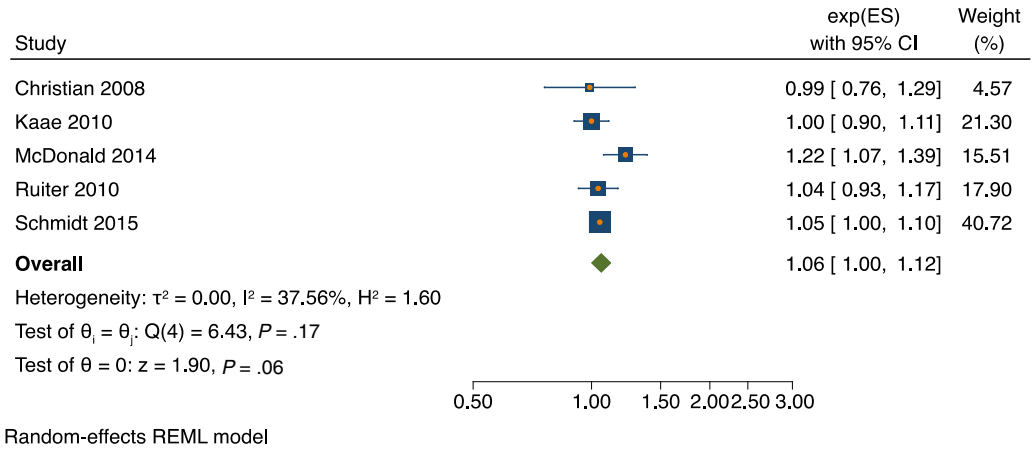

Figure 6. Sensitivity analysis of diuretics and BCC. Ruiter et al (2010) reported on 2 diuretic groups (loop and K+ sparing); this sensitivity analysis is with K+ sparing (smaller n). Kaae et al (2010) reported on 2 diuretic groups (butanamide and furosemide). The butanamide group had a smaller n; however, it was included in both primary and sensitivity analyses for BCC because the furosemide group was excluded from analyses owing to the 95% CI overlapping with the effect estimate, making it impossible to calculate an SE necessary for meta-analysis. In Denmark (Kaae et al, 2010; Schmidt et al, 2015), hydrochlorothiazide is prescribed almost exclusively in combination with other antihypertensive drugs; cumulative dose of hydrochlorothiazide was analyzed. BCC, basal cell carcinoma; CI, confidence interval; REML, restricted maximum likelihood; SE, standard error.

skin cancer would benefit from including patient factors such as skin type, immune status, and sun exposure; accounting for latency; and addressing prior or concurrent use of other antihypertensives.

Antihypertensive medications are commonly used, are often part of a long-term disease management strategy, and are critically important because cardiovascular disease is the number one cause of death globally (World Health Organization, 2019). A causal association between antihypertensives and skin cancer could be important not only on a population level but also on an individual level: for example, a causal 36% relative increased risk of SCC for thiazide use, as observed in this study, could certainly prompt a discussion of whether there is an effective alternative antihypertensive medication for a patient already at high risk for skin cancers. The current analysis does not provide definitive evidence for causal association of some antihypertensive medications with skin cancer, but our results, particularly for SCC and both thiazides and diuretics, provide some further evidence for association, and this topic deserves continued study.

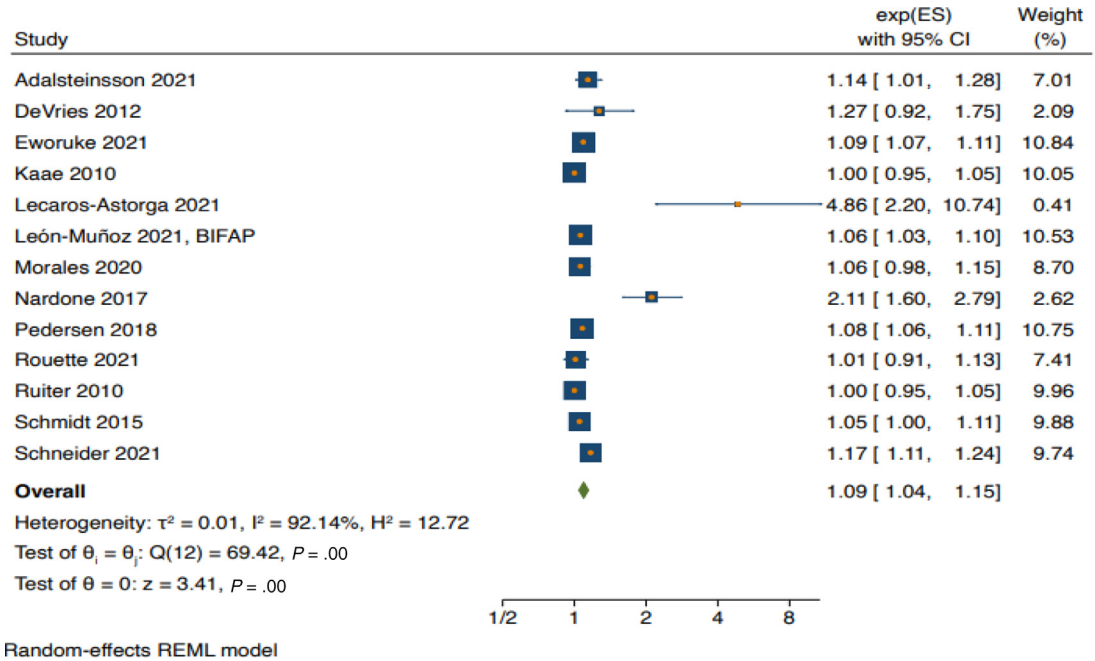

Figure 7. Sensitivity analysis of thiazides and BCC. Morales et al (2020) reported a 2-year lag time and a 5-year lag time analysis; this sensitivity analysis is with the 5-year lag time analysis (smaller n, secondary analysis in original article). In Denmark (Kaae et al, 2010; Pedersen et al, 2018; Schmidt et al, 2015), hydrochlorothiazide is prescribed almost exclusively in combination with other antihypertensive drugs; cumulative dose of hydrochlorothiazide was analyzed. BCC, basal cell carcinoma; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria; REML, restricted maximum likelihood.

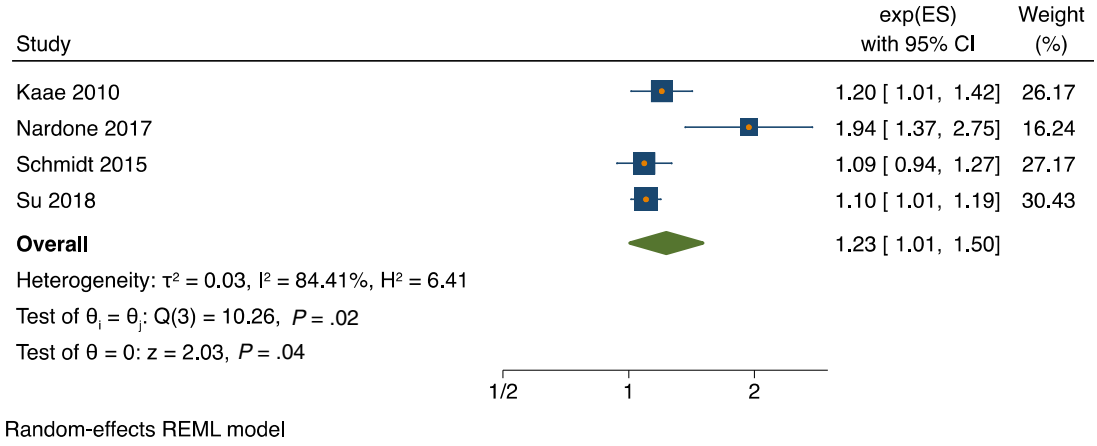

Figure 8. Sensitivity analysis of ACEI and SCC. Kaae et al (2010) reported on 2 ACEI groups (captopril and enalapril); this sensitivity analysis is with captopril group (smaller n). In Denmark (Kaae et al, 2010; Schmidt et al, 2015), hydrochlorothiazide is prescribed almost exclusively in combination with other antihypertensive drugs; cumulative dose of hydrochlorothiazide was analyzed. ACEI, angiotensin-converting enzyme inhibitor; REML, restricted maximum likelihood; SCC, squamous cell carcinoma.

MATERIALS AND METHODS

This systematic review was performed and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher et al, 2009) and Meta-analysis Of Observational Studies in Epidemiology (Stroup et al, 2000) statements. The review protocol was registered on PROSPERO (International Prospective Register of Systematic Reviews) in October 2019 (registration number CRD42019136335).

Search strategy

We systematically searched for articles indexed in PubMed (February 28, 2023), EMBASE (March 14, 2023), and Cochrane library (March 15, 2023). The concepts used to search these databases were antihypertensive medications and skin cancer (complete strategy is provided Supplementary Materials and Methods). The search was limited to human studies published in English. The reference lists of recent reviews and included studies were screened for additional references. Authors were contacted directly when full texts or supplementary data were not readily accessible.

Study selection, inclusion, and exclusion criteria

We included population-based studies (eg, cohort, case control, cross-sectional) or randomized control trials that compared users of antihypertensive medications with nonusers and included a measure of risk (eg ORs, hazard ratio, risk ratio) for SCC, BCC, melanoma, or a combination. Studies that reported on users of any individual medication, medication class, or other groupings of medications considered to be antihypertensive agents were included. Studies conducted in specific populations (eg, transplant recipients) or on specific body parts (eg, lip cancer) were excluded owing to a lack of generalizability. We also excluded case reports, case series, reviews, editorials, and conference abstracts.

All stages of screening were performed in Covidence (2019), an online systematic review management software. Four authors (OGC, MT, CM, and CLH) independently screened all titles and abstracts. Authors then independently reviewed the full text of any article considered eligible. Any disagreement in full-text screening was resolved by a fifth author (MRW). Full-text articles that met inclusion criteria were evaluated prior to data extraction. When multiple

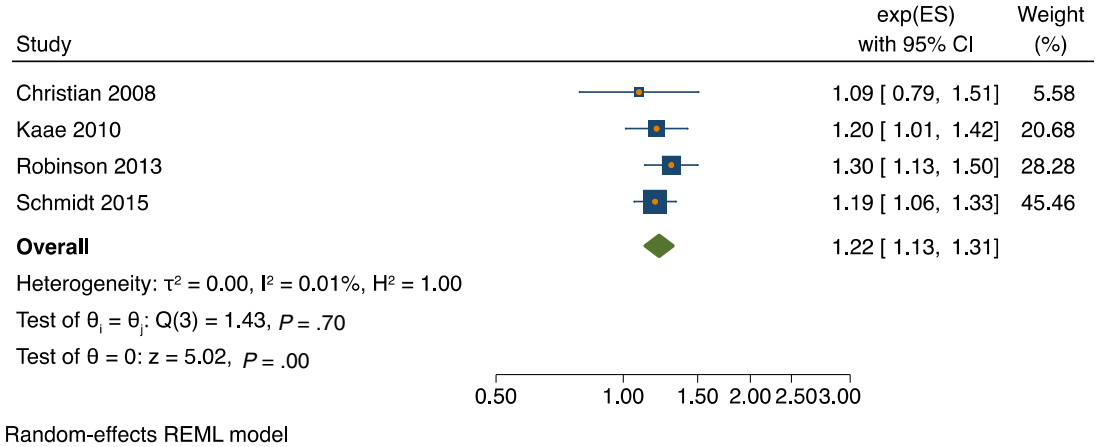

Figure 9. Sensitivity analysis of diuretics and SCC. Kaae et al (2010) reported on 2 diuretic groups (furosemide and butanamide); this sensitivity analysis is with butanamide group (smaller n). In Denmark (Kaae et al, 2010; Schmidt et al, 2015), hydrochlorothiazide is prescribed almost exclusively in combination with other antihypertensive drugs; cumulative dose of hydrochlorothiazide was analyzed. REML, restricted maximum likelihood; SCC, squamous cell carcinoma.

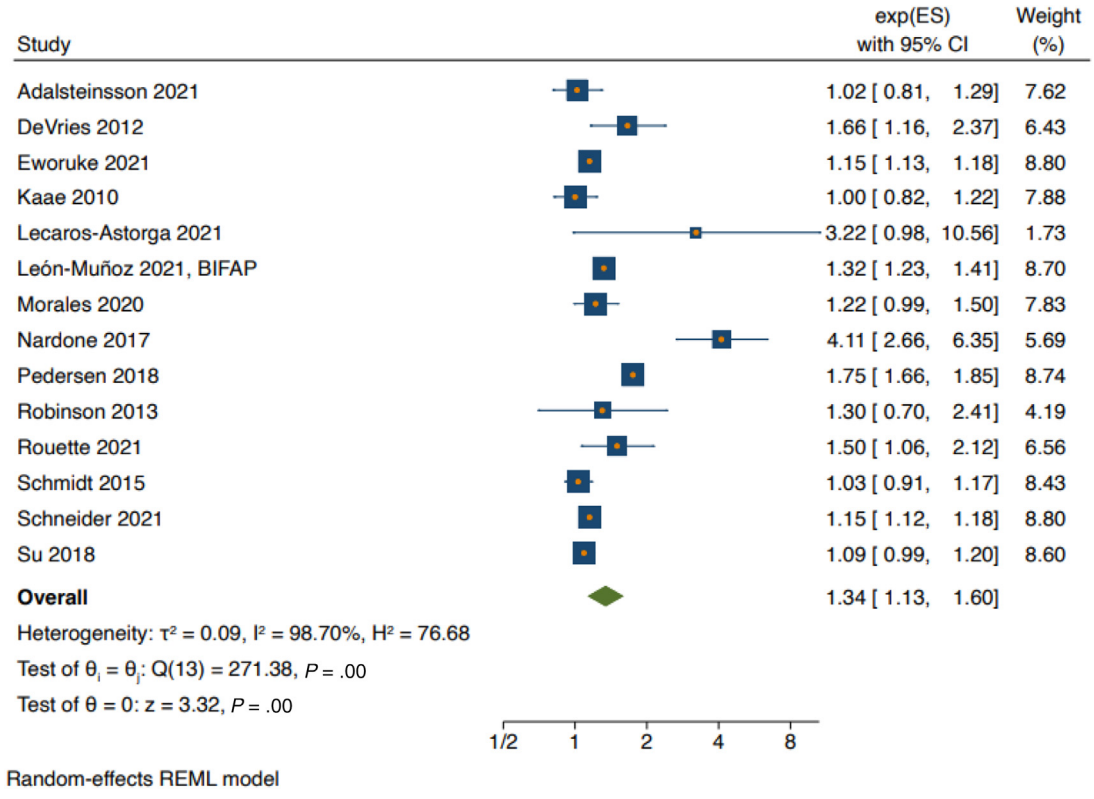

Figure 10. Sensitivity analysis of thiazides and SCC. Adalsteinsson et al (2021) reported on 2 SCC groups (SCC in situ and invasive SCC); this sensitivity analysis is with invasive SCC (smaller n). Morales et al (2020) reported a 2-year lag time and a 5-year lag time analysis; this sensitivity analysis is with the 5-year lag time analysis (smaller n, secondary analysis in original article). In Denmark (Kaae et al, 2010; Pedersen et al, 2018; Schmidt et al, 2015), hydrochlorothiazide is prescribed almost exclusively in combination with other antihypertensive drugs; updated cumulative dose of hydrochlorothiazide was analyzed. BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria; REML, restricted maximum likelihood; SCC, squamous cell carcinoma.

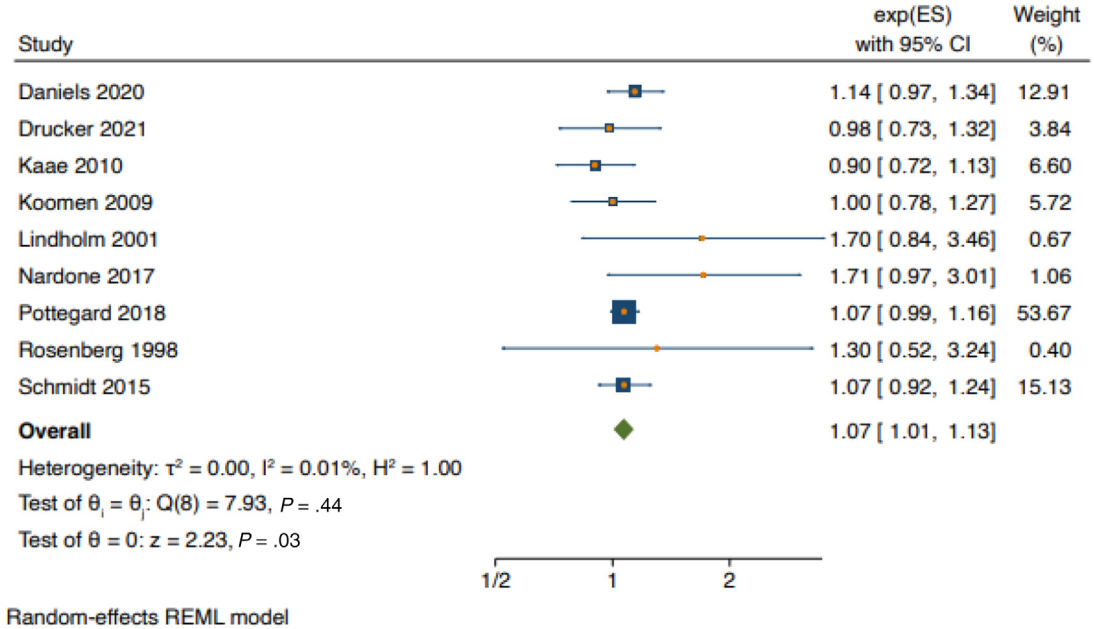

Figure 11. Sensitivity analysis of ACEI and MM. Kaae et al (2010) reported on 2 ACEI groups (captopril and enalapril); this sensitivity analysis is with captopril group (smaller n). In Denmark (Kaae et al, 2010; Pottegård et al, 2018; Schmidt et al, 2015), hydrochlorothiazide is prescribed almost exclusively in combination with other antihypertensive drugs; cumulative dose of hydrochlorothiazide was analyzed. ACEI, angiotensin-converting enzyme inhibitor; MM, melanoma; REML, restricted maximum likelihood.

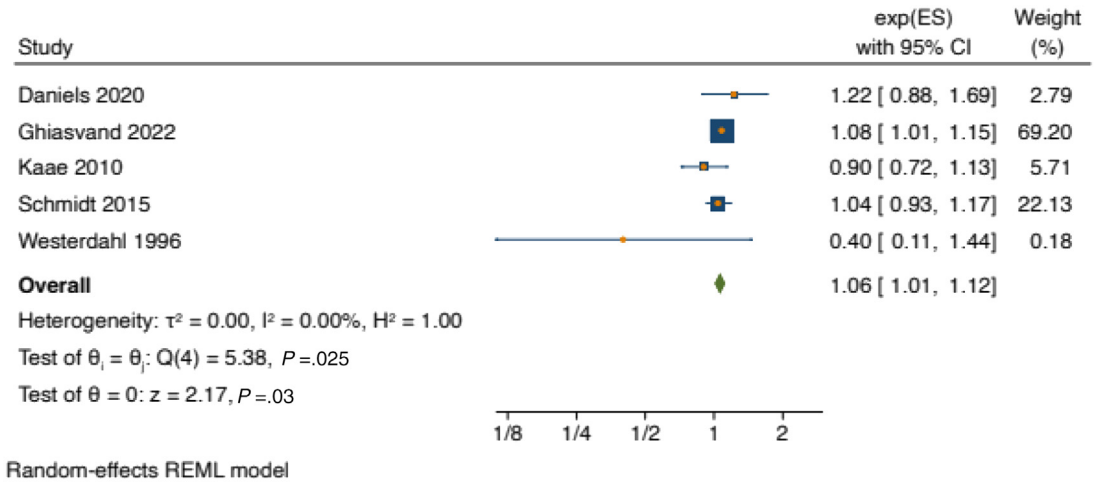

Figure 12. Sensitivity analysis of diuretics and MM. Kaae et al (2010) reported on 2 diuretic groups (furosemide and butanamide); this sensitivity analysis is with butanamide group (smaller n). Daniels et al (2020) reported on 2 diuretic groups (furosemide and indapamide); this sensitivity analysis is with indapamide group (smaller n). In Denmark (Kaae et al, 2010; Schmidt et al, 2015), hydrochlorothiazide is prescribed almost exclusively in combination with other antihypertensive drugs; cumulative dose of hydrochlorothiazide was analyzed. MM, melanoma; REML, restricted maximum likelihood.

studies reported overlapping data for the same medications and skin cancer outcomes in the same population and thus were not independent from one another, the study with the largest study population was chosen. In cases of equal or similar size, the most recent study was included to avoid duplicative accounting of the same data.

Data extraction

Data on the characteristics of each included study were extracted independently by 2 authors (OGC, MT, CM, or MRW) using an adapted Cochrane data extraction template. Extracted data included (i) study design, study country/location, study population/dataset, and number of participants; (ii) antihypertensive medication(s) reported on; (iii) type of effect estimates reported; (iv) type of skin cancer outcomes reported; (v) study results (effect estimates) for each combination of antihypertensive medication agent, class, or group and skin cancer outcome and adjustment variables used; and (vi) methodologies and results for all dose–response analyses. Adjusted values for effect estimates were extracted when available.

Data analysis

Our analysis was grouped by class of antihypertensive medications. On the basis of the divisions we found in the literature, we divided diuretics into thiazide only (because several studies reported thiazide-only results) and nonspecific diuretics (which included any diuretics the study included). We synthesized effect estimates of SCC, BCC, melanoma, or a combination using a random-effects meta-analysis model if 3 or more independent studies reported on that outcome for a specific antihypertensive medication or class. We combined observational and randomized control trial data. All analyses were conducted using the metan packages in Stata, version 16 (StataCorp, 2019), and yielded summary RRs.

When studies reported more than 1 analysis model, the model which accounted for the largest number of possible confounders and/or the longest lag time between medication use and outcome ascertainment was used. If a study reported results for multiple medications in the same class in the same population, we used the medication with the largest number of users for primary analysis. If an effect estimate or CIs were not available but observed and expected cases were reported, we calculated these using the mid-p exact test (Soe and Sullivan, 2019). In the case of a CI overlapping exactly with an effect estimate (effect estimates of 1.0 with 95% CI = 1.0–1.0 for furosemide and enalapril BCC outcomes, according to Kaae et al, [2010]), Kaae et al, (2010) authors were contacted directly, requesting more exact data so that a standard error could be calculated for use in meta-analysis. If authors could not be reached, or more exact data were not available, the result was excluded from meta-analysis, and an alternate result from the same medication class was used.

We assessed the heterogeneity between included studies using the measure of consistency (I^2) and chi-square tests for heterogeneity. I^2 values indicate the percentage of observed heterogeneity that is attributable to variability between studies rather than sampling error within the studies themselves. I^2 values of $\geq$50% are generally felt to represent substantial or considerable heterogeneity, although the Cochrane Handbook recommends that "…use of simple thresholds to diagnose heterogeneity should be avoided" (Deeks et al, 2023). Chi-square tests for heterogeneity evaluates whether differences in study results are due to chance alone, and a low *P*-value indicates heterogeneity between studies (Deeks et al, 2023). Measures of small study effects and publication bias (eg, funnel plots, Beggs test, Eggers test) were not performed because 18 of the 21 of the meta-analyses had <10 included studies (Page et al, 2023).

Risk of bias and quality of evidence

We conducted a risk-of-bias assessment of each of the methodological quality of the included studies using 2 tools on the basis of the design of the study. The Newcastle–Ottawa Scale (Wells et al, 2019) was used for nonrandomized studies, and the Cochrane Risk of Bias 2.0 tool (Sterne et al, 2019) was used for randomized trials. We used Grading of Recommendations, Assessment, Development and Evaluation to evaluate the quality of evidence at the outcome level.(2013).

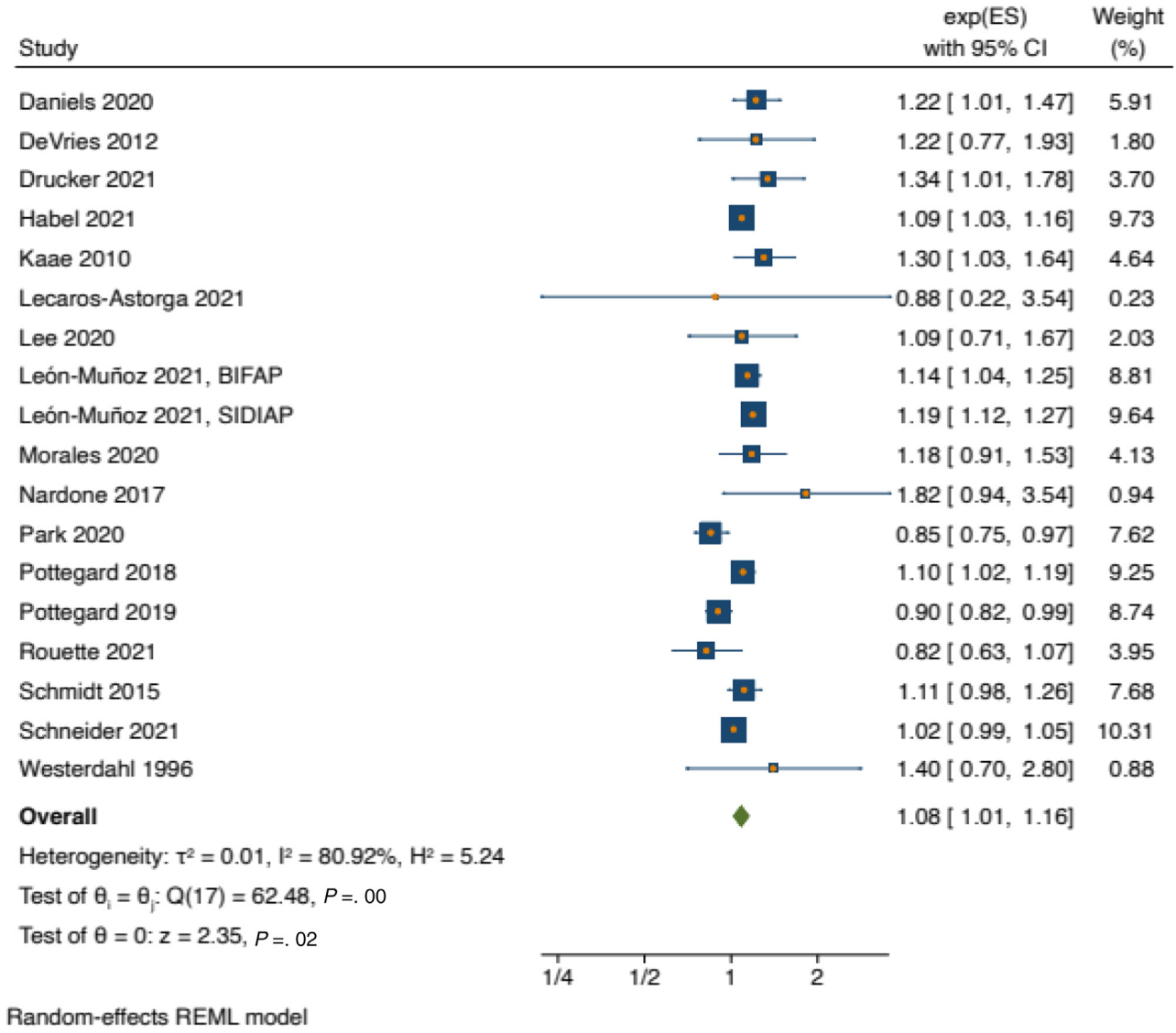

Figure 13. Sensitivity analysis of thiazides and MM. Pottegard et al (2018) reported on 2 thiazide groups (HCTZ and bendroflumethiazide); this sensitivity analysis is with bendroflumethiazide. Morales et al (2020) reported a 2-year lag time and a 5-year lag time analysis; this sensitivity analysis is with the 5-year lag time analysis (smaller n, secondary analysis is in original article). Lee et al (2020) reported on 3 thiazide groups (HCTZ only, ever use of HCTZ in any formulation, and use of HCTZ in combination with other antihypertensives); this sensitivity analysis is with ever use of HCTZ in combination and alone. In Denmark (Kaae et al, 2010; Pottegård et al, 2019, 2018;Schmidt et al, 2015), hydrochlorothiazide is prescribed almost exclusively in combination with other antihypertensive drugs; cumulative dose of hydrochlorothiazide was analyzed. BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria; HCTZ, hydrochlorothiazide; MM, melanoma; REML, restricted maximum likelihood; SIDIAP, The Information System for Research in Primary Care.

DATA AVAILABILITY STATEMENT

No datasets were generated or analyzed during this study.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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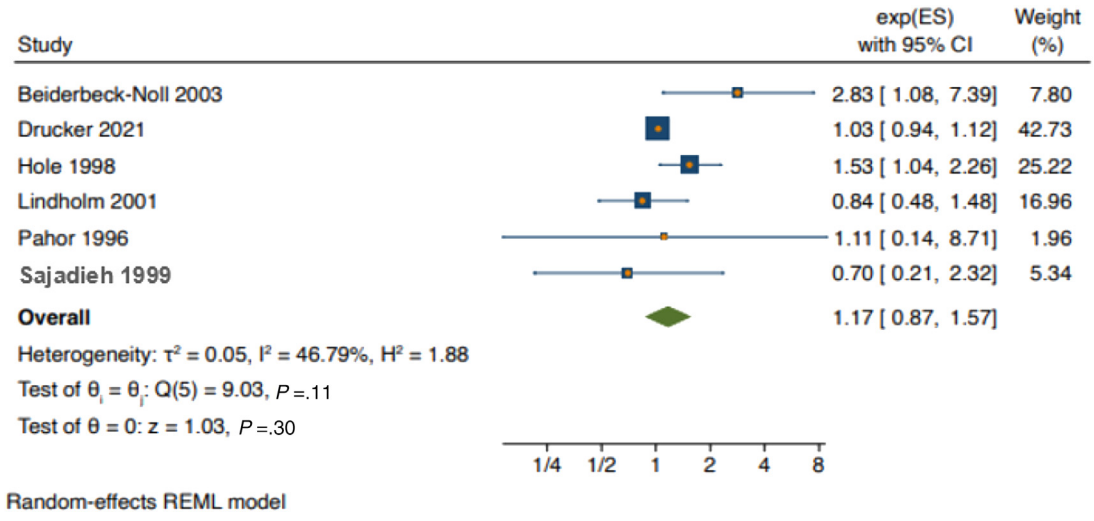

Figure 14. Sensitivity analysis of CCB and combination skin cancer. Sajadieh et al (1999) reported on male and female patients separately; this sensitivity analysis is with women (smaller n). In Denmark (Sajadieh et al, 1999), hydrochlorothiazide is prescribed almost exclusively in combination with other antihypertensive drugs; cumulative dose of hydrochlorothiazide was analyzed. CCB, calcium channel blocker; REML, restricted maximum likelihood.

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AUTHOR CONTRIBUTIONS

Conceptualization: MRW, OGC, SML; Data Curation: MRW, OGC, MT, CM, KTN, CLH, SHG, SML, DJM; Formal Analysis: MRW, OGC; Funding Acquisition: MRW; Investigation: MRW, OGC, MT, CM, KTN, CLH, SHG, SML, DJM; Methodology: MRW, OGC, SML; Project Administration: MRW, CLH; Resources: MRW; Supervision: MRW; Visualization: MRW, OGC, MT, CM, CLH; Writing — Original Draft Preparation: MRW, OGC, CM, CLH; Writing — Review and Editing: MRW, OGC, MT, CM, KTN, CLH, SHG, SML, DJM

DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) OR LARGE LANGUAGE MODELS (LLMs)

No AI or LLM tools were used to prepare this manuscript.

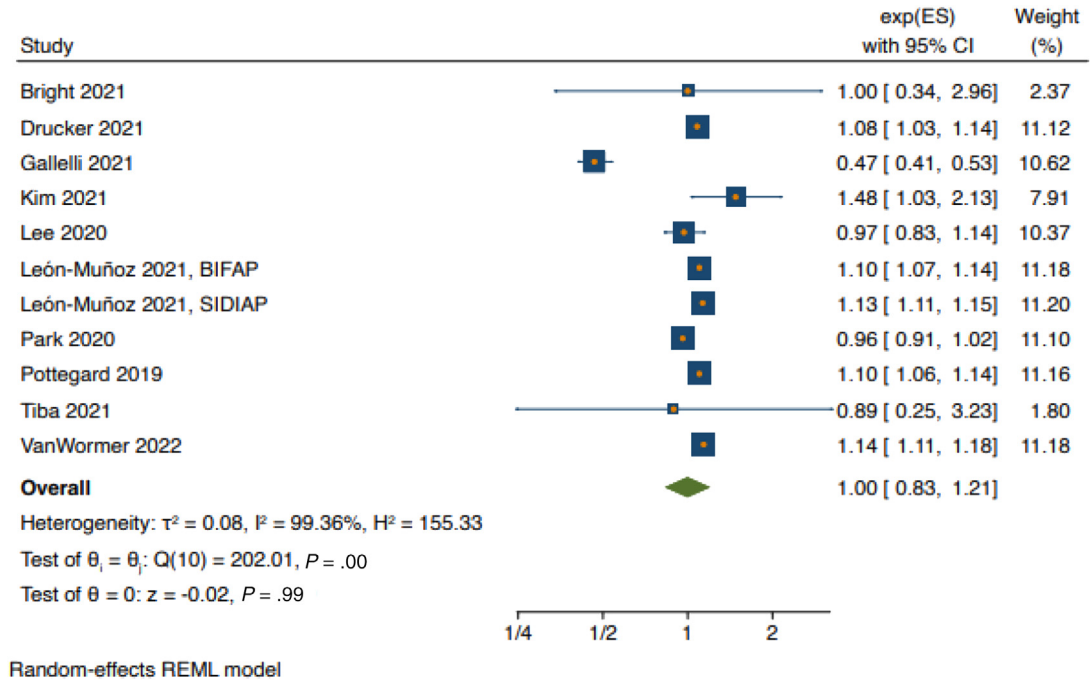

Figure 15. Sensitivity analysis of thiazides and nonmelanoma skin cancer outcomes. Lee et al (2020) reported on 3 thiazide groups (HCTZ only, ever use of HCTZ in any formulation, and HCTZ in combination with other antihypertensives); this sensitivity analysis is with ever use of HCTZ in any formulation. In Denmark (Pottegård et al, 2019), hydrochlorothiazide is prescribed almost exclusively in combination with other antihypertensive drugs; cumulative dose of hydrochlorothiazide was analyzed. BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria; HCTZ, hydrochlorothiazide; REML, restricted maximum likelihood; SIDIAP, The Information System for Research in Primary Care.

Table 7. Dose–Response Analyses

Study Name	Methods of Dose–Response Evaluation	Drug Name or Subclass (if Specified)	Effect Estimates						Other Results
			BCC (Primary Analysis, Any Use)	BCC (Highest Dose)	SCC (Primary Analysis, Any Use)	SCC (Highest Dose)	MM (Primary Analysis, Any Use)	MM (Highest Dose)	
α-Agonists									
Kaae et al, 2010	5 y of treatment versus <5 y of treatment	Methyldopa	**1.3**	**1.7**	1.3	0.4	1.5	1.1	
ACEIs									
Drucker et al, 2021	Risk associated with increasing cumulative dose								Risk of keratinocyte carcinoma associated with increasing cumulative dose: adjusted HR per unit increase of 1.08, 95% CI = 0.95–1.06
Kaae et al, 2010	5 y of treatment versus <5 y of treatment	Captopril	1.0	0.9	1.2	0.9	0.9	1.0	
Kaae et al, 2010	5 y of treatment versus <5 y of treatment	Enalapril	1.0	1.0	1.1	1.1	1.1	1.0	
Koomen et al, 2009	Increasing (i) cumulative duration, (ii) cumulative dose, and (iii) average day dose; (shown) >1200 DDD[1]						1.0	0.9	
Rosenberg et al, 1998	≥1 y of use; (shown) >5 y of use						1.3	1.7	
Schmidt et al, 2015	Short-term low intensity, short-term high intensity, long-term low intensity, (shown) long-term high intensity (≥5 y of use, use of ≥50% days coverage/duration)		1.02	0.92	1.09	0.93	1.07	1.05	
ARBs									
Drucker et al, 2021	Risk associated with increasing cumulative dose								Risk of keratinocyte carcinoma associated with increasing cumulative dose: adjusted HR per unit increase of 1.09, 95% CI = 0.91–1.29)
Koomen et al, 2009	Increasing (i) cumulative prescription duration, (ii) cumulative dose, and (iii) average day dose; (shown) >1000 defined daily doses[2]						1.0	0.7	
Schmidt et al, 2015	Short-term low intensity, short-term high intensity, long-term low intensity, (shown) long-term high intensity (≥5 y of use, use of ≥50% days coverage/duration)		**1.09**	1.27	1.16	0.78	1.14	1.44	

(*continued*)

Table 7. Continued

Study Name	Methods of Dose–Response Evaluation	Drug Name or Subclass (if Specified)	Effect Estimates						Other Results
			BCC (Primary Analysis, Any Use)	BCC (Highest Dose)	SCC (Primary Analysis, Any Use)	SCC (Highest Dose)	MM (Primary Analysis, Any Use)	MM (Highest Dose)	
β-Blockers									
Drucker et al, 2021	Risk associated with increasing cumulative dose								Risk of keratinocyte carcinoma associated with increasing cumulative dose: adjusted HR per unit increase of 0.98, 95% CI = 0.93–1.04
Kaae et al, 2010	5 y of treatment versus <5 y of treatment	Atenolol	1.0	1.0	1.0	**1.3**	1.0	1.2	
Rosenberg et al, 1998	≥1 y of use; (shown) >5 y of use						1.2	1.3	
Schmidt et al, 2015	Short-term low intensity, short-term high intensity, long-term low intensity, (shown) long-term high intensity (≥5 y of use, use of ≥50% days coverage/duration)		**1.09**	1.06	1.08	0.86	**1.15**	**1.67**	
CCBs									
Drucker et al, 2021	Risk associated with increasing cumulative dose								Risk of keratinocyte carcinoma associated with increasing cumulative dose: adjusted HR per unit increase of 1.03, 95% CI = 0.95–1.13
Ghiasvand et al, 2023	Dose–response patterns, ranging from cumulative DDD of 0 to >2114 mg[3]								No dose–response relationship was found between the cumulative DDDs and melanoma
Kaae et al, 2010	5 y of treatment versus <5 y of treatment	Verapamil	**1.2**	0.9	1.1	1.1	1.1	1.0	
Rosenberg et al, 1998	≥1 y of use; (shown) >5 y of use						1.6	1.6	
Schmidt et al, 2015	Short-term low intensity, short-term high intensity, long-term low intensity, (shown) long-term high intensity (≥5 y of use, use of ≥50% days coverage/duration)		**1.15**	0.98	1.13	1.16	0.97	1.05	
Diuretics									
Ghiasvand et al, 2023	Dose–response patterns, ranging from cumulative DDD of 0 to >1584 mg[3]								No dose–response relationship was found between the cumulative DDDs and melanoma
Kaae et al, 2010	5 y of treatment versus <5 y of treatment	Furosemide	1.0	0.9	**1.4**	**1.1**	**2.0**	1.0	
Kaae et al, 2010	5 y of treatment versus <5 y of treatment	Bumetanide	1.0	1.0	1.2	1.3	0.9	1.4	

(*continued*)

Table 7. Continued

Study Name	Methods of Dose–Response Evaluation	Drug Name or Subclass (if Specified)	Effect Estimates: BCC (Primary Analysis, Any Use)	BCC (Highest Dose)	SCC (Primary Analysis, Any Use)	SCC (Highest Dose)	MM (Primary Analysis, Any Use)	MM (Highest Dose)	Other Results
McDonald et al, 2014	Length of use <6 mo, 6 mo–2 y, (shown) >2 y		**1.22**	**1.38**					**Adjusted HR significant for >2 y of use; test for trend statistically significant over duration categories**
Ruiter et al, 2010	Cumulative days of use (test for trend); (shown) highest category reported >923 days of use (K+ sparing diuretics)	Diuretics (K+ sparing)	**1.04**	0.9					Test for trend not statistically significant over dose categories
Ruiter et al, 2010	Cumulative days of use (test for trend); (shown) highest category reported >1360 days of use (loop diuretics)	Diuretics (loop)	**1.07**	**1.62**					**Test for trend statistically significant over dose categories**
Schmidt et al, 2015	Short-term low intensity, short-term high intensity, long-term low intensity, (shown) long-term high intensity (≥5 y of use, use of ≥50% days coverage/duration)		1.05	0.87	**1.19**	1.44	1.04	0.81	
Thiazides									
Adalsteinsson et al, 2021	Cumulative dosage categories (test for trend); (shown) highest amount (>1500 daily dose units or >37.5K mg)	Hydrochlorothiazide	**1.14**	**1.42**	**1.24** (in situ) 1.02 (invasive)	1.35 (in situ) **1.69** (invasive)			**BCC test for trend statistically significant over dose categories**; SCC in situ and invasive tests for trend not statistically significant over dose categories
Daniels et al, 2020[4]	Cumulative amount categories, (shown) highest amount (>25K mg)	Hydrochlorothiazide					**1.22**	1.22	
Drucker et al, 2021	Risk associated with increasing cumulative dose								Risk of keratinocyte carcinoma associated with increasing cumulative dose: adjusted HR per unit increase of 1.08, 95% CI = 1.03–1.14
Eworuke et al, 2021	Cumulative amount categories, (shown) highest amount (>100k mg)	Hydrochlorothiazide	0.99	1.12	**1.04**	1.32			
Habel et al, 2021	Cumulative amount categories, (shown) highest amount (>100k mg)	Hydrochlorothiazide					**1.09**	1.06	
Kaae et al, 2010	5 y of treatment versus <5 y of treatment	Bendroflumethiazide	1.0	0.9	1.0	1.5	1.3	1.3	
Lee et al, 2020[5]	Tertiles of cumulative dose, (shown) highest tertile dose	Hydrochlorothiazide	0.80 (NMSC primary analysis)		1.15 (NMSC highest dose)		1.19	1.08	

(*continued*)

Table 7. Continued

Study Name	Methods of Dose–Response Evaluation	Drug Name or Subclass (if Specified)	Effect Estimates						Other Results
			BCC (Primary Analysis, Any Use)	BCC (Highest Dose)	SCC (Primary Analysis, Any Use)	SCC (Highest Dose)	MM (Primary Analysis, Any Use)	MM (Highest Dose)	
León-Muñoz et al, 2021; SIDIAP	Cumulative amount categories, (shown) highest amount (>200k mg)	Hydrochlorothiazide	1.13 (NMSC primary analysis)		1.31 (NMSC highest dose)			**1.19**	1.05
León-Muñoz et al, 2021; BIFAP	Cumulative amount categories (shown) highest amount (>200k mg)	Hydrochlorothiazide	**1.06**	1.02	**1.32**	2.05	**1.14**	1.10	
Morales et al, 2020	Cumulative amount categories, (shown) 5-y lag-time highest category (>50K mg)[6]	Hydrochlorothiazide	1.06	**1.44**			1.18	0.37	
Park et al, 2020	Cumulative dose (mg, quartiles [test for trend]) and cumulative duration (y [test for trend]); (shown) highest dose (>50K mg)	Hydrochlorothiazide	0.96 (NMSC primary analysis)		**0.20** (NMSC highest dose)		**0.85**	**0.18**	**Test for trend statistically significant over dose categories (mg and quartiles) and duration categories, showing decreased risk for both melanoma and NMSC**
Pedersen et al, 2018[7]	High use (>2000 discrete daily doses); cumulative dose categories (test for trend), (shown) highest category >200K mg	Hydrochlorothiazide	**1.08**	**1.54**	**1.75**	**7.38**			**BCC and SCC test for trend statistically significant over dose categories**
Pottegård et al, 2018[7]	High use (>50,000 mg cumulative); cumulative dose categories (test for trend), (shown) highest category >100K	Hydrochlorothiazide					**1.17**	**1.21**	Test for trend not statistically significant over dose categories
Pottegård et al, 2019[7]	High use (>2000 discrete daily doses); cumulative dose categories, (shown) highest category reported 100,000 −150,000 mg	Hydrochlorothiazide					**0.90**	1.22	
Rouette et al, 2021	Cumulative amount categories (shown) highest amount (>100k mg)	Hydrochlorothiazide	1.01	1.31	**1.50**	**4.96**	0.82	1.17	
Ruiter et al, 2010	Cumulative days of use (test for trend), (shown) highest category reported >1646 day of use		1.00	1.10					Test for trend not statistically significant over dose categories
Schneider et al, 2021	Short-term (<20 prescriptions) versus long-term duration (≥20 prescriptions)	Overall	**1.24**	**1.17**	**1.07**	**1.15**	**1.11**	1.02	
Schneider et al, 2021	Short-term (<20 prescriptions) versus long-term duration (≥20 prescriptions)	Hydrochlorothiazide	0.99	1.04	**1.29**	**1.95**	**1.06**	1.03	
Schneider et al, 2021	Short-term (<20 prescriptions) versus long-term duration (≥20 prescriptions)	Bendroflumethiazide	0.95	**1.07**	**1.07**	**1.11**	**1.36**	1.02	

(*continued*)

Table 7. Continued

Study Name	Methods of Dose–Response Evaluation	Drug Name or Subclass (if Specified)	Effect Estimates						Other Results
			BCC (Primary Analysis, Any Use)	BCC (Highest Dose)	SCC (Primary Analysis, Any Use)	SCC (Highest Dose)	MM (Primary Analysis, Any Use)	MM (Highest Dose)	
Schneider et al, 2021	Short-term (<20 prescriptions) versus long-term duration (≥20 prescriptions)	Indapamide	0.98	0.99	**1.20**	0.99	**1.14**	**1.43**	
Other									
Ghiasvand et al, 2023	Dose–response patterns, ranging from cumulative DDD of 0 to >3190 mg[3]	Renin-angiotensin system agents							No dose–response relationship was found between the cumulative DDDs and melanoma
Robinson et al, 2013	>1 y of use	Cardiovascular medications[8]			**1.3**	**1.4**			
Su et al, 2018	Nonusers compared with 1–7 prescription fills, 8–15 fills, (shown) >16 fills	Photosensitizing antihypertensives[9]			**1.17**	**1.41**			

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BCC, basal cell carcinoma; BIFAP, Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria; CCB, calcium channel blocker; CI, confidence interval; DDD, defined daily dose; HR, hazard ratio; K, thousand; NMSC, nonmelanoma skin cancer; SCC, squamous cell carcinoma.

Bold text indicates significance as determined by 95% CI not overlapping null value of 1.0. NMSCs include BCC, SCC, and other NMSC types.

[1]This cumulative dose equates to approximately 3.25 years of daily use.

[2]This cumulative dose equates to approximately 2.75 years of daily use.

[3]DDD was defined as the average maintenance dose per day for a drug used for its main indication for adults. Total cumulative dose was based on the number of DDDs filled and categorized it in tertiles of use.

[4]In Australia, hydrochlorothiazide is often prescribed in combination with other antihypertensive drugs; cumulative dose of hydrochlorothiazide was analyzed.

[5]Ever use of any hydrochlorothiazide alone or in combination and hydrochlorothiazide only reported separately; hydrochlorothiazide only was chosen for primary analysis and extracted for dose–response analysis accordingly.

[6]Two-year and 5-year lag time available; 5-year lag time chosen was because this would be highest cumulative dose.

[7]In Denmark, hydrochlorothiazide is prescribed almost exclusively in combination with other antihypertensive drugs; cumulative dose of hydrochlorothiazide was analyzed.

[8]Cardiovascular medications included more than antihypertensives (thiazides, loop diuretics, CCBs, K+-sparing diuretics, α-agonists, amiodarone, quinidine, sulfonylureas).

[9]Photosensitizing antihypertensives included loop diuretics, K-sparing diuretics, thiazide, combination thiazides, and α-2-receptor agonists.

Table 8. Summary of Findings

Outcomes	Medication	Number of Participants (Studies) Follow-Up	Quality of the Evidence (GRADE)	Estimate (95% CI)
BCC	ACEI	5,241,145 (CC-1, Co-2) 10–12 y	⊕◯◯◯ (very low) owing to risk of bias, inconsistency of results, and imprecision	1.30 (0.78–2.16)
	β-Blocker	5,017,727 (CC-2, Co-1, RCT-1) 6–12 y	⊕◯◯◯ (very low) owing to risk of bias, inconsistency of results, and indirectness of evidence	1.05 (0.97–1.13)
	CCB	5,017,727 (CC-2, Co-1, RCT-1) 6–12 y	⊕⊕◯◯ (low) owing to risk of bias and indirectness of evidence	1.17 (1.11–1.22)
	Diuretics	5,092,006 (CC-2, Co-3, RCT-1) 6–24 y	⊕⊕◯◯ (low) owing to risk of bias and indirectness of evidence	1.06 (1.03–1.10)
	Thiazides	36,149,624 (CC-8, Co-6) 10–17 y	⊕◯◯◯ (very low) owing to risk of bias, inconsistency of results, imprecision	1.10 (1.04–1.16)
SCC	ACEI	9,014,979 (CC-1, Co-3) 10–12 y	⊕⊕◯◯ (low) owing to risk of bias and inconsistency of results	1.20 (0.98–1.47)
	ARB	4,253,230 (CC-1, Co-2) 10–11 y	⊕◯◯◯ (very low) owing to risk of bias, inconsistency of results, imprecision	1.29 (0.83–2.00)
	β-Blocker	5,046,084 (CC-1, Co-2, RCT-1) 6–12 y	⊕⊕◯◯ (low) owing to risk of bias and indirectness of evidence	1.03 (0.97–1.08)
	CCB	5,046,084 (CC-1, Co-2, RCT-1) 6–12 y	⊕⊕◯◯ (low) owing to risk of bias and indirectness of evidence	1.08 (1.01–1.14)
	Diuretics	5,022,799 (CC-2, Co-1, RCT-1) 6–12 y	⊕◯◯◯ (very low) owing to risk of bias, inconsistency of results, and indirectness of evidence	1.29 (1.17–1.43)
	Thiazides	36,166,987 (CC-8, Co-6) 10–15 y	⊕⊕◯◯ (low) owing to risk of bias and inconsistency of results	1.36 (1.15–1.61)
Malignant melanoma	ACEI	10,145,355 (CC-5, Co-3, RCT-1) 5–12 y	⊕⊕◯◯ (low) owing to risk of bias and indirectness of evidence	1.09 (1.03–1.14)
	ARB	9,514,884 (CC-4, Co-3) 10 y	⊕⊕◯◯ (low) owing to risk of bias and inconsistency of results	1.03 (0.86–1.23)
	β-Blocker	6,073,421 (CC-5, Co-2) 12–19 y	⊕◯◯◯ (very low) owing to risk of bias, inconsistency of results, and indirectness of evidence	1.04 (0.93–1.16)
	CCB	6,302,455 (CC-5, Co-3, RCT-1) 5–16 y	⊕⊕◯◯ (low) owing to risk of bias and indirectness of evidence	1.08 (1.03–1.12)
	Diuretics	5,161,091 (CC-4, Co-1) 12 y	⊕⊕◯◯ (low) owing to risk of bias and inconsistency of results	1.07 (0.78–1.48)
	Thiazides	17,945,703 (CC-10, Co-7) 10–15 y	⊕⊕◯◯ (low) owing to risk of bias and inconsistency of results	1.09 (1.02–1.17)
Combination skin cancer	CCB	929,754 (Co-4, RCT-2) 5–16 y	⊕◯◯◯ (very low) owing to risk of bias, inconsistency of results, indirectness of evidence	1.11 (0.81–1.53)
	Thiazides	6,607,293 (CC-5, Co-4) 10–15 y	⊕⊕◯◯ (low) owing to risk of bias and inconsistency of results	0.98 (0.81–1.20)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BCC, basal cell carcinoma; CCB, calcium channel blocker; CI, confidence interval; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; RCT, randomized controlled trial; SCC, squamous cell carcinoma.

Risk of bias was based primarily on failure to adequately control confounding. Inconsistency of results was based primarily on I^2 values of 75% or larger or statistically significant chi-square for heterogeneity tests. Indirectness of evidence was based primarily on differences in population, with findings rated down for nonpopulation-based cohorts. Imprecision was primarily based on an Optimal Information Size (sample size) of 7682 for a hypothetical trial with a 10% baseline risk of skin cancer and 12% risk with an antihypertensive drug. Findings were rated down if they had sample sizes less than this or if nonstatistically significant results had an effect estimate of 1.25 or larger, per the threshold recommended in GRADE Handbook 5.2.4.2 imprecision in systematic reviews. We did not rate down for publication bias because measures of small study effects and publication bias (eg, funnel plots, Beggs test, Eggers test) were not performed because all but 1 of the meta-analyses had <10 included studies.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.xjidi.2024.100272.

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SUPPLEMENTARY RESULTS

Description of sensitivity analyses

For the basal cell carcinoma diuretics sensitivity analysis, we used K-sparing diuretics rather than loop diuretics from Ruiter et al, (2010) and found a nonstatistically significant result with effect estimate similar to that of the primary statistically significant result. For the basal cell carcinoma thiazides sensitivity analysis, we used the result from 5-year rather than 2-year lag time sample from Morales et al, (2020) and found a nonstatistically significant result with effect estimate similar to that of the primary statistically significant result. For the squamous cell carcinoma (SCC) angiotensin-converting enzyme inhibitor sensitivity analysis, we used the result from captopril rather than that from enalapril from Kaae et al, (2010) and found a statistically significant result with effect estimate similar to that of the primary nonstatistically significant result. For the SCC diuretics sensitivity analysis, we used the result from bumetanide rather than that from furosemide from Kaae et al, (2010) and found a statistically significant result with an effect estimate similar to that of the primary statistically significant result. For the SCC thiazides sensitivity analysis, we used the result from the 5-year lag time sample from Morales et al, (2020) and from invasive SCC rather than SCC in situ from Adalsteinsson et al, (2021) and found nonstatistically significant results with effect estimate similar to that of the primary statistically significant result in both cases. For the melanoma angiotensin-converting enzyme inhibitor sensitivity analysis, we used the result from captopril rather than those from enalapril from Kaae et al, (2010) and found a nonstatistically significant result with effect estimate similar to that of the primary statistically significant result. For the melanoma diuretics sensitivity analysis, we used the result from bumetanide rather than those from furosemide from Kaae et al, (2010) and found a nonstatistically significant result with effect estimate similar to that of the primary nonstatistically significant result. For the melanoma thiazides sensitivity analysis, we used the result from bendroflumezide rather than that from hydrochlorothiazide from Pottegård et al, (2018), the result from the 5-year lag time from Morales et al, (2020), and the result from hydrochlorothiazide ever use rather than that from hydrochlorothiazide only from Lee et al, (2020) and found consistent nonstatistically significant results with effect estimates similar to that of the primary results in all 3 cases. For the combination skin cancer outcomes and thiazides analysis, we used the result from hydrochlorothiazide ever use rather than that from hydrochlorothiazide only from Lee et al, (2020) and found consistent nonstatistically significant results with effect estimates similar to those of the primary analysis.

SUPPLEMENTARY MATERIALS AND METHODS

Complete search strategy

PubMed. Filters applied—species: humans: "antihypertensive agents"[Mesh] OR "Agents, Antihypertensive" OR "Antihypertensives" OR "Anti-Hypertensives" OR "anti hypertensives" OR "Antihypertensive Drugs" OR "Drugs, Antihypertensive" OR "Anti-Hypertensive Agents" OR "Agents, Anti-Hypertensive" OR "Anti Hypertensive Agents" OR "Anti-Hypertensive Drugs" OR "Anti Hypertensive Drugs" OR "Drugs, Anti-Hypertensive" OR "Adrenergic alpha-Antagonists"[Mesh] OR "Adrenergic alpha Antagonists" OR "alpha-Adrenergic Receptor Blockaders" OR "alpha Adrenergic Receptor Blockaders" OR "alpha-Adrenergic Blocking Agents" OR "Agents, alpha-Adrenergic Blocking" OR "Blocking Agents, alpha-Adrenergic" OR "alpha Adrenergic Blocking Agents" OR "Adrenergic alpha-Blockers" OR "Adrenergic alpha Blockers" OR "alpha-Adrenergic Blockers" OR "Blockers, alpha-Adrenergic" OR "alpha Adrenergic Blockers" OR "alpha-Adrenergic Antagonists" OR "Antagonists, alpha-Adrenergic" OR "alpha Adrenergic Antagonists" OR "Adrenergic alpha-Receptor Blockaders" OR "Adrenergic alpha Receptor Blockaders" OR "Adrenergic alpha-1 Receptor Antagonists"[Mesh] OR "Adrenergic alpha-2 Receptor Antagonists"[Mesh] OR "Adrenergic alpha 1 Receptor Antagonists" OR "Adrenergic alpha-1 Antagonists" OR "Adrenergic alpha 1 Antagonists" OR "Adrenergic alpha1-Antagonists" OR "Adrenergic alpha1 Antagonists" OR "alpha-1 Adrenergic Blocking Agents" OR "alpha 1 Adrenergic Blocking Agents" OR "alpha1-Adrenoceptor Blocker" OR "alpha1 Adrenoceptor Blocker" OR "alpha1-Adrenergic Antagonists" OR "Antagonists, alpha1-Adrenergic" OR "alpha1 Adrenergic Antagonists" OR "Adrenergic alpha-1 Receptor Blockers" OR "Adrenergic alpha 1 Receptor Blockers" OR "Adrenergic alpha 2 Receptor Antagonists" OR "alpha-2 Adrenergic Blocking Agents" OR "alpha 2 Adrenergic Blocking Agents" OR "Adrenergic alpha2-Antagonists" OR "Adrenergic alpha2 Antagonists" OR "alpha2-Adrenergic Antagonists" OR "Antagonists, alpha2-Adrenergic" OR "alpha2 Adrenergic Antagonists" OR "Adrenergic alpha-2 Antagonists" OR "Adrenergic alpha 2 Antagonists" OR "Adrenergic beta-Antagonists"[Mesh] OR "Adrenergic beta Antagonists" OR "beta-Antagonists, Adrenergic" OR "beta-Adrenoceptor Antagonists" OR "Antagonists, beta-Adrenoceptor" OR "beta Adrenoceptor Antagonists" OR "beta-Blockers, Adrenergic" OR "Adrenergic beta-Blockers" OR "beta Blockers, Adrenergic" OR "beta-Adrenergic Receptor Blockaders" OR "beta Adrenergic Receptor Blockaders" OR "beta-Adrenergic Blocking Agents" OR "Agents, beta-Adrenergic Blocking" OR "beta Adrenergic Blocking Agents" OR "beta-Adrenergic Blockers" OR "Blockers, beta-Adrenergic" OR "beta Adrenergic Blockers" OR "beta-Adrenergic Antagonists" OR "Antagonists, beta-Adrenergic" OR "beta Adrenergic Antagonists" OR "Adrenergic beta-Receptor Blockaders" OR "Adrenergic beta Receptor Blockaders" OR "Angiotensin-Converting Enzyme Inhibitors"[Mesh] OR "Angiotensin Converting Enzyme Inhibitors" OR "Kininase II Inhibitors" OR "Angiotensin I-Converting Enzyme Inhibitors" OR "Angiotensin I Converting Enzyme Inhibitors" OR "Antagonists, Angiotensin-Converting Enzyme" OR "Antagonists, Angiotensin Converting Enzyme" OR "Inhibitors, ACE" OR "ACE Inhibitors" OR "Inhibitors, Angiotensin-Converting Enzyme" OR "Inhibitors, Angiotensin Converting Enzyme" OR "Angiotensin-Converting Enzyme Antagonists" OR "Angiotensin Converting Enzyme Antagonists" OR "Ganglionic Blockers"[Mesh] OR "Blockers, Ganglionic" OR "Ganglioplegic Agents" OR "Nicotinic Antagonists"[Mesh] OR "Antagonists, Nicotinic" OR "Antagonist*, Nicotinic" OR "Vasodilator Agents"[Mesh] OR "Agents, Vasodilator" OR "Vasodilators" OR "Vasorelaxants"

OR "Vasodilator Drugs" OR "Drugs, Vasodilator" OR "Vasoactive Antagonists" OR "Antagonists, Vasoactive" OR "Endothelium-Dependent Relaxing Factors"[Mesh] OR "Endothelium Dependent Relaxing Factors" OR "Endothelium-Dependent Vasodilators" OR "Endothelium-Derived Relaxant Factor" OR "Endothelium Derived Relaxant Factor" OR "Relaxing Factor, Endothelium-Derived" OR "Diuretics"[Mesh] OR "Diuretics, Osmotic"[Mesh] OR "Diuretics, Potassium Sparing"[Mesh] OR "Epithelial Sodium Channel Blockers"[Mesh] OR "Sodium Chloride Symporter Inhibitors"[Mesh] OR "Sodium Potassium Chloride Symporter Inhibitors"[Mesh] OR "Mineralocorticoid Receptor Antagonists"[Mesh] OR "Diuretic" OR "Diuretic Effect" OR "Effect, Diuretic" OR "Diuretic Effects" OR "Effects, Diuretic" OR "Osmotic Diuretics" OR "Potassium Sparing Diuretics" OR "Epithelial Sodium Channel Inhibitors" OR "ENaC Channel Blockers" OR "Diuretics, Thiazide" OR "Thiazide Diuretics" OR "Benzothiadiazine Diuretics" OR "Diuretics, Benzothiadiazine" OR "Potassium Depleting Diuretics" OR "Loop Diuretics" OR "Diuretics, Loop" OR "High Ceiling Diuretics" OR "Antagonists, Mineralocorticoid Receptor" OR "Mineralocorticoid Antagonists" OR "Aldosterone Receptor Antagonists" OR "Carbonic Anhydrase Inhibitors"[Mesh] OR "Inhibitors, Carbonic Anhydrase" OR "Carbonate Dehydratase Inhibitors" OR "Carboxyanhydrase Inhibitors" OR "antihypertensive*" OR "beta blocker*" OR "angiotensin receptor blocker*" OR "calcium channel block*" OR "Angiotensin-Converting enzyme Inhibitor*" OR "ACE inhibitor*" OR "angiotensin receptor blocker*" OR "ARB" OR "Benzothiadiazines" OR "diuretic*" OR "thiazide*" OR captopril OR benazepril OR enalapril OR fosinopril OR imidapril OR lisinopril OR perindopril OR quinapril OR ramipril OR trandolapril OR zofenopril OR azilsartan OR irbesartan OR losartan OR olmesartan OR telmisartan OR alprenolol OR bucindolol OR carteolol OR carvedilol OR labetalol OR nadolol OR oxprenolol OR penbutolol OR pindolol OR propranolol OR sotalol OR timolol OR acebutolol OR atenolol OR betaxolol OR bisoprolol OR celiprolol OR esmolol OR metoprolol OR nebivolol OR amlodipine OR aranidipine OR azelnidipine OR barnidipine OR benidipine OR cilnidipine OR clevidipine OR isradipine OR efonidipine OR felodipine OR lercanidipine OR nicardipine OR nifedipine OR nilvadipine OR nimodipine OR nisoldipine OR nitrendipine OR pranidipine OR verapamil OR diltiazem OR benzothiadiazine OR chlorothiazide OR hydrochlorothiazide OR bendrofluazide) AND ("Carcinoma, Squamous Cell"[Mesh] OR "squamous cell carcinoma*" OR "Carcinomas, Squamous Cell" OR "Squamous Cell Carcinomas" OR "Squamous Cell Carcinoma" OR "Carcinoma, Squamous" OR "Carcinomas, Squamous" OR "Squamous Carcinoma" OR "Squamous Carcinomas" OR "Carcinoma, Epidermoid" OR "Carcinomas, Epidermoid" OR "Epidermoid Carcinoma" OR "Epidermoid Carcinomas" OR "Carcinomas, Planocellular" OR "Planocellular Carcinoma" OR "Planocellular Carcinomas" OR "SCC" OR "Carcinoma, Basal Cell"[Mesh] OR "basal cell carcinoma*" OR "Basal Cell Carcinoma" OR "Basal Cell Carcinomas" OR "Carcinomas, Basal Cell" OR "basal cell epithelioma*" OR "Epithelioma, Basal Cell" OR "Basal Cell Epithelioma" OR "Basal Cell Epitheliomas" OR "BCC" OR "non melanoma skin cancer" OR "NMSC" OR "NMSC*" OR "non melanoma skin cancer*" OR "nonmelanoma skin cancer*" OR "non-melanoma skin cancer*" OR "keratinocyte cancer*" OR "keratinocyte carcinoma*" OR "Melanoma"[Mesh] OR "Melanoma, Amelanotic"[Mesh] OR "melanoma*" OR "malignant melanoma*" OR "Melanomas" OR "Malignant Melanoma" OR "Malignant Melanomas" OR "Melanoma, Malignant" OR "Melanomas, Malignant" OR "Amelanotic Melanoma" OR "Amelanotic Melanomas" OR "Melanomas, Amelanotic" OR "skin cancer*" OR "Cancer of Skin" OR "Skin Cancers" OR "Cancer of the Skin" OR "Skin Cancer" OR "Cancer, Skin" OR "Cancers, Skin")

Embase (Ovid). (exp antihypertensive agent/ or exp adrenergic receptor blocking agent/ or exp alpha 1 adrenergic receptor blocking agent/ or exp alpha adrenergic receptor blocking agent/ or exp alpha 2 adrenergic receptor blocking agent/ or exp beta adrenergic receptor blocking agent/ or exp dipeptidyl carboxypeptidase inhibitor/ or exp ganglion blocking agent/ or exp nicotinic receptor blocking agent/ or exp vasodilator agent/ or exp endothelium derived relaxing factor/ or exp diuretic agent/ or exp thiazide diuretic agent/ or exp epithelial sodium channel blocking agent/ or exp potassium sparing diuretic agent/ or exp osmotic diuretic agent/ or exp loop diuretic agent/ or exp mineralocorticoid antagonist/ or exp carbonate dehydratase inhibitor/) AND (exp melanoma/ or exp amelanotic melanoma/ or exp non melanoma skin cancer/ or exp keratinocyte carcinoma/ or exp basal cell carcinoma/ or exp squamous cell carcinoma/)

Cochrane library. Antihypertensive and skin cancer.

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