Supplemental Online Content

Wallach JD, Yoon S, Doernberg H, et al. Associations Between Surrogate Markers and Clinical Outcomes for Nononcologic Chronic Disease Treatments. *JAMA*. Published online April 22, 2024. doi:10.1001/jama.2024.4175

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eFigure 31. Type 2 Diabetes Mellitus

eReferences.

This supplementary material has been provided by the authors to give readers additional information about their work.

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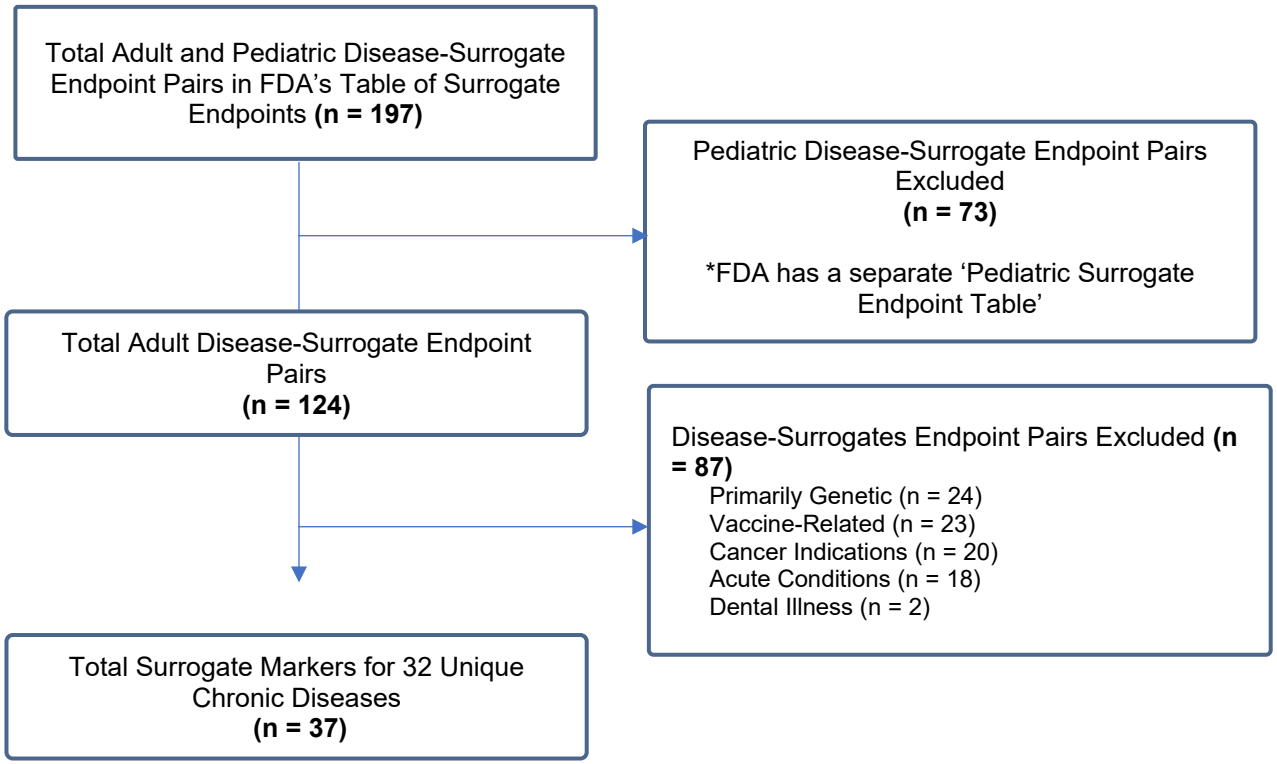
eMethods

Surrogate marker – indications excluded

The US Food and Drug Administration's (FDA's) Adult Surrogate Endpoint Table provides a list of surrogate markers that can form basis of drug approval or licensure across different diseases. On August 2, 2022, we accessed FDA's downloaded table and identified 197 surrogate markers used as primary end points for clinical trials. We did not consider FDA's Pediatric Surrogate Endpoint Table and excluded any surrogate markers for diseases listed in FDA's Adult Surrogate Endpoint Table that were acute illnesses (e.g., skin infection), primarily genetic (e.g., Fabry disease, cystic fibrosis), or vaccine-related. We also excluded surrogates for oncologic diseases, as those have been the focus of previous reviews.[1-4] For each surrogate marker, we then recorded the disease or use, patient population, and type of approval (traditional vs. accelerated approval).



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Trial-level meta-analyses

The FDA has not established standards for validating surrogate markers as primary endpoints or clarified the criteria for the use of surrogate markers for chronic diseases.[5] Although different methods have been proposed for the validation of surrogate markers,[6,7] evidence suggests that FDA has often relied on a multiple trial approach to validate surrogate markers. In this two-stage approach, it is first necessary to demonstrate that individual changes in a surrogate marker caused by the treatment are correlated with individual changes in the clinical outcome. Next, meta-analyses of multiple randomized controlled trials (i.e., trial-level surrogacy) are needed to confirm that treatment effects with respect to the surrogate marker are correlated with treatment effects with respect to the clinical outcome.[8] As in previous evaluations of surrogate markers in oncology, we focus on identifying evidence from trial-level meta-analyses.[1-4]

Search strategy

We developed and performed 31 broad searches of the Medline (Ovid ALL, 1946) database (**eTable 1)**. Each search included three main concepts: study design (specific search terms to identify meta-analyses, systematic reviews, and pooled analyses); surrogate marker (specific search terms for each surrogate marker in FDA's Table), correlation (specific search terms for the conception of correlation or association), and disease (specific search terms for the relevant diseases listed for each surrogate marker in FDA's Table). When the same surrogate markers were listed for multiple diseases in FDA's Table (e.g., urine free cortisol for Cushing's syndrome and Cushing's disease) or multiple surrogate markers were listed for one disease (undetectable plasma HIV RNA, serum HIV antibody, and greater than 0.5 log reduction in plasma HIV RNA for HIV-1), we conduct one search. The study design search strategy contained elements from a published search filter, which has been used in previous umbrella reviews conducted by our team.[9] The search strategies for surrogate markers and correlation were modified based on previously developed search strings.[1,4]

Although our initial set of Ovid searches were performed and downloaded November 28, 2022, we expanded our searches on March 19, 2023, to capture a broader sample of potentially eligible trial-level meta-analyses. In particular, after starting the first round of title and abstract screening, we decided to remove the search strategy focused on capturing the broad concept of surrogate markers, as we realized that these terms may not be consistently reported in titles

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and/or abstracts of trial-level meta-analyses. To supplement our original search, we added surrogate-specific terms to each search based on the language used to describe each surrogate marker in FDA's Table.

Eligibility criteria

We identified all unique associations between treatment effects measured using the surrogate marker and any clinical outcome (i.e., surrogate marker-clinical outcome pairs). Earlier versions of updated meta-analyses were excluded unless they reported unique surrogate marker-clinical outcome pairs (e.g., an earlier meta-analysis reported associations based on surrogate markers or clinical outcomes with slightly different definitions). Discrepancies were resolved by discussion and consensus (JDW, SY, HD, RR, JSR).

For hemoglobin A1c (HbA1c) as a surrogate marker used in clinical trials for type 2 diabetes mellitus treatment, we excluded trial-level meta-analyses that only included trials comparing more versus less intensive control (these were classified as 'wrong aim'). However, if meta-analyses incorporated these trials along with trials comparing at least two treatment groups in their analyses, they were considered eligible.

Data Extraction

For each eligible meta-analysis, three reviewers (JDW, SY, HG) recorded study characteristics: the first author; publication year; journal name; funding source; study design (i.e., meta-analysis, systematic review and meta-analysis, pooled analysis); number and total sample size of the component studies; chronic diseases; interventions; and definitions of the evaluated surrogate markers and clinical outcomes.

Results

Eligible studies:

- Alzheimer's disease[10-12]
- Primary glomerular disease[13]

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- Chronic kidney disease[14,15]
- Chronic obstructive pulmonary disease[16-21]
- Gout[22,23]
- HIV[24,25]
- Hypercholesterolemia[26-36]
- Hyperphosphatemia[37]
- Hypertension[38-47]
- Hypertriglyceridemia[32,33,35]
- Osteoporosis[48-53]
- Pulmonary fibrosis[54]
- Secondary hyperparathyroidism[37]
- Type 2 diabetes mellitus[55-63]

Discussion (additional text)

Surrogate markers used as primary end points in clinical trials supporting approval of oncologic medical products are often weakly associated with clinical outcomes.[1-4] For example, a previous study assessed the underlying evidence for the surrogate end points for solid tumors listed in FDA's Table and found that none were strongly correlated with overall survival in systematic reviews, meta-analyses, and correlation studies.[1] This study builds upon those findings focused on oncology treatment, demonstrating similarly weak or inconsistent associations in published meta-analyses for many surrogate markers listed by FDA as eligible for use in clinical trials supporting traditional approval of non-oncologic chronic disease treatments, including blood pressure for hypertension and bone mineral density for osteoporosis.

Searches

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eTable 1. Original search results

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	Alzheimer's Disease	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	Alzheimer*.mp.	192206

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20	11 AND 12 AND 17 AND 19	466

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Asthma**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0

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19	asthma*.mp.	197912
20	11 AND 12 AND 17 AND 19	227

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Chronic Kidney Disease**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820

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18	[disease-specific search term]	0
19	chronic kidney disease OR CKD).mp.	75083
20	11 AND 12 AND 17 AND 19	220

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Chronic Obstructive Pulmonary Disease (COPD)**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243

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17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	(chronic obstructive pulmonary disease OR COPD).mp.	76459
20	11 AND 12 AND 17 AND 19	156

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Cushing's disease/syndrome**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611

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16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	Cushing*.mp.	19701
20	11 AND 12 AND 17 AND 19	13

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Exocrine pancreatic insufficiency**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881

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15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	pancreatic insufficiency.mp.	4417
20	11 AND 12 AND 17 AND 19	1

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Gout**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	

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14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	gout*.mp.	21777
20	11 AND 12 AND 17 AND 19	28

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Hepatitis B virus (HBV)**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508

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13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	(hepatitis B OR HBV).mp.	112562
20	11 AND 12 AND 17 AND 19	134

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Hepatitis C virus (HCV)**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157

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12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	(hepatitis C OR HCV).mp.	105098
20	11 AND 12 AND 17 AND 19	115

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Hepatitis D virus (HDV)**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113

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11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	(hepatitis D OR HDV).mp.	4281
20	11 AND 12 AND 17 AND 19	1

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Human Immunodeficiency Virus-1 (HIV-1)**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644

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10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	(human immunodeficiency virus* OR HIV).mp.	403760
20	11 AND 12 AND 17 AND 19	184

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Hypertension**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0

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9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	hypertension.mp.	547605
20	11 AND 12 AND 17 AND 19	541

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Hypercholesterolemia**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917

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8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	hypercholesterolemia.mp.	44992
20	11 AND 12 AND 17 AND 19	70

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Hyperphosphatemia**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0

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7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	hyperphosphatemia.mp.	4480
20	11 AND 12 AND 17 AND 19	5

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Hypertriglyceridemia**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201

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6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	hypertriglyceridemia.mp.	15439
20	11 AND 12 AND 17 AND 19	21

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Hypothyroidism**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930

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5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	hypothyroidism.mp.	46824
20	11 AND 12 AND 17 AND 19	36

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Lupus nephritis**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595

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4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	lupus*.mp.	99147
20	11 AND 12 AND 17 AND 19	163

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Mycobacterium avium complex (MAC) lung disease**	
1	[review focused search]	0

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2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	(mycobacterium avium complex lung disease OR MAC).mp.	19246
20	11 AND 12 AND 17 AND 19	14

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Nonalcoholic steatohepatitis (NASH)**	

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1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	nonalcoholic steatohepatitis or NASH.mp.	15032
20	11 AND 12 AND 17 AND 19	62

Ovid MEDLINE(R) ALL <1946	**Opioid use disorder**	

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to November 28, 2022>		
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	(OUD OR opioid use disorder OR opioid abuse OR opioid dependence OR opioid addiction).mp	11368
20	11 AND 12 AND 17 AND 19	4

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Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	Osteoporosis	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	osteoporosis.mp.	98387
20	11 AND 12 AND 17 AND 19	107

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Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	Paget's disease	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	Paget*.mp.	10604

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20	11 AND 12 AND 17 AND 19	6

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Primary biliary cholangitis**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0

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19	biliary cholangitis.mp.	1642
20	11 AND 12 AND 17 AND 19	3

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Primary glomerular diseases associated with significant proteinuria**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820

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18	[disease-specific search term]	0
19	glomerular disease.mp	3587
20	11 AND 12 AND 17 AND 19	5

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Primary hyperparathyroidism**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243

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17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	hyperparathyroidism.mp.	30977
20	11 AND 12 AND 17 AND 19	14

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Pulmonary fibrosis**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611

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16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	pulmonary fibrosis.mp.	34701
20	11 AND 12 AND 17 AND 19	34

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Pulmonary tuberculosis**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881

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15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	pulmonary tuberculosis.mp.	35540
20	11 AND 12 AND 17 AND 19	18

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Secondary hyperparathyroidism associated with chronic kidney disease**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	

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14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	hyperparathyroidism AND (chronic kidney disease or CKD).mp.	2911
20	11 AND 12 AND 17 AND 19	7

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Systemic sclerosis-interstitial lung disease**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508

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13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	(systemic sclerosis interstitial lung disease or systemic sclerosis-interstitial lung disase).mp.	57
20	11 AND 12 AND 17 AND 19	1

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Tobacco dependence**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157

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12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	(tobacco dependence or nicotine dependence).mp.	7806
20	11 AND 12 AND 17 AND 19	7

Ovid MEDLINE(R) ALL <1946 to November 28, 2022>	**Type 2 diabetes mellitus**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	206595
4	systematic review.pt.	220930
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14201
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	433917
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	13644
10	(metaanalysis or meta-analysis).af.	261113

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11	3 OR 4 OR 5 OR 7 OR 9 OR 10	506157
12	(correlat* OR associat* OR regress* OR validat*).mp.	8724508
13	[surrogate search term]	
14	biomarker*.mp. or exp biomarkers/	1080881
15	surrogate*.mp.	66611
16	intermediate*.mp.	377243
17	14 OR 15 OR 16	1492820
18	[disease-specific search term]	0
19	(type 2 diabetes or type II diabetes or T2D).mp.	167982
20	11 AND 12 AND 17 AND 19	580

Update search results

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Alzheimer's Disease**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0

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7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
	[correlation focused search terms]	
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
	[disease-specific search term]	0
14	Alzheimer*.mp.	196852
15	[surrogate specific search term]	0
16	(amyloid* OR beta-amyloid OR betaamyloid OR neuritic OR senile OR peptide* OR plaque*).mp.	1138775
17	11 AND 12 AND 14 AND 16	508

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Asthma**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208

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8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	asthma*.mp.	200443
15	[surrogate specific search term]	0
16	(FEV* OR forced expiratory volume OR respiratory function OR vital capacity)mp.	366758
17	11 AND 12 AND 14 AND 16	473

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Chronic Kidney Disease**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123

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10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	**[disease-specific search term]**	0
14	(chronic kidney disease OR CKD).mp.	77800
15	[surrogate specific search term]	0
16	eGFR OR GFR OR glomerular filtration OR creatinine.mp.	271961
17	11 AND 12 AND 14 AND 16	599

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Chronic Obstructive Pulmonary Disease (COPD)**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827

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12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	(chronic obstructive pulmonary disease OR COPD).mp.	78106
15	[surrogate specific search term]	0
16	(FEV* OR forced expiratory volume OR respiratory function OR vital capacity).mp.	366758
17	11 AND 12 AND 14 AND 16	454

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Cushing's disease/syndrome**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0

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14	Cushing*.mp.	19916
15	[surrogate specific search term]	0
16	(UFC OR urine OR cortisol).mp.	455995
17	11 AND 12 AND 14 AND 16	52

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Exocrine pancreatic insufficiency**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	pancreat*.mp.	320289
15	[surrogate specific search term]	0

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16	(CFA OR coefficient of fat absorption OR (fecal adj4 fat)).mp.	13250
17	11 AND 12 AND 14 AND 16	7

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Gout**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	gout*.mp.	22197
15	[surrogate specific search term]	0
16	(uric acid OR urate).mp.	48781
17	11 AND 12 AND 14 AND 16	181

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Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	Hepatitis B Virus (HBV)	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	(hepatitis B OR HBV).mp.	113939
15	[surrogate specific search term]	0
16	(undetectable OR HBsAg OR surface anti*).mp.	100673
17	11 AND 12 AND 14 AND 16	211

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Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	Hepatitis C Virus (HCV)	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	(hepatitis C OR HCV).mp.	106159
15	[surrogate specific search term]	0
16	((sustained adj4 response) OR SVR).mp.	23194
17	11 AND 12 AND 14 AND 16	319

Ovid MEDLINE(R) ALL <1946	Hepatitis D Virus (HDV)	

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to March 19, 2023>		
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	(hepatitis D OR HDV).mp.	4353
15	[surrogate specific search term]	0
16	(ALT OR LFT OR liver function test OR alanine transaminase).mp.	68385
17	11 AND 12 AND 14 AND 16	2

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Human Immunodeficiency Viurs-1 (HIV-1)**	

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1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	(human immunodeficiency virus* OR HIV).mp.	408572
15	[surrogate specific search term]	0
16	(undetectable OR RNA OR antibody test OR antibod* OR plasma OR RNA).mp.	3343917
17	11 AND 12 AND 14 AND 16	375

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Hypertension**	
1	[review focused search]	0
2	[concept: SRs]	0

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3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	(HTN OR hypertension OR blood pressure)mp.	869218
15	[surrogate specific search term]	0
16	(BP OR blood pressure).mp.	630099
17	11 AND 12 AND 14 AND 16	5192

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Hypercholesterolemia**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463

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5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	(hypercholesterolemia OR cholesterol).mp.	338307
15	[surrogate specific search term]	0
16	Exp Cholesterol/ OR cholesterol.mp.	321901
17	11 AND 12 AND 14 AND 16	3455

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Hyperphosphatemia**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0

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7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	(hyperphosphatemia OR phosphate).mp.	311047
15	[surrogate specific search term]	0
16	phosphate.mp.	308948
17	11 AND 12 AND 14 AND 16	555

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Hypertriglyceridemia**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208

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8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	(hypertriglyceridemia OR triglyceride*).mp.	171689
15	[surrogate specific search term]	0
16	triglyceride*.mp.	165068
17	11 AND 12 AND 14 AND 16	1869

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Hypothyroidism**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123

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10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	(hypothyroidism OR thyroid).mp.	255731
15	[surrogate specific search term]	0
16	(TSH OR thyroid stimulating OR thyroid-stimulating).mp.	41303
17	11 AND 12 AND 14 AND 16	338

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Lupus nephritis**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827

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12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	lupus*.mp.	100524
15	[surrogate specific search term]	0
16	(CRR OR complete renal response OR proteinuria OR albuminuria OR (urin* adj4 protein) OR UPCR OR (protein adj4 creatinine) OR eGFR OR GFR OR glomerular filtration OR serum creatinine OR (creatine adj4 blood) OR renal function).mp.	270834
17	11 AND 12 AND 14 AND 16	62

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Mycobacterium avium complex (MAC) lung disease**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827

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12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	(mycobacterium avium complex OR MAC).mp.	22315
15	[surrogate specific search term]	0
16	((culture adj4 conversion) OR (smear adj4 conversion) OR (culture adj4 negative)).mp.	12752
17	11 AND 12 AND 14 AND 16	5

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Nonalcoholic steatohepatitis (NASH)**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0

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14	(nonalcoholic steatohepatitis OR NASH OR NAFLD OR (fatty liver adj4 disease)).mp. OR Non-alcoholic Fatty Liver Disease/	43578
15	[surrogate specific search term]	0
16	((resolution OR no worsening OR improvement) AND fibrosis).mp.	14570
17	11 AND 12 AND 14 AND 16	35

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Opioid use disorder**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0

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14	(OUD OR opioid use disorder OR opioid abuse OR opioid dependence OR opioid addiction).mp OR Opioid-Related Disorders/	25840
15	[surrogate specific search term]	0
16	urine.mp.	392211
17	11 AND 12 AND 14 AND 16	29

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Osteoporosis**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	osteoporosis.mp.	100134

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15	[surrogate specific search term]	0
16	(fracture* OR BMD OR bone density OR bone mineral*).mp.	425199
17	11 AND 12 AND 14 AND 16	1323

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Paget's Disease**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	Paget*.mp.	10722
15	[surrogate specific search term]	0
16	(alkaline phosphatase OR ALP OR LFT OR liver function test).mp.	110904

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17	11 AND 12 AND 14 AND 16	9

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Primary biliary cholangitis**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	(cholangitis OR PBC).mp.	25863
15	[surrogate specific search term]	0
16	(alkaline phosphatase OR ALP OR bilirubin OR LFT OR liver function test).mp.	155243
17	11 AND 12 AND 14 AND 16	30

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Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	Primary glomerular disease associated with significant proteinuria	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	glomerular disease.mp.	3675
15	[surrogate specific search term]	0
16	(proteinuria OR albuminuria OR (urin* adj4 albumin) OR (urine* adj4 protein)).mp.	86752
17	11 AND 12 AND 14 AND 16	16

Ovid MEDLINE(R) ALL <1946	Primary hyperparathyroidism	

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to March 19, 2023>		
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	(hyperparathyroidism OR parathyroid).mp.	77170
15	[surrogate specific search term]	0
16	(calcium OR blood test OR hypercalcemia).mp.	664360
17	11 AND 12 AND 14 AND 16	218

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Pulmonary fibrosis**	

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1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	pulmonary fibrosis.mp.	35388
15	[surrogate specific search term]	0
16	(FVC OR forced vital capacity).mp.	22234
17	11 AND 12 AND 14 AND 16	56

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Pulmonary tuberculosis**	
1	[review focused search]	0
2	[concept: SRs]	0

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3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	pulmonary tuberculosis.mp.	35924
15	[surrogate specific search term]	0
16	(culture adj4 negative).mp.	11671
17	11 AND 12 AND 14 AND 16	3

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Secondary hyperparathyroidism associated with chronic kidney disease**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463

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5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	((hyperparathyroidism or parathyroid) AND (chronic kidney disease OR CKD)).mp.	5224
15	[surrogate specific search term]	0
16	(iPTH or parathyroid).mp.	66411
17	11 AND 12 AND 14 AND 16	51

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Systemic sclerosis-interstitial lung disease**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0

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7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	(systemic sclerosis interstitial lung disease OR systemic sclerosis-interstitial lung disease OR systemic sclerosis ILD).mp.	66
15	[surrogate specific search term]	0
16	(FVC or forced vital capacity).mp.	22234
17	11 AND 12 AND 14 AND 16	4

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Tobacco dependence**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208

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8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123
10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	(tobacco dependence or nicotine dependence).mp. OR Tobacco Use Disorder/	16195
15	[surrogate specific search term]	0
16	((exhaled adj4 carbon) or carbon monoxide OR CO).mp.	733809
17	11 AND 12 AND 14 AND 16	20

Ovid MEDLINE(R) ALL <1946 to March 19, 2023>	**Type 2 diabetes mellitus**	
1	[review focused search]	0
2	[concept: SRs]	0
3	(systematic adj4 review).ti.	217307
4	systematic review.pt.	223463
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	14296
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	451208
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	14123

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10	(metaanalysis or meta-analysis).af.	270617
11	3 OR 4 OR 5 OR 7 OR 9 OR 10	525827
12	(correlat* OR associat* OR regress* OR validat*).mp.	8916597
13	[disease-specific search term]	0
14	(type 2 diabetes or type II diabetes or T2D*).mp.	229769
15	[surrogate specific search term]	0
16	(HbA1c or hemoglobin or gly* hemoglobin or A1c).mp.	200674
17	11 AND 12 AND 14 AND 16	1334

eTable 1a. Surrogate marker-clinical outcome pairs from meta-analyses of clinical trials with correlation coefficients, coefficients of determination, or results from meta-regression analyses

Characteristics				Meta-analyses with correlation coefficients or coefficients of determination				Meta-analyses with regression-based analyses only		
Chronic disease	**Surrogate Marker**	**Clinical Outcome**	**Meta-analyses identified, No.**	**Total, No. (%)**	**Meta-analyses providing statistically significant evidence (P<0.05)**	**Meta-analyses providing statistically significant and high-strength evidence (r>0.85)[a]**	**Meta-analyses providing mixed evidence**	**Total, No. (%)**	**Meta-analyses providing statistically significant evidence (P<0.05)**	**Meta-analyses providing mixed evidence**
Overall	NA	NA	200	81	51	10	4	119	64	15
Surrogate markers appropriate for accelerated approval										
Alzheimer's disease	Amyloid beta plaque	CDR-SB	3	1	0	0	0	2	1	0
		ADAS-Cog	2	1	1	0	0	1	1	0
		MMSE	2	0	0	0	0	2	1	0

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Primary glomerular disease	Proteinuria	Doubling of serum creatinine, ESRD, or death	1	1	1	1	0	0	0	0
Surrogate markers appropriate for traditional approval										
Chronic kidney disease	eGFR	Doubling of serum creatinine, GFR,15 mL/min per 1.73 m^2, treated ESRD	2	1	1	1	0	1	1	0
		Doubling of serum creatinine, GFR,15 mL/min per 1.73 m^2, treated ESRD, death	1	0	0	0	0	1	1	0
		Treated ESRD	1	0	0	0	0	1	1	0
COPD	Trough FEV1	Moderate-severe exacerbation rate	3	3	3	0	0	0	0	0
		Rescue medication use	2	2	2	0	0	0	0	0
		SGRQ	4	4	3	0	1	0	0	0
		Time to first occurrence of a moderate-severe exacerbation	1	1	1	1	0	0	0	0
		TDI	4	4	4	0	0	0	0	0
		Mild, moderate, or severe exacerbation rate	1	1	1	0	0	0	0	0
		Time to first exacerbation	1	1	1	0	0	0	0	0
		At least one exacerbation	1	1	1	0	0	0	0	0
		Exacerbations per year	2	1	1	0	0	1	0	0
		Time to first exacerbation, number of patients with at least one exacerbation,	1	1	1	0	0	0	0	0

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		or exacerbations per year								
		Severe exacerbations per year	1	1	0	0	1	0	0	0
Gout	Serum uric acid	Gout flair	1	1	0	0	0	0	0	0
		HAQ-DI	1	0	0	0	0	1	1, but wrong direction so classified as not significant	0
		SDS	1	0	0	0	0	1	1, but wrong direction so classified as not significant	0
		SF-36 MCS	1	0	0	0	0	1	1, but wrong direction so classified as not significant	0
		PGA	1	0	0	0	0	1	1, but wrong direction so classified as not significant	0
		Pain in the last week	1	0	0	0	0	1	1, but wrong direction so classified as not significant	0
		SF-36 PCS	1	0	0	0	0	1	1, but wrong direction so classified as not significant	0
HIV	HIV-1 RNA viral load <50 copies/mL	Progression to AIDS or death at 48 weeks (findings largely consistent at 24 weeks and 96 weeks)	1	1	0	0	0	0	0	0
	HIV-1 RNA viral load <200 copies/mL		1	1	0	0	1	0	0	0
	HIV-1 RNA viral load <400 copies/mL		1	1	0	0	0	0	0	0
	Mean HIV-1 RNA level	Progression to AIDS or death over treatment	1	0	0	0	0	1	1	0
Hypercholesterolemia	LDL-C	Major vascular events, as	4	1	1	1	0	3	3	0

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		defined by each meta-analysis								
		MACE, Major CV events	2	0	0	0	0	2	1	1
		Non-fatal MI or cardiac mortality	1	1	1	0	0	0	0	0
		Major coronary events, as defined by each meta-analysis	3	1	1	1	0	2	2	0
		CHD mortality and non-fatal MI	1	1	1	0	0	0	0	0
		All-cause mortality	3	2	2	0	1	1	1	0
		CHD mortality	2	1	1	0	0	1	1	0
		Vascular mortality	2	1	1	1	0	1	1	0
		Cancer	1	0	0	0	0	1	0	0
		Fatal or non-fatal stroke	4	1	1	0	0	3	3	0
		Non-CV mortality	1	1	1	0	0	0	0	0
		Non-vascular mortality	1	0	0	0	0	1	0	0
		Coronary revascularization	1	0	0	0	0	1	1	0
Hyperphosphatemia	Serum phosphorus	All-cause mortality	1	1	0	0	0	0	0	0
		CV mortality	1	1	0	0	0	0	0	0
Hypertension	Systolic blood pressure	MACE and Major CV events, as defined by each meta-analysis	3	0	0	0	0	3	2	1
		Fatal or non-fatal stroke, ‘stroke’, 5-year risk of stroke	6	1	1	0	0	5	5	0
		Disabling or fatal stroke	1	0	0	0	0	1	0	0
		Ischemic Heart Disease	1	0	0	0	0	1	1	0
		HF or HF causing	4	0	0	0	0	4	3	1

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		hospitalization or death, 5-year risk of HF								
		CV mortality; 5-years risk of CV mortality	5	1	0	0	0	4	1	3
		All-cause mortality	6	1	0	0	0	5	2	2
		Recurrent stroke	1	0	0	0	0	1	1	0
		MI	2	0	0	0	0	2	1	0
		CHD; 5-year risk of CHD	3	0	0	0	0	3	0	2
		Kidney failure	1	0	0	0	0	1	0	0
		MI, stroke, CHF, and CV mortality	1	0	0	0	0	1	1	0
		5-year risk of CVD	1	0	0	0	0	1	0	1
		CHD and stroke	1	0	0	0	0	1	1	0
	Diastolic blood pressure	All-cause mortality	2	1	0	0	0	1	1	0
		CV mortality	1	1	0	0	0	0	0	0
		MI	1	0	0	0	0	1	0	0
		Recurrent stroke	1	0	0	0	0	1	1	0
		Fatal and non-fatal stroke; ‘stroke’	2	1	1	0	0	1	1	0
		MI, stroke, CHF, and CV mortality	1	0	0	0	0	1	1	0
	Systolic and diastolic blood pressure	Fatal and non-fatal stroke	2	0	0	0	0	2	2	0
		CHD	2	0	0	0	0	2	2	0
		HF hospitalization	1	0	0	0	0	1	1	0
		Fatal and non-fatal stroke and CHD	1	0	0	0	0	1	1	0
		Fata and non-fatal stroke, CHD, HF hospitalization	1	0	0	0	0	1	1	0
		CV mortality	1	0	0	0	0	1	1	0
		All-cause mortality	1	0	0	0	0	1	1	0

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Hypertriglyceridemia	Serum triglycerides	Major vascular events, as defined by each component study	2	0	0	0	0	2	0	2
		Stroke	1	0	0	0	0	1	0	0
Osteoporosis	Hip BMD	Vertebral fractures	3	2	2	1	0	1	1	0
		Hip fractures	2	2	2	0	0	0	0	0
		Non-vertebral fractures	3	2	1	0	0	1	1	0
	Femoral neck BMD	Vertebral fractures	2	2	2	0	0	0	0	0
		Hip fractures	2	2	1	0	0	0	0	0
		Non-vertebral fractures	3	2	1	0	0	1	0	0
	Spine BMD	Vertebral fractures	4	2	2	0	0	2	2	0
		Hip fractures	2	2	1	0	0	0	0	0
		Non-vertebral fractures	4	2	1	0	0	2	1	0
Idiopathic pulmonary fibrosis	FVC	Mortality	1	0	0	0	0	1	1	0
		Disease progression	1	0	0	0	0	1	1	0
Secondary hyperparathyroidism	Target serum parathyroid hormone	All-cause mortality	1	1	0	0	0	0	0	0
		CV mortality	1	1	0	0	0	0	0	0
	Continuous serum parathyroid hormone	All-cause mortality	1	1	1	0	0	0	0	0
		CV mortality	1	1	0	0	0	0	0	0
T2DM	HbA1c	All-cause mortality	7	3	0	0	0	4	1	0
		MACE, as defined individual by each study	4	2	2	2	0	2	1	0
		MI	3	1	0	0	0	2	1	0
		Non-fatal MI	1	1	0	0	0	0	0	0
		Stroke (unspecified)	2	1	1	0	0	1	1	0
		Non-fatal stroke	1	1	1	1	0	0	0	0
		Fatal and non-fatal stroke	2	0	0	0	0	2	0	0

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		Hospitalization for HF	3	1	0	0	0	2	0	0
		HF	2	1	0	0	0	1	0	0
		Kidney injury, as defined by component study	1	1	0	0	0	0	0	0
		CV mortality	4	1	0	0	0	3	0	0
		Composite kidney outcome	1	0	0	0	0	1	0	0
		CHD	1	0	0	0	0	1	0	1
		CHD and fatal or non-fatal stroke	1	0	0	0	0	1	1	0
		CHD and fatal or non-fatal stroke and hospitalization for HF	1	0	0	0	0	1	0	1
		Hypoglycemia	1	0	0	0	0	1	0	0
		Severe hypoglycemia	2	0	0	0	0	2	0	0
		Retinopathy	1	0	0	0	0	1	0	0
		Microalbuminuria	1	0	0	0	0	1	0	0
		Neuropathy	1	0	0	0	0	1	0	0
		Peripheral vascular events	1	0	0	0	0	1	0	0

[a] Classified as providing high-strength evidence using criteria proposed by the Institute for Quality and Efficiency in Health Care (IQWiG) ($r \geq 0.85$ or $R^2 \geq 0.72$).[64]
ADAS-Cog, Alzheimer's Disease Assessment Scale – Cognitive Subscale; AIDS, acquired immunodeficiency syndrome; BMD, bone mineral density; CDR-SB; Clinical Dementia Rating – Sum of Boxes; CHD, coronary heart disease; CHF, coronary heart failure; CV, cardiovascular; ESRD, end-stage kidney disease; FEV1, forced expiratory volume in 1 second; GFR, glomerular filtration rate; HAQ-DI, Health Assessment Questionnaire Disabilty Index; HbA1c, hemoglobin A1c; HF, heart failure; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein; MACE, major adverse cardiovascular event; MI, myocardial infarction; mL, milliliter; MMSE, Mini-Mental State Examination; PGA, Patient Global Assessment; r, correlation coefficient; SDS, Sheehan Disability Scale; SF-36 MCS, Short form 36 mental component; SGRQ, St. George's Respiratory Questionnaire; TDI, Townsend Deprivation Index;

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eTable 1b. Surrogate marker-clinical outcome pairs from meta-analyses of clinical trials with correlation coefficients, coefficients of determination, or results from meta-regression analyses classification for Figure 2.

Chronic disease	Surrogate Marker	Clinical Outcome	Meta-analyses identified, No.	Strong evidence[a]	Moderate evidence[b]	Modest evidence[c]	Weak evidence[d]	Limited evidence[e]	No evidence[f]
Surrogate markers appropriate for accelerated approval									
Alzheimer's disease	Amyloid beta plaque	CDR-SB	**3**	**0**	**0**	**0**	**0**	**1**	**0**
		ADAS-Cog	**2**	**0**	**0**	**0**	**1**	**0**	**0**
		MMSE	**2**	**0**	**0**	**0**	**0**	**1**	**0**
Primary glomerular disease	Proteinuria	Doubling of serum creatinine, ESRD, or death	**1**	**1**	**0**	**0**	**0**	**0**	**0**
Surrogate markers appropriate for traditional approval									
Chronic kidney disease	eGFR	Doubling of serum creatinine, GFR,15 mL/min per 1.73 m^2, treated ESRD	**2**	**0**	**0**	**1**	**0**	**0**	**0**
		Doubling of serum creatinine, GFR,15 mL/min per 1.73 m^2, treated ESRD, death	**1**	**0**	**0**	**0**	**1**	**0**	**0**
		Treated ESRD	**1**	**0**	**0**	**0**	**1**	**0**	**0**
COPD	Trough FEV1	Moderate-severe exacerbation rate	**3**	**0**	**0**	**0**	**0**	**0**	**1**
		Rescue medication use	**2**	**0**	**0**	**0**	**0**	**0**	**1**
		SGRQ	**4**	**0**	**0**	**0**	**0**	**1**	**0**
		Time to first occurrence of a	**1**	**1**	**0**	**0**	**0**	**0**	**0**

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		moderate-severe exacerbation							
		TDI	**4**	**0**	**0**	**0**	**1**	**0**	**0**
		Mild, moderate, or severe exacerbation	**1**	**0**	**0**	**0**	**1**	**0**	**0**
		Time to first exacerbation	**1**	**0**	**0**	**0**	**1**	**0**	**0**
		At least one exacerbation	**1**	**0**	**0**	**0**	**1**	**0**	**0**
		Exacerbations per year	**2**	**0**	**0**	**0**	**0**	**1**	**0**
		Time to first exacerbation, number of patients with at least one exacerbation, or exacerbations per year	**1**	**0**	**0**	**0**	**1**	**0**	**0**
		Severe exacerbations per year	**1**	**0**	**0**	**0**	**0**	**1**	**0**
Gout	Serum uric acid	Gout flair	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		HAQ-DI	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		SDS	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		SF-36 MCS	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		PGA	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		Pain in the last week	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		SF-36 PCS	**1**	**0**	**0**	**0**	**0**	**0**	**1**
HIV	HIV-1 RNA viral load <50 copies/mL	Progression to AIDS or death at 48 weeks (findings largely consistent at 24 weeks and 96 weeks)	**1**	**0**	**0**	**0**	**0**	**0**	**1**
	HIV-1 RNA viral load <200 copies/mL		**1**	**0**	**0**	**0**	**0**	**1**	**0**
	HIV-1 RNA viral load <400 copies/mL		**1**	**0**	**0**	**0**	**0**	**0**	**1**
	Mean HIV-1 RNA level	Progression to AIDS or death over treatment	**1**	**0**	**0**	**0**	**0**	**1**	**0**
Hypercholesterolemia	LDL-C	Major vascular events, as defined by each meta-analysis	**4**	**0**	**0**	**1**	**0**	**0**	**0**
		MACE Major CV events	**2**	**0**	**0**	**0**	**0**	**1**	**0**

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		Non-fatal MI or cardiac mortality	**1**	**0**	**0**	**0**	**1**	**0**	**0**
		Major coronary events, as defined by each meta-analysis	**3**	**0**	**0**	**1**	**0**	**0**	**0**
		CHD mortality and non-fatal MI	**1**	**0**	**0**	**0**	**1**	**0**	**0**
		All-cause mortality	**3**	**0**	**0**	**0**	**1**	**0**	**0**
		CHD mortality	**2**	**0**	**0**	**0**	**1**	**0**	**0**
		Vascular mortality	**2**	**0**	**0**	**1**	**0**	**0**	**0**
		Cancer	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		Fatal or non-fatal stroke	**4**	**0**	**0**	**0**	**1**	**0**	**0**
		Non-CV mortality	**1**	**0**	**0**	**0**	**1**	**0**	**0**
		Non-vascular mortality	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		Coronary revascularization	**1**	**0**	**0**	**0**	**1**	**0**	**0**
Hyperphosphatemia	Serum phosphorus	All-cause mortality	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		CV mortality	**1**	**0**	**0**	**0**	**0**	**0**	**1**
Hypertension	Systolic blood pressure	MACE and Major CV events, as defined by each meta-analysis	**3**	**0**	**0**	**0**	**0**	**1**	**0**
		Fatal or non-fatal stroke, ‘stroke’, 5-year risk of stroke	**6**	**0**	**0**	**0**	**1**	**0**	**0**
		Disabling or fatal stroke	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		Ischemic Heart Disease	**1**	**0**	**0**	**0**	**1**	**0**	**0**
		HF or HF causing hospitalization or death, 5-year risk of HF	**4**	**0**	**0**	**0**	**0**	**1**	**0**
		CV mortality; 5-years risk of CV mortality	**5**	**0**	**0**	**0**	**0**	**1**	**0**
		All-cause mortality	**6**	**0**	**0**	**0**	**0**	**1**	**0**
		Recurrent stroke	**1**	**0**	**0**	**0**	**1**	**0**	**0**
		MI	**2**	**0**	**0**	**0**	**0**	**1**	**0**
		CHD; 5-year risk of CHD	**3**	**0**	**0**	**0**	**0**	**1**	**0**
		Kidney failure	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		MI, stroke, CHF, and CV mortality	**1**	**0**	**0**	**0**	**1**	**0**	**0**
		5-year risk of CVD	**1**	**0**	**0**	**0**	**0**	**1**	**0**
		CHD and stroke	**1**	**0**	**0**	**0**	**1**	**0**	**0**

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	Diastolic blood pressure	All-cause mortality	**2**	**0**	**0**	**0**	**0**	**1**	**0**
		CV mortality	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		MI	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		Recurrent stroke	**1**	**0**	**0**	**0**	**1**	**0**	**0**
		Fatal and non-fatal stroke; 'stroke'	**2**	**0**	**0**	**0**	**1**	**0**	**0**
		MI, stroke, CHF, and CV mortality	**1**	**0**	**0**	**0**	**1**	**0**	**0**
	Systolic and diastolic blood pressure	Fatal and non-fatal stroke	**2**	**0**	**0**	**0**	**1**	**0**	**0**
		CHD	**2**	**0**	**0**	**0**	**1**	**0**	**0**
		HF hospitalization	**1**	**0**	**0**	**0**	**1**	**0**	**0**
		Fatal and non-fatal stroke and CHD	**1**	**0**	**0**	**0**	**1**	**0**	**0**
		Fata and non-fatal stroke, CHD, HF hospitalization	**1**	**0**	**0**	**0**	**1**	**0**	**0**
		CV mortality	**1**	**0**	**0**	**0**	**1**	**0**	**0**
		All-cause mortality	**1**	**0**	**0**	**0**	**1**	**0**	**0**
Hypertriglyceridemia	Serum triglycerides	Major vascular events, as defined by each component study	**2**	**0**	**0**	**0**	**0**	**1**	**0**
		Stroke	**0**	**0**	**0**	**0**	**0**	**0**	**1**
Osteoporosis	Hip BMD	Vertebral fractures	**3**	**0**	**0**	**1**	**0**	**0**	**0**
		Hip fractures	**2**	**0**	**0**	**0**	**1**	**0**	**0**
		Non-vertebral fractures	**3**	**0**	**0**	**0**	**0**	**1**	**0**
	Femoral neck BMD	Vertebral fractures	**2**	**0**	**0**	**0**	**1**	**0**	**0**
		Hip fractures	**2**	**0**	**0**	**0**	**0**	**1**	**0**
		Non-vertebral fractures	**3**	**0**	**0**	**0**	**0**	**1**	**0**
	Spine BMD	Vertebral fractures	**4**	**0**	**0**	**0**	**1**	**0**	**0**
		Hip fractures	**2**	**0**	**0**	**0**	**0**	**1**	**0**
		Non-vertebral fractures	**4**	**0**	**0**	**0**	**0**	**1**	**0**
Idiopathic pulmonary fibrosis	Forced vital capacity	Mortality	**1**	**0**	**0**	**0**	**1**	**0**	**0**
		Disease progression	**1**	**0**	**0**	**0**	**1**	**0**	**0**
Secondary hyperparathyroidism	Target serum parathyroid hormone	All-cause mortality	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		CV mortality	**1**	**0**	**0**	**0**	**0**	**0**	**1**
	Continuous serum parathyroid hormone	All-cause mortality	**1**	**0**	**0**	**0**	**1**	**0**	**0**
		CV mortality	**1**	**0**	**0**	**0**	**0**	**0**	**1**
T2DM	HbA1c	All-cause mortality	**7**	**0**	**0**	**0**	**0**	**1**	**0**
		MACE, as defined individual by each study	**4**	**0**	**0**	**1**	**0**	**0**	**0**

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		MI	**3**	**0**	**0**	**0**	**0**	**1**	**0**
		Non-fatal MI	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		Stroke (unspecified)	**2**	**0**	**0**	**0**	**1**	**0**	**0**
		Non-fatal stroke	**1**	**1**	**0**	**0**	**0**	**0**	**0**
		Fatal and non-fatal stroke	**2**	**0**	**0**	**0**	**0**	**0**	**1**
		Hospitalization for HF	**3**	**0**	**0**	**0**	**0**	**0**	**1**
		HF	**2**	**0**	**0**	**0**	**0**	**0**	**1**
		Kidney injury, as defined by component study	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		CV mortality	**4**	**0**	**0**	**0**	**0**	**0**	**1**
		Composite kidney outcome	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		CHD	**1**	**0**	**0**	**0**	**0**	**1**	**0**
		CHD and fatal or non-fatal stroke	**1**	**0**	**0**	**0**	**1**	**0**	**0**
		CHD and fatal or non-fatal stroke and hospitalization for HF	**1**	**0**	**0**	**0**	**0**	**1**	**0**
		Hypoglycemia	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		Severe hypoglycemia	**2**	**0**	**0**	**0**	**0**	**0**	**1**
		Retinopathy	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		Microalbuminuria	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		Neuropathy	**1**	**0**	**0**	**0**	**0**	**0**	**1**
		Peripheral vascular events	**1**	**0**	**0**	**0**	**0**	**0**	**1**

Strong evidence: *r* or R^2 values reported for all associations examined, and all associations classified as statistically significant and high-strength according to criteria proposed by the Institute for Quality and Efficiency in Health Care (IQWiG) ($r \geq 0.85$ or $R^2 \geq 0.72$).[64]); Moderate evidence: *r* or R^2 values reported for all associations examined, and one or more (but not all) classified as statistically significant and high-strength; Modest evidence: *r* or R^2 values reported for some associations examined, and one or more (but not all) classified as statistically significant and high-strength. Any other *r*, R^2 , slopes, effect estimates, or results from meta-regression analyses classified as statistically significant; Weak evidence: No *r* or R^2 values classified as both statistically significant and high-strength, but all *r*, R^2, slopes, effect estimates, or results from meta-regression analyses classified as statistically significant; Limited evidence: No *r* or R^2 values classified as both statistically significant and high-strength, some *r*, R^2, slopes, effect estimates, or results from meta-regression analyses classified as statistically significant and some not; No evidence: No *r* or R^2 values classified as statistically significant and high-strength, and all *r*, R^2, slopes, effect estimates, or results from meta-regression analyses classified as non-statistically significant.

ADAS-Cog, Alzheimer's Disease Assessment Scale – Cognitive Subscale; AIDS, acquired immunodeficiency syndrome; BMD, bone mineral density; CDR-SB; Clinical Dementia Rating – Sum of Boxes; CHD, coronary heart disease; CHF, coronary heart failure; CV, cardiovascular; ESRD, end-stage kidney disease; FEV1, forced expiratory volume in 1 second; GFR, glomerular filtration rate; HAQ-DI, Health Assessment Questionnaire Disability Index; HbA1c, hemoglobin A1c; HF, heart failure; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein; MACE, major adverse cardiovascular event; MI, myocardial infarction; mL, milliliter; MMSE, Mini-Mental State Examination; PGA, Patient Global Assessment; r, correlation coefficient; SDS, Sheehan Disability Scale; SF-36 MCS, Short form 36 mental component; SGRQ, St. George's Respiratory Questionnaire; TDI, Townsend Deprivation Index;

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eTable 2. Alzheimer's disease												
Author, Year	**Study design**	**Indication**	**Interventions**	**Funding source**	**Design of included studies**	**Surrogate marker**	**Clinical endpoint**	**No. studies**	**Overall sample size | No. surrogate measures | No. clinical outcomes**	**Evidence**	**Author's conclusion**	**Plaintext summary**
Pang 2022[11]	MA	Alzheimer's Disease	aducanumab bapineuzumab bexarotene donanemab gantenerumab; lecanemab-irmb semagacestat solanezumab verubecestat	Industry	RCT	Amyloid beta plaque by PET	CDR-SB	15	NR | 4592 | 10611	A 0.1 unit decrease in PET Aβ SUVR is associated with a decreased reduction in the CDR-SB score of 0.09 (0.034 to 0.15)	"This meta-analysis provides statistically significant evidence of a likely causal relationship between a reduction in Aβ plaque and a reduction in cognitive and functional decline in patients with AD."	Using two additional RCTs, updating trial results, and correcting inconsistencies found in Ackley 2021, reductions in Aβ plaque were associated with decreased reductions on several cognitive rating scales. Further analysis suggested a causal relationship between the two.
							ADAS-Cog	15	NR | 4467 | 11885	A 0.1 unit decrease in PET Aβ SUVR is associated with a decreased reduction in ADAS-Cog score of 0.33 (0.12 to 0.55)		
							MMSE	16	NR | 4612 | 11747	A 0.1 unit decrease in PET Aβ		

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										SUVR is associated with a decreased reduction in MMSE score of 0.13 (0.017 to 0.24)		
Ackley 2021[10]	MA		bapineuzumab bexarotene gantenerumab lecanemab-irmb semagacestat solanezumab verubecestat	Government	RCT		CDR-SB	10[1]	NR | 3868 | 7238	A 0.1 unit decrease in PET Aβ SUVR is associated with a decreased reduction in CDR-SB score of 0.051 (-0.027 to 0.13)	"Pooled evidence from available trials reporting both reduction in amyloid levels and change in cognition suggests that amyloid reduction strategies do not substantially improve cognition."	In pooled estimates from 14 RCTs, there was no significant association between reductions in Aβ plaque as measured by PET and cognitive decline as measured by several cognitive rating scales.
							MMSE	14[2]	NR | 4345 | 13609	A 0.1 unit decrease in PET Aβ SUVR is associated with a decreased reduction in MMSE score of 0.087 (-0.042 to 0.22)		
Avgerinos 2021[12]	SRMA		aducanumab bapineuzumab gantenerumab solanezumab	Government	RCT		ADAS-Cog	9[3, 4]	10966 | 2804 | 7968	Pearson's correlation coefficient between the effect sizes of PET Aβ SUVR and change in	"We found that reductions in Aβ brain deposition were associated with improvements of cognition... However,	Reductions in Aβ brain deposition were associated with improvements in cognition as measured by the MMSE, but not significantly

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										ADAS-Cog score 0.68, p=0.02	reduction on amyloid PET SUVR was not significantly correlated with improvement on CDR-SB…"	correlated with improvements on the CDR-SB, which also takes functional status into account.
							CDR-SB	9[3, 4]	10966 | 2804 | 7717	Pearson's correlation coefficient between the effect sizes of PET Aβ SUVR and change in CDR-SB score 0.51, p=0.09		

CDR-SB: Clinical Dementia Rating Scale–sum of boxes; MMSE: Mini Mental State Examination; ADAS-Cog: Alzheimer's Disease Assessment Scale–Cognitive subscale; PET Aβ SUVR: Positron Emission Tomography Amyloid-Beta Standardized Uptake Volume Ratio; RCT: Randomized Control Trial

1: A discrepancy was present between the number of studies noted in the text and in the tables

2: 2 studies used other clinical rating scales that were converted

3: Using the same counting method as the above meta-analyses

4: There is a lack of clarity on the number of Solanezumab trials used in this specific analysis

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eTable 3. Primary Glomerular Disease												
Author, Year	**Study design**	**Indication**	**Interventions**	**Funding source**	**Design of included studies**	**Surrogate marker**	**Clinical outcome**	**No. studies**	**Overall sample size | No. surrogate measures | No. clinical outcomes**	**Evidence**	**Author's conclusion**	**Plaintext Summary**
Inker 2016[13]	IPD MA	IgA Nephropathy	dipyridamole fish oil immunosuppression (mycophenolate, azathioprine) steroids RAAS blockade	University	RCT	Median 9 month (range: 5-12 months) change in proteinuria	Doubling of serum creatinine, ESRD, or death	11	830 | NA | 128	For a 50% decline in proteinuria in treatment groups at 9 months, hazard ratio of the composite clinical outcome over longer follow-up in a fully-adjusted model based off of individual patient data 0.40 (0.32 to 0.49), p<0.001 For a given treatment effect on urine protein excretion, the treatment effect on the	"Overall, the evidence presented here suggests that when considered in conjunction with the evidence from experimental studies, findings from our analyses may be sufficient to recommend the use of proteinuria as a surrogate endpoint in interventions that work by a similar mechanism evaluated in the current analysis…"	A decrease in proteinuria at 9 months for patients with IgA nephropathy was associated with decreased likelihood of the composite clinical outcome of doubling of serum creatinine, ESRD, or death over a longer period of follow-up.

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										composite clinical outcome is expected to be 2.15 (95% Bayesian credible interval 0.10 to 4.32), the treatment effect on urine protein excretion when the respective treatment effects are expressed on the log hazard ratio and log geometric mean scales. R^2 0.91, (95% Bayesian credible interval 0.47 to 1.0)		
RAAS: Renin-angiotensin aldosterone system; ESRD: End-stage renal disease												

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eTable 4. Chronic kidney disease

Author, Year	Study design	Indication	Interventions	Funding source	Included studies' designs	Surrogate marker	Clinical endpoint	No. studies	Overall sample size | No. surrogate measures | No. clinical outcomes	Evidence	Author's conclusion	Plaintext summary
Inker 2019[14] [1]	SRMA	CKD (unspecified), diabetic nephropathy, hypertensive nephropathy, diabetes, polycystic kidney disease, IgA nephropathy, lupus nephritis, membranous nephropathy	allopurinol empagliflozin RAAS blockade simvastatin + ezetimibe sulodexide immunosuppression albuminuria targeted protocol intensive BP control intensive glucose control nurse care	Non-profit	RCT only	GFR change in 3 years or changes in GFR from 3 months after treatment initiation to study end	Treated ESRD, eGFR <15 mL/min per 1.73 m^2, doubling of serum creatinine	47	60620 | NR | 7115	Median R^2 0.97, 95% Bayesian credible interval 0.78 to 1.00 for the treatment effects on the baseline to 3-year GFR slope compared to treatment effects on the clinical endpoints Median R^2 0.96, 95% Bayesian credible interval 0.63 to 1.00 for the treatment effects on the GFR slope beginning 3 months after	"With large enough sample sizes, GFR slope may be a viable surrogate for clinical end points in CKD RCTs."	When averaged across a large number of trial participants and when compared to a control group, a treatment's effects on GFR from baseline to 3 year mark and from 3 months post-treatment initiation to the end of each study were predictive of its effects on a standard clinical endpoint.

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										trial onset to trial end compared to treatment effects on the clinical endpoint		
Heerspink 2014[15]	IPD MA	CKD (unspecified), diabetic nephropathy, hypertensive nephropathy, IgA nephropathy, lupus nephritis, membranous nephropathy	RAAS blockade low protein diet intensive BP control immunosuppression	Industry	RCT only	GFR change in 12 months	Treated ESRD	37	9488 | NR | 2661	Compared to a 0% decline in eGFR from baseline in 12 months, hazard ratio of this clinical endpoint after a 30% decline in a fully adjusted model: 9.8 (7.0 to 13.7) For a 40% decline in the same model: 21.0, (13.4 to 32.7)	"These results provide further support for the validity of these alternative eGFR-based end points in clinical trials of CKD progression" / The consistent associations that we observed are not sufficient to claim surrogacy and should be interpreted in conjunction with additional analyses"	When compared to trial participants who had no change in eGFR within 12 months, those who had either a 30% or 40% reduction in were significantly more likely to progress to a currently accepted clinical endpoint, though the authors caution against using this study alone to claim surrogacy.
							Treated ESRD, eGFR <15 mL/min per 1.73 m^2, doubling of serum creatinine			Compared to a 0% decline in eGFR from baseline in 12 months, hazard ratio of developing these clinical endpoints after a 30% decline in a fully adjusted		

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										model: 9.6 (7.3 to 12.6) For a 40% decline in the same model: 20.3 (14.1 to 29.2)		
							Treated ESRD, eGFR <15 mL/min per 1.73 m^2, doubling of serum creatinine, and death			Compared to a 0% decline in eGFR from baseline in 12 months, hazard ratio of developing these clinical endpoints after a 30% decline in a fully adjusted model: 7.3 (5.6 to 9.5) For a 40% decline in the same model: 14.2 (10.0 to 20.2)		

ESRD: End-stage renal disease; RAAS: Renin-angiotensin aldosterone system; GFR: Glomerular filtration rate; eGFR: Estimated glomerular filtration rate

[1] We did not consider an additional study from Inker et al. 2014 (PMID: 25441438), which was found to be largely overlapping with the other Inker et al. 2019 study.

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eTable 5. Chronic obstructive pulmonary disease

Author, Year	Study design	Indication	Interventions	Funding source	Design of included studies	Surrogate marker	Clinical endpoint	No. studies	Overall sample size | No. surrogate measures | No. clinical outcomes |	Evidence	Author's conclusion	Plaintext Summary
Donohue 2018[17]	Pooled analysis	COPD	indacaterol formoterol glycopyrrolate salmeterol tiotropium indacaterol/glycopyrrolate	Industry	RCT	Trough FEV1	Moderate/severe exacerbation rate/yr[1]	23	23213 | NR | NR	Spearman's rank correlation between change in trough FEV1 from baseline and exacerbation rate -0.05, p<0.001	"Our data suggest that, at a population level, improvements in FEV1 post-bronchodilation correlate with improvements in SGRQ, TDI and exacerbation rate endpoints,..."	Across 23 RCTs, improvements in trough FEV1 from baseline were correlated with both subjective clinical outcomes (measured by the SGRQ and TDI) and objective ones (rescue medication use and moderate-severe exacerbation rate). Greater improvements in FEV1 generally correlated better clinical outcomes. However, the correlation coefficients were all low-strength.
							Rescue medication use (puffs/day)			Pearson's correlation coefficient between change in trough FEV1 and rescue medication use -0.11, p<0.001		
							SGRQ			Pearson's correlation coefficient between change in trough FEV1 and SGRQ -0.16, p<0.001		

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							TDI			Pearson's correlation coefficient between change in trough FEV1 from baseline and TDI 0.16, p<0.001		
Zider 2017[16]	SRMA		aclidinium aclidinium/formoterol arformoterol azithromycin beclomethasone/formoterol budesonide/formoterol cilomilast erythromycin fluticasone/vilanterol formoterol formoterol + terbutaline glycopyrrolate indacaterol indacaterol/glycopyrrolate losmapimod MK-7123 mometasone mometasone/formoterol moxifloxacin	University	RCT		Moderate-severe exacerbation rate/yr[2]	94	119227 | NR | NR	For a 100mL greater change in trough FEV1 between treatment and control, the absolute exacerbation rate decreased 0.06/yr (-0.11 to -0.02), p=0.009; R^2 0.05 | Relative risk 0.86 (0.81 to 0.91), slope -0.16 (-0.21 to -0.1) p<0.001; R^2 0.20	"This meta-regression analysis revealed a robust correlation between the reduction in risk of COPD exacerbations and therapeutic improvements in lung function..."	Across 94 RCTs utilizing many different therapies, greater improvements in trough FEV1 in treatment versus control arms were associated with both decreases in exacerbation rate and increases in time to first exacerbation from trial start. However, when stratified across medications, the associations were more consistently artistically significant ot high-strength for bronchodilators.
							Time to moderate-severe exacerbation beginning from trial initiation	39	73475 | NR | NR	Overall: For a 100mL greater change in trough FEV1 between treatment and control, the hazard ratio to first exacerbation was 0.79 (0.74 to 0.83), slope -0.23 (-		

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			roflumilast salmeterol salmeterol + fluticasone salmeterol + roflumilast sibenadet tiotropium tiotropium + salmeterol tiotropium + salmeterol/fluticasone umeclidinium umeclidinium/vilanterol vilanterol vitamin D							0.28 to -0.18); $p<0.001$; R^2 0.85		
de la Loge 2016[18]	SRMA	Studies of COPD not limited to only COPD from α1-antitrypsin deficiency	aclidinium aclidinium/formoterol fluticasone glycopyrrolate indacaterol indacaterol/glycopyrronium salmeterol tiotropium tiotropium/olodaterol umeclidinium	Industry	RCT		SGRQ	38 in the full text, 39 in the supplement	49561 | NR | NR	Pearson's correlation coefficient of the difference between first and last trough FEV1 measurements regardless of treatment arm, including placebo, and change in SGRQ in a weighted analysis -0.68 (-0.77 to -0.57), $p<0.0001$	"Our primary analysis showed a large and highly significant association between SGRQ and trough FEV1. Analyses with other pairings of spirometric measurements and PROs showed correspondingly large correlation	Across 52 RCTs, improvements in trough FEV1 either in any treatment arms including placebo, or in treatment arms excluding placebo, were associated with improvements in subjective measurements (the patient reported outcomes of SGRQ and TDI) and objective ones (any

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			umeclidinium/vilanterol vilanterol							For every 100mL change in trough FEV1, there was a corresponding 5.89 reduction in SGRQ	coefficients, and a similar trend”	exacerbation, or moderate-severe exacerbations only).
							TDI	22 in the full text, 21 in the supplement	25336 | NR | NR	Pearson’s correlation coefficient of the difference between first and last trough FEV1 measurement regardless of treatment arm, including placebo, and change in TDI in a weighted analysis 0.57 (0.38 to 0.71) For every 100mL change in trough FEV1, there was a corresponding 1.88 increase in TDI		
							Mild, moderate, or severe exacerbation rate/yr[3]	10	9530 | NR | NR	Pearson’s correlation coefficient of the difference between first and last trough FEV1 measurement regardless of treatment arm, including placebo, and		

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										change in rate for any type of COPD exacerbation - 0.69 (-0.85 to -0.39) An improvement in 100mL of FEV1 corresponds to an exacerbation rate of 0.49/yr, while no change corresponds to a rate of 2.30/yr p=0.0002		
							Moderate or severe exacerbation rate/yr[3]	23	30068 | NR | NR	Pearson's correlation coefficient - 0.57 (-0.71 to -0.39) An improvement in 100mL of FEV1 corresponds to an exacerbation rate of 0.66/yr, while no change corresponds to a rate of 0.94/yr p<0.0001		

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Martin 2016[19]	SRMA		aclidinium beclomethasone/formoterol budesonide/formoterol fluticasone + vilanterol fluticasone/salmeterol formoterol glycopyrrolate ipratropium idacaterol roflumilast salmeterol salmeterol/fluticasone tiotropium theophylline umeclidinium umeclidinium/vilanterol vilanterol	Industry	RCT		Time to first exacerbation[4]	12 (21 observations)	20704 | NR | 6077 exacerbations (data incomplete)	For a 100mL difference in trough FEV1 between treatment arms, the corresponding change in log relative risk of time to first mild, moderate, or severe exacerbation: slope -3.56, p=0.0001 R^2 0.5568 (adjusted 0.5335)	"In conclusion, this study demonstrates a significant association between improvements in FEV1…and lower risk for COPD exacerbations."	Across 12 studies, greater changes in FEV1 when comparing between treatment arms were associated with longer times to first exacerbations and improvements in exacerbation rate when defined as moderate/severe, but was only associated with longer times to first exacerbation when defined as mild/moderate/severe. However, in the cases where there was a significant association, the R^2 values were not high-strength.
							Exacerbations /yr			For a 100mL difference in trough FEV1 between treatment arms, the corresponding rate of change of relative risk of mild, moderate, or severe exacerbations per year: slope: 0.078, p=0.9199		
							Time to first exacerbation, number of patients with at least one exacerbation, or	12 (26 observations)	22472 | NR | 9042 exacerbations (data incomplete)	For a 100mL difference in trough FEV1 between treatment arms, the corresponding change in log		

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							exacerbations/ yr,			relative risk of time to first moderate, or severe exacerbation: slope -1.46, p=0.045 R^2 0.1574 (adjusted 0.1223)		
Jones 2011[20]	Pooled analysis	COPD from smoking only	formoterol indacaterol tiotropium	Industry	RCT		TDI	3	2781 | NR | NR	Pearson's correlation coefficient between individual changes in trough FEV1 and improvements in TDI at 12 weeks 0.15, p<0.001; Between five cohorts grouped by trough FEV1 change and TDI: 0.90	"...improvement in FEV1 is significantly related to changes in the patient-reported outcomes of TDI, SGRQ, exacerbation rate and rescue medication use…These relationships were significant at both an individual and population level, although correlations were much stronger in the population-based analyses…These results suggest that larger improvements in FEV1 are likely to be associated	In a pooled analysis of three trials of indacaterol, changes in FEV1 were associated with improvements in subjective outcomes–TDI and SGRQ–and objective ones–exacerbations per year and rescue medication use. These associations were significantly stronger on a population level than at individual one, though they were statistically significant in both.
									2208 | NR | NR	Pearson's correlation coefficient between individual changes in trough FEV1 and improvements in TDI at 24/26 weeks 0.14, p<0.001; Between five cohorts		

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										grouped by trough FEV1 change and TDI: 0.88 For a 100mL change in trough FEV1 regardless of treatment group, there was a corresponding 0.46 increase in TDI at 24/26 weeks, p<0.0001	with larger patient-reported benefits across a range of clinical outcomes."	
									1099 | NR | NR	Pearson's correlation coefficient between individual changes in trough FEV1 and improvements in TDI at 52 weeks 0.18, p<0.001; Between five cohorts grouped by trough FEV1 change and TDI: 0.92		
							SGRQ		3141 | NR | NR	Pearson's correlation coefficient between individual changes in trough FEV1 and improvements		

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										in SGRQ at 12 weeks -0.12, p<0.001; Between five cohorts grouped by trough FEV1 change and SGRQ: -0.90		
									2215 | NR | NR	Pearson's correlation coefficient between individual changes in trough FEV1 and improvements in SGRQ at 24/26 weeks -0.07, p<0.001; Between five cohorts grouped by trough FEV1 change and SGRQ: -0.79		
									1115 | NR | NR	Pearson's correlation coefficient between individual changes in trough FEV1 and improvements in SGRQ at 52 weeks -0.16, p<0.001 Between five cohorts		

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										grouped by trough FEV1 change and SGRQ: -0.95		
							Exacerbations ^{5}/yr		3158 | NR | NR	Pearson's correlation coefficient between individual changes in trough FEV1 and exacerbations /yr -0.06, p<0.001 Between five cohorts grouped by trough FEV1 change and exacerbations /yr: -0.89 For a 100mL change in trough FEV1 regardless of treatment group, there was a corresponding 12% decrease in exacerbations /yr, p=0.002		
							Severe exacerbations/ yr		3158 | NR | NR	Pearson's correlation coefficient between individual changes in trough FEV1 and severe exacerbations		

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										/yr -0.03, p=0.1 Between five cohorts grouped by trough FEV1 change and severe exacerbations /yr: -0.81		
							Rescue medication use (puffs/day)		3158 | NR | NR	Pearson's correlation coefficient between individual changes in trough FEV1 and puffs/day of rescue medication -0.11, p<0.001 Between five cohorts grouped by trough FEV1 change and rescue medication use: -0.88 For a 100mL change in trough FEV1 regardless of treatment group, there was a corresponding 10% decrease in rescue medication		

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										use, p<0.0001		
Westwood 2011[21]	SRMA	COPD	arformoterol formoterol salmeterol tiotropium	Industry	RCT		SGRQ	22	23245 | NR | NR	Pearson's correlation coefficient between change in trough FEV1 in any study arm and change in SGRQ -0.46, p<0.001 A 100mL increase in FEV1 in any treatment arm was associated with an improvement of SGRQ of 2.5 (1.9 to 3.1) A 100mL increase in trough FEV1 over baseline change in SGRQ for ΔFEV1=0mL across all treatment arms was associated with an additional 1.6 (0.7 to 2.5) point improvement	"Our analyses indicate, at a study level, that improvement in mean trough FEV1 is associated with proportional improvements in health status."	Increases in trough FEV1 are significantly correlated with improvements in the patient-reported outcomes of SGRQ and TDI and objective measurements of at least one exacerbation across any treatment arm, even when accounting for subjective improvements without FEV1 change into account. The strength of the correlation between SGRQ and increases in trough FEV1 increased with time.
								5	1633 | NR | NR	Pearson's correlation coefficient		

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										between change in trough FEV1 in any study arm and change in SGRQ at 3 months: -0.44, p=0.08		
								7	3952 | NR | NR	Pearson's correlation coefficient between change in trough FEV1 in any study arm and change in SGRQ at 6 months: -0.61, p=0.004		
								9	17395 | NR | NR	Pearson's correlation coefficient between change in trough FEV1 in any study arm and change in SGRQ at 12 months: -0.74, p<0.001		
							TDI	8	3980 | NR | NR	Pearson's correlation coefficient between change in trough FEV1 across all treatment groups and proportion of		

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										patients experiencing at least one exacerbation 0.56 p=0.02 A 100mL increase in trough FEV1 over baseline change in TDI for ΔFEV1=0mL across all treatment arms was associated with an additional 5 point increase in TDI.		
							At least one exacerbation	29	23063 | NR | NR	Pearson's correlation coefficient between change in trough FEV1 across all treatment groups and proportion of patients experiencing at least one exacerbation -0.27 p=0.049; A 100mL increase in trough FEV1 over baseline change for ΔFEV1=0mL[6] across all treatment arms was		

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										associated with an additional 6.0% (0.04% to 11.9%) decrease in the proportion of patients experiencing at least one exacerbation.		

Moderate-severe exacerbation: Exacerbation requiring an emergency room visit, hospitalization, or an additional medication; Trough FEV1: FEV1 measured immediately before treatment initiation or 23-24 hours after a given dose; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnea Index; ICS: Inhaled corticosteroids; PRO: Patient reported outcome

1: Defined in this study as requiring intervention–either medication or oxygen, ER visit or hospitalization, or worsening of symptoms for >3 days

2: Defined in this study as an addition of a medication or hospitalization

3: Defined by each included study individually

4: Defined by each included study individually

5: Defined as requiring an ER visit/hospitalization, an additional medication or oxygen, or worsening of a respiratory symptom for >3 days

6: Calculated theoretically from regression modelling

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eTable 6. Gout												
Author, Year	Study design	Indications	**Interventions**	**Funding source**	**Design of included studies**	**Surrogate marker**	**Clinical outcome**	**No. studies**	**Overall sample size | No. surrogate measures | No. clinical outcomes |**	**Evidence**	**Author's conclusion**	**Plaintext Summary**
Topless 2022[22]	Pooled analysis	Gout	allopurinol febuxostat lesinurad varying prophylaxis	Government; university	RCT and 1 open label	Change in serum urate within 6 months	HAQ-DI (higher scores indicate poorer outcome)	5 (4 RCTs and 1 open-label)	3272 | NR | 7229	Within the first 6 months of initiation of a new or escalation in an established urate-lowering therapy, the absolute change in serum urate concentration over the most recent month and HAQ-QI had a slope	"A novel study finding was that recent SU level fluctuations associated with reduced HRQOL/function or health status in the first 6-months with ULT initiation or change of ULT in gout, primarily driven by the effects of reduction in SU despite the use of anti-inflammatory	Pooling several RCTs and an open label extension study, reductions in serum urate concentration within 6 months after the initiation or up-titration of a urate-lowering agent were associated with worsened

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									0.013 (0.007 to 0.019)	prophylaxis, usually with colchicine."	patient reported outcomes across several scales. However, baseline serum urate was correlated with frequency of gout flares and poorer patient reported outcomes.
							SDS (higher scores indicate poorer outcome)		3175 | NR | 6463	Within the first 6 months of initiation of a new or escalation in an established urate-lowering therapy, the absolute change in serum urate concentration over the most recent month and SDS score had a slope of 0.19 (0.05 to 0.32)		
							SF-36 MCS (lower score indicate poorer outcome)		3272 | NR | 7209	Within the first 6 months of initiation of a new or escalation in an established urate-lowering therapy, the absolute change in serum urate concentration over the most recent month and SD-36 MCS score had a slope of -0.33 (-0.47 to -0.18)		
							PGA (higher scores indicate		3279 | NR | 8459	Within the first 6 months of initiation of a new or escalation in		

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							poorer outcome)			an established urate-lowering therapy, the absolute change in serum urate concentration over the most recent month and PGA score had a slope 0.49 (0.09 to 0.89)		
							Pain in the last week (higher scores indicate poorer outcome)		1708 | NR | 4588	Within the first 6 months of initiation of a new or escalation in an established urate-lowering therapy, the absolute change in serum urate concentration over the most recent month and pain score had a slope of 0.68 (0.18 to 1.18)		
							SF-36 PCS (lower scores indicate poorer outcomes)		3272 | NR | 7209	Within the first 6 months of initiation of a new or escalation in an established urate-lowering therapy, the absolute change in serum urate concentration over the most		

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										recent month and SD-36 PCS had a slope of -0.13 (-0.27 to 0.01)		
Stamp 2018[23]	SRMA		allopurinol aproprazone febuxostat lesinurad pegloticase varying prophylaxis	None (industry competing interests)	RCT and open label extension studies	Serum urate < 6 mg/dL	Gout flare	10 RCTs	6010 | NR | NR	Proportion of individuals reaching target serum urate of <6 mg/dL at 3 months[1] and flare risk ratio, p=0.47 R^2 for log-RR = 0.0779	"...there was low-quality evidence to suggest that ULT may be beneficial for the prevention of gout flares…Whilst SU can be considered a biomarker, it did not reach the required level of evidence to be considered a surrogate according to the BSES-3 framework…Despite the current failure of SU to reach the threshold for validation as a surrogate using the BSES-3 framework, the evidence is supportive of a relationship between SU and gout flares.	In 10 RCTs, reduction of serum urate within 3 months had no association with the proportion of patients experiencing a gout flare. From these short RCTs, it appears that serum urate is a poor surrogate measure of clinical outcomes. However, evidence points to associations between longer-term reductions in serum urate with decreases in gout flares.
HAQ-DI: Health Assessment Questionnaire Disability Index; SDS: Sheehan Disability Scale; PGA: Patient Global Assessment; SF-36 PCS: Short-form 36 physical component summary SF-36 MCS: Short-form 36 mental component summary; ULT: Urate-lowering therapy												

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eTable 7. HIV												
Author, Year	**Study design**	**Indication**	**Interventions**	**Funding source**	**Design of included studies**	**Surrogate marker**	**Clinical outcome**	**No. studies**	**Overall sample size | No. surrogate measures | No. clinical outcomes**	**Evidence**	**Author's conclusion**	**Plaintext Summary**
Mills 2008[24]	SRMA	HIV-1	HAART	Industry; government	RCT	HIV-1 RNA viral load <50 copies/mL	Progression to AIDS or death[1] at 48 weeks	28	10795 | 5369 | 345	Regression coefficient of the hazard ratio of achievement of a viral load of <50 copies/mL in the treatment relative to the control arm versus log Peto OR for progression to AIDS/death between arms -0.04, (-0.31 to 0.20), p=0.71 R^2 0.09, p=0.56 (from weighted linear regression of the hazard ratio of achievement of a viral load of <50 copies/mL in the treatment relative to the	"…our findings indicate it is not possible to estimate the proportion of treatment effect associated with surrogate endpoints. We do not imply that the relationship is invalid, rather that the differences observed in…HIV RNA between treatments do[es] not result in meaningful differences in AIDS/death events during the relatively short time period of the RCTs (i.e. 48–96 weeks).	Across RCTs using HAART, differences in proportions of participants achieving low HIV-1 RNA viral loads was not significantly associated with changes in the odds ratio of progression to AIDS or death, though the number of events and scatter of studies was small.

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										control arm at 48 weeks versus log Peto OR for progression to AIDS/death between arms weighted by inverse variance)		
						HIV-1 RNA viral load <200 copies/mL		5	645 | 466 | 7	Regression coefficient of the hazard ratio of achievement of a viral load of <200 copies/mL in the treatment relative to the control arm at 48 weeks versus log Peto OR for progression to AIDS/death between arms 0.43, (-1.14 to 1.9), p=0.58 R^2 0.86, p=0.02 (from weighted linear regression of the hazard ratio of achievement of a viral load of <200 copies/mL in the treatment relative to the control arm at 48 weeks versus log Peto OR for progression to AIDS/death		

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										between arms weighted by inverse variance)		
						HIV-1 RNA viral load <400 copies/mL		15	7218 | 4380 | 156	Regression coefficient of the hazard ratio of achievement of a viral load of <400 copies/mL in the treatment relative to the control arm at 48 weeks versus log Peto OR for progression to AIDS/death between arms 0.05 (-0.12 to 0.22), p=0.49 R^2 0.04, p=0.38 from weighted linear regression of the hazard ratio of achievement of a viral load of <400 copies/mL in the treatment relative to the control arm versus log Peto OR for progression to		

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										AIDS/death between arms		
						HIV-1 RNA viral load <50 copies/mL	Progression to AIDS or death at 24 weeks	10	NR | NR | NR	Regression coefficient of the hazard ratio of achievement of a viral load of <50 copies/mL in the treatment relative to the control arm at 24 weeks versus log Peto OR for progression to AIDS/death between arms -0.37 (-1.31 to 0.55), p-0.42 From weighted linear regression: R^2 0.14, p=0.26		
						HIV-1 RNA viral load <200 copies/mL		3	NR | NR | NR	Regression coefficient of the hazard ratio of achievement of a viral load of <200 copies/mL in the treatment relative to the control arm at 24 weeks versus log Peto OR for progression to AIDS/death between arms 0.44 (-1.17 to 2.04), p=0.58		

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										From weighted linear regression: R^2 0.24, p=0.66		
						HIV-1 RNA viral load <400 copies/mL		6	NR | NR | NR	Regression coefficient of the hazard ratio of achievement of a viral load of <400 copies/mL in the treatment relative to the control arm at 24 weeks versus log Peto OR for progression to AIDS/death between arms -0.51 (-2.30 to 1.27), p=0.57 From weighted linear regression: R^2 0.11, p=0.50		
						HIV-1 RNA viral load <50 copies/mL	Progression to AIDS or death at 96 weeks	3	NR | NR | NR	Regression coefficient of the hazard ratio of achievement of a viral load of <500 copies/mL in the treatment relative to the control arm at 96 weeks versus log Peto OR for progression to AIDS/death between arms 0.68 (-1.51 to 2.86), p=0.54		

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										From weighted linear regression: R^2 0.39, p=0.56		
Staszewski 1998[25]	Pooled analysis	HIV-1	lamivudine lamivudine + loviride zidovudine zidovudine + didanosine zidovudine + lamivudine zidovudine + lamivudine + loviride zidovudine + zalcitabine	Not reported	RCT, RCT followed by open-label trial	HIV-1 RNA level	Progression to AIDS or death during treatment	6	1488 | NR | 175	For every 1 log reduction in mean HIV-1 RNA level during treatment, relative hazard ratio to progression to AIDS or death 0.41 (0.25 to 0.66) Averaged over 8-52 weeks of treatment, increased HIV-1 RNA levels are associated with higher rates of adverse events associated with AIDS, reported as "progression," all-cause mortality.	"There was a strong correlation between mean HIV-1 RNA level [averaged over weeks 8-52 of the trial] and the incidence of progression."	In several RCTs, increased levels of HIV-1 RNA averaged across the length of the trial were associated with higher rates of progression to AIDS, defined by AIDS-defining illnesses, and all-cause mortality.
1: Defined by each study–not necessarily AIDS-related												

eTable 8. Hypercholesterolemia

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Author, Year	Study design	Indication	Interventions	Funding source	**Design of included studies**	**Surrogate marker**	**Clinical outcome**	**No. studies**	**Overall sample size | No. surrogate measures | No. clinical outcomes**	**Evidence**	**Author's conclusion**	**Plaintext Summary**
Marston 2019[33]	SRMA	Participants in triglyceride-lowering trials	unspecified fibrates niacin omega-3 fatty acid unspecified statins	None; industry competing interests	RCT, open-label	LDL-C	Major vascular events[1]	44	374358 | NR | 46180	For a 1 mmol/L reduction in LDL-C, relative risk for major vascular events 0.80 (0.76 to 0.85), p<0.0001 With the REDUCE-IT trial removed: For a 1 mmol/L reduction in LDL-C, relative risk for major vascular events 0.79 (0.76 to 0.83), p<0.0001	"...triglyceride lowering…is associated with lower risk of cardiovascular events, but to a lesser extent per absolute amount of reduction than with LDL-C…"	Across 44 RCTs, reductions in serum LDL-C were associated with decreased risk of major vascular events.
Vallejo-Vaz 2018[36]	Pooled analysis	Non-familial or heterozygous familial hypercholesterolemia	statin + alirocumab statin + ezetimibe	Industry	RCT only	LDL-C	MACE[13]	10	4972 | NR | 104	For a 1 mmol/L decrease LDL-C in the treatment arms, hazard	"In the present analysis of a pooled cohort from 10 ODYSSEY phase 3 trials	Across 10 RCTs evaluating alirocumab combined with a statin,

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										ratio: 0.74 (0.62 to 0.89), p=0.0016 For a 50% decrease LDL-C from baseline in the treatment arms, hazard ratio 0.70 (0.56 to 0.88), p=0.0020	of alirocumab versus ezetimibe or placebo (added to background statin therapy in most patients)...we observed that…both women and men showed a significant and similar lower risk of MACE with lower achieved LDL-C levels (lower on-treatment LDL-C or greater percentage reductions in LDL-C from baseline)."	further reductions in serum LDL-C were associated with decreased risks of MACEs in both men and women.

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Hourcade-Poteller et 2015[31]	SRMA	Primary or secondary prevention of CVD	unspecified statins unspecified fibrates niacin ezetimibe	None; industry competing interests	RCTs	LDL-C	Non-fatal MI or cardiac death	45	132949 | NR | NR	For a 1 mg/dL greater absolute difference in LDL-C between treatment and control, the change in log relative risk of a non-fatal MI or cardiac death 0.00497, SE 0.00094, $p<0.0001$; R^2 0.396	NA - no explicit mention of these analyses in the Discussion section	Across 45 trials, greater decreases in LDL-C between treatment and control groups were associated with decreased risk of cardiovascular death and MI. However, no high-strength associations were observed. Furthermore, stratified associations were reported across medications groups (statins, fibrates, niacin; no statistically significant associations were reported for niacin)
Stauffer 2013[35]	SRMA	Participants in triglyceride-lowering trials	atorvastatin lovastatin pravastatin simvastatin simvastatin/ezetimibe rosuvastatin	Industry	RCT	LDL-C	Major vascular events[2]	40	200593 | NR | 16843	The proportional change of LDL-C between treatment in control arms and the log ratio of event rates between	"...LDL-C [was] predictive of cardiovascular events in both primary and secondary populations."	Across 40 RCTs, decreases in LDL-C between arms were associated with fewer events between those arms.

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			bezafibrate fenofibrate gemfibrozil niacin niacin/gemfibrozil/cholestyramine simvastatin/niacin estrogen-progestin omega-3 fatty acids cholestyramine diet							treatment and control arms of major vascular events across all studies has a slope of 0.624, p<0.001		
Labreuche 2010[32]	SRMA	Participants on lipid-modifying treatments	atorvastatin cerivastatin fluvastatin lovastatin pravastatin simvastatin bezafibrate clofibrate fenofibrate gemfibrozil niacin pioglitazone rosiglitazone troglitazone metformin glimepiride	Non-profit	RCT	LDL-C	Fatal or non-fatal stroke	≤64	≤195488 | NA | ≤6063	For each 10 mg/dL greater reduction in LDL-C between treatment and control arms, the absolute change in the relative risk of stroke was 4.5% (1.7% to 7.2%), p=0.003 (fixed effects; analysis consistent with random effects)	"This analysis also confirmed that drug-induced LDL-C reduction was associated with a decrease in stroke incidence."	Across 64 trials, greater changes in LDL-C between treatment and control arms was associated with decreased relative risk of stroke.

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			glyburide clofibrate + niacin colestipol + niacin gemfibrozil + niacin + cholestyramine simvastatin + ezetimibe statin + ezetimibe + fibrate or niacin statin + niacin									
Boekholdt 2012[28]	IPD MA	Statin-treated population	atorvastatin lovastatin pravastatin rosuvastatin simvastatin	None; industry competing interests	RCT	LDL-C	Major CV events[3]	8	38153 | NR | 6286 events (in 5387 participants)	The increase in hazard ratio for a major cardiovascular event per 1-SD (32 mg/dL) increase in LDL-C in statin-treated arms 1.13 (1.10 to 1.17), p<0.001	"In conclusion, among statin-treated patients, levels of LDL-C, non–HDL-C, and apoB were each strongly associated with the risk of major cardiovascular events, but non–HDL-C was more strongly associated than LDL-C and apoB."	Across 8 RCTs and analyzing only patients treated with statins, those who achieved lower LDL-C levels had lower rates of cardiovascular events. No significant difference was noted between patients achieving an LDL-C of <100 mg/dL and those with an LDL-C >100 mg/dL if the non-HDL-C level was below 130 mg/dL.
									26299 | NR | 3227 participants with events	Hazard ratio of a major cardiovascular event for patients achieving a non-HDL-C of <130 mg/dL and LDL-C of >100 mg/dL compared to patients achieving a non-HDL-C of <130		

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										mg/dL and LDL-C of <100 mg/dL on statins 1.01 (0.92 to 1.12), p=0.85		
							Major coronary events[4]	8	38153 | NR | 4583 participants with events	The increase in hazard ratio for a major coronary event per 1-SD (32 mg/dL) increase in LDL-C in statin-treated arms 1.14 (1.10 to 1.18), p<0.001		
							Fatal and non-fatal stroke	8	38153 | NR | 1029	The increase in hazard ratio for a major cerebrovascular event per 1-SD (32 mg/dL) increase in LDL-C in statin-treated arms 1.10 (1.02 to 1.17), p=0.01		

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Briel 2009[29]	SRMA	Hypercholesterolemia	atorvastatin fluvastatin lovastatin pravastatin simvastatin bezafibrate fenofibrate gemfibrozil cholestyramine niacin (+ statin, fibrate, or resin) ezetimibe pactimibe probucol omega-3 FAs pioglitazone rosiglitazone estrogen + progestin raloxifene torcetrapib diet bowel surgery	Industry; government	RCT	LDL-C	CHD mortality and non-fatal MI	95	288260 | NR | 18324	The slope of the log relative risk of CHD death or non-fatal MI per 10 mg/dL elevation in LDL-C in a univariable model: 4.9 (3.4 to 6.5), p<0.001; R^2 0.32 In a bivariable model accounting for other lipoprotein subfractions: 5.1 (3.6 to 6.7), p<0.001; R^2 0.33 In a multivariable model accounting for other lipoprotein subfractions and drug class: 7.1 (4.5 to 9.8), p<0.001; R^2 0.46	"We found a statistically significant, substantial association between change in low density lipoprotein cholesterol and risk ratios for coronary heart disease events, coronary heart disease deaths, or total deaths, adjusted for other lipid subfractions and drug class."	Across about 100 RCTs, changes in LDL-C were significantly positively correlated with risk of CHD death, all-cause mortality, and CHD death + non-fatal MI even when adjusting for HDL levels.
							All-cause mortality	107	298472 | NR | NR	The slope of the log relative risk		

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										of total death per 10 mg/dL elevation in LDL-C in a univariable model: 2.8 (1.4 to 4.3), p<0.001; R^2 0.12 In a bivariable model accounting for other lipoprotein subfractions: 3.1 (1.7 to 4.6), p<0.001; R^2 0.15 In a multivariable model accounting for other lipoprotein subfractions and drug class: 4.4 (1.6 to 7.2), p=0.002; R^2 0.28		

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							CHD mortality	94	295307 | NR | NR	The slope of the log relative risk of CHD death per 10 mg/dL elevation in LDL-C in a univariable model: 4.5 (2.4 to 6.6), p<0.001; R^2 0.16 In a bivariable model accounting for other lipoprotein subfractions: 4.8 (2.6 to 7.0), p<0.001; R^2 0.17 In a multivariable model accounting for other lipoprotein subfractions and drug class: 7.2 (3.1 to 11.3), p=0.001; R^2 0.33		
Johnson 2009[27]	SRMA	Statin-treated population	atorvastatin fluvastatin	Not reported	RCT	LDL-C	All-cause mortality	16	87642 | NA | 8067	For a 1.0 mmol/L greater decrease in	"We show that an overall survival gain could only be	Access 16 RCTs, greater reductions in LDL-C

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			lovastatin pravastatin simvastatin							LDL-C between treatment and control arms, relative risk reduction of all-cause mortality 0.115, R^2 0.41; Regression coefficient 0.342 (0.125 to 0.560), p=0.004	predicted with LDL-cholesterol differences >1.5 mmol/L and a cardiovascular survival gain with LDL-cholesterol differences >1.4 mmol/L. These cutoffs could function as benchmarks for evaluating and planning future statin trials"	between trial arms was associated with improved all-cause and cardiovascular mortality.
							CV mortality		87642 | NA | 4592	For a 1.0 mmol/L greater decrease in LDL-C between treatment and control arms, relative risk reduction of CV mortality 0.174; Regression coefficient 0.370 (0.125 to 0.616), p=0.006 R^2 0.39		
Delahoy 2009[30]	SRMA	Participants in triglyceride-lowering trials	atorvastatin fluvastatin lovastatin pravastatin rosuvastatin	None; industry competing interests	RCT	LDL-C	Vascular mortality	25	155613 | NA | 6321	Decrease in log relative risk between the treatment versus control arms for every 25 mg/dL greater	"Based on meta-regression analysis of these trials, there was a significant positive relationship	Across 25 RCTs investigating statin therapy, greater decreases in LDL-C at 1 year between arms were

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			simvastatin							reduction in serum LDL-C between those arms at 1 year 0.89 (0.87 to 0.92); R^2 0.75	between reduction in LDL-C and reduction in the risk for major cardiovascular events.”	associated with improved cardiovascular outcomes.
							Major coronary events[6]		155613 | NA | 11357	Decrease in log relative risk between the treatment versus control arms for every 25 mg/dL greater reduction in serum LDL-C between those arms arms at 1 year 0.84 (0.82 to 0.86); R^2 0.87		
							Major vascular events[7]		155613 | NA | 23791	Decrease in log relative risk between the treatment versus control arms for every 25 mg/dL greater reduction in serum LDL-C between those arms arms at 1 year 0.86 (0.84 to 0.88); R^2 0.84		

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							Fatal and non-fatal stroke		155613 | NA | 4717	Decrease in log relative risk between the treatment versus control arms for every 25 mg/dL greater reduction in serum LDL-C between those arms arms at 1 year 0.90 (0.86 to 0.94); R^2 0.47		
Razzolini 2008[34]	SRMA		atorvastatin fluvastatin lovastatin pravastatin simvastatin	NR	RCT	LDL-C	All-cause mortality	29	90480 | NA | NR	Pearson's correlation coefficient between LDL-C at the end of the study period and annualized all-cause mortality in the treatment groups - 0.4678, p=0.0105; In the control groups - 0.3462, p=0.061	"A trend of increased non-cardiovascular mortality with decreased LDL exists both in placebo and treatment groups. However, at each given LDL cholesterol level, non-cardiovascular mortality is lower in treated patients. Therefore, statin therapy may improve the biological impact of LDL on non-	Across 29 RCTs investigating statins, decreasing LDL -C at the trial end was associated with increases in both all-cause mortality and non-cardiovascular mortality. However, at all LDL-C levels, all-cause and non-cardiovascular mortality were lower in the treatment versus control groups.
							Non-cardiovascular mortality			Pearson's correlation coefficient between LDL-C at the end of the study period		

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										and annualized non-cardiovascular mortality in the treatment groups - 0.4471, p=0.0171; In the control groups - 0.5292, p=0.0032	cardiovascular mortality”	
Baigent 2005[26]	SRMA	Participants in triglyceride-lowering trials	atorvastatin fluvastatin lovastatin pravastatin simvastatin	NR	RCT	LDL-C	All-cause mortality	14	90056 | NR | 8186	For a 1 mmol/L reduction in LDL-C at 1 year in the treatment versus control arms, relative rate ratio for all-cause mortality at study end 0.88 (0.84 to 0.91), p<0.0001	“The results of the present meta-analysis indicate that the proportional reductions in the incidence of major coronary events, coronary revascularisations, and strokes were approximately related to the absolute reductions in LDL cholesterol achieved with the statin regimens studied, and that the proportional reductions in such major	Across 14 RCTs investigating statin therapy, greater reductions in LDL-C at 1 year were associated with improved all-cause and vascular mortality, as well as decreased rates of strokes and coronary revascularizations.
							Cancer		79751 | NR | 5103	For a 1 mmol/L reduction in LDL-C at 1 year in the treatment versus control arms, relative rate ratio for all-cause mortality at study end		

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										1.00 (0.95 to 1.06), p=0.9	vascular events per mmol/L LDL cholesterol reduction were similar irrespective of the pretreatment cholesterol concentrations or other characteristics (eg, age, sex, or pre-existing disease) of the study participants.”	
							Vascular mortality[8]		90056 | NR | 4655	For a 1 mmol/L reduction in LDL-C at 1 year in the treatment versus control arms, relative rate ratio for vascular mortality at study end 0.83 (0.79 to 0.87)		
							Non-vascular mortality[9]		90056 | NR | 3531	For a 1 mmol/L reduction in LDL-C at 1 year in the treatment versus control arms, relative rate ratio for non-vascular mortality at study end 0.95 (0.90 to 1.01) p=0.1		
							CHD mortality		90056 | NR | 3508	For a 1 mmol/L reduction in LDL-C at 1 year in the treatment versus control arms, relative rate ratio for CHD mortality at		

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										study end 0.81 (0.76 to 0.85), p<0.0001		
							Major coronary event[10]		90056 | NR | 7757 participants with event	For a 1 mmol/L reduction in LDL-C at 1 year in the treatment versus control arms, relative rate ratio for a major coronary event at study end 0.77 (0.74 to 0.80), p<0.0001		
							Major vascular event		90056 | NR | 14348 participants with event	For a 1 mmol/L reduction in LDL-C at 1 year in the treatment versus control arms, relative rate ratio for a major vascular event at study end 0.79 (0.77 to 0.81), p<0.0001		
							Coronary revascularization[11]		90056 | NR | 6054 participa	For a 1 mmol/L reduction in LDL-C at 1 year in the		

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									nts with event	treatment versus control arms, relative rate ratio for coronary revascularization at study end 0.76 (0.73 to 0.80), p<0.0001		
							Fatal or non-fatal stroke	9	65138 | NR | 2957 participants with event	For a 1 mmol/L reduction in LDL-C at 1 year in the treatment versus control arms, relative rate ratio for any stroke at study end 0.83 (0.78 to 0.88), p<0.0001		

LDL-C: Low-density lipoprotein cholesterol; MACE: Major adverse cardiovascular event; MI: Myocardial infarction

1: Defined by each study, but often including stroke, coronary heart disease-related death, myocardial infarction, coronary revascularization; sometimes as all-cause mortality, any acute coronary syndrome

2: Defined by each study, but most often coronary heart disease-related death, myocardial infarction; sometimes as coronary revascularization, stroke, angina, or acute coronary syndrome

3: MI, cardiac death, hospitalization for unstable angina, or fatal or non-fatal stroke

4: MI, cardiac death, or hospitalization for unstable angina

5: This study is an update of Baigent et al., 2005

6: Non-fatal MI, CHD death

7: Non-fatal MI, CHD death, coronary revascularization, fatal and non-fatal stroke

8: CHD death, stroke, other vascular

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9: Cancer, respiratory-, trauma-related, or other

10: Non-fatal MI, CHD death

11: CABG, PTCA, unspecified

12: Defined as CHD death, non-fatal MI, ischemic stroke, or diagnosis of unstable angina

eTable 9. Hyperphosphatemia

Author, Year	Study design	Indication	**Interventions**	**Funding source**	**Design of included studies**	**Surrogate marker**	**Clinical outcome**	**No. studies**	**Overall sample size | No. surrogate measure**	**Evidence**	**Author's conclusion**	**Plaintext Summary**

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									s | No. clinical outcomes			
Palmer 2015[37]	SRMA	Hyperphosphatemia in CKD treated with hemodialysis	Bisphosphonates; cinacalcet; phosphate binders; vitamin D	Government	RCTs only	Change in serum phosphorus	All-cause mortality	12	< 5504 | NR | NR	Pearson's correlation coefficient of the log ratio of mean serum phosphorus between treatment arms at trial end and the log relative risk of all-cause mortality between those treatment arms: 0.23 (-0.48 to 0.69)	"We found that the effects of a broad range of drugs used widely in CKD to correct perturbed serum PTH, phosphorus, and calcium levels generally do not correlate with cardiovascular and all-cause mortality in randomized trials, although the effects of these drugs in standard clinical practice are universally measured based on improvements in levels of such biomarkers. "	Across several trials, in those with CKD undergoing hemodialysis, greater improvement of serum phosphorus in treatment groups versus the control arms was not associated with improvements in all-cause or cardiovascular mortality.
							Cardiovascular mortality	4	< 3329 | NR | NR	Pearson's correlation coefficient of the log ratio of mean serum phosphorus between treatment arms at trial end and the log relative risk of cardiovascular mortality between those treatment arms: 0.54 (-0.98 to 1.0)		

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eTable 10. Hypertension												
Author, Year	Study design	Indication	Interventions	Funding source	Design of included studies	Surrogate marker	Clinical outcome	No. studies	Overall sample size | No. surrogate measures | No.	Evidence	Author's conclusion	Plaintext Summary

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									clinical outcomes			
The Blood Pressure Lowering Treatment Trialists' Collaboration 2021[38]	IPD SRMA	Patients in blood pressure reduction trials without baseline HF	ACE inhibitors ACE inhibitor + CCB ARBs ARB + CCB ARB + diuretic alpha blockers beta blockers beta blocker + CCB beta blocker + diuretic CCBs diuretics	Government; not for profit	RCT	Systolic blood pressure	Major CV events[1]	48	342426 | NA | 42324	In participants without baseline CV disease, for a 5 mm Hg reduction in systolic blood pressure at the end of follow up, hazard ratio of a major CV event between intervention and control 0.91 (0.89 to 0.94) In those with baseline CV disease: 0.89 (0.86 to 0.92) There was an association between a greater reduction in systolic blood pressure between treatment and control and decreased hazard ratio	"In this largest source of randomised evidence of blood pressure-lowering effects on cardiovascular disease and death, we found the proportional effects of blood pressure-lowering on cardiovascular outcomes to be similar in people with or without previous cardiovascular disease and across categories of baseline systolic blood pressure down to less than 120 mm Hg. On average, a 5 mm Hg reduction of systolic blood pressure reduced the risk of a major cardiovascular event by about 10%; the corresponding proportional risk reductions for stroke, heart	Across 48 RCTs, greater reductions in systolic BP were associated with decreased incidence of major cardiovascular events, including all strokes, CHD, and heart failure, regardless of baseline CV disease.

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										of major CV events (no data shown)	failure, ischaemic heart disease, and cardiovascular death were 13%, 13%, 8%, and 5%, respectively.”	
							Fatal or non-fatal stroke	48	343544 | NA | 13772	In participants without baseline CV disease, for a 5 mm Hg reduction in systolic blood pressure at the end of follow up, hazard ratio of a fatal or non-fatal stroke between intervention and control 0.85 (0.80 to 0.90) In those with baseline CV disease: 0.89 (0.85 to 0.94)		
							Ischemic heart disease	48	343360 | NA | 19452	In participants without baseline CV disease, for a 5 mm Hg reduction in systolic blood pressure at the end of follow up, hazard ratio		

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										of ischemic heart disease between intervention and control 0.95 (0.91 to 0.99) In those with baseline CV disease: 0.90 (0.86 to 0.95)		
							HF causing hospitalization or death	43	313971 | NA | 7833	In participants without baseline CV disease, for a 5 mm Hg reduction in systolic blood pressure at the end of follow up, hazard ratio of HF causing hospitalization or death between intervention and control 0.83 (0.77 to 0.89) In those with baseline CV disease: 0.89 (0.83 to 0.95)		

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							CV mortality	44	319914 | NA | 10935	In participants without baseline CV disease, for a 5 mm Hg reduction in systolic blood pressure at the end of follow up, hazard ratio of CV mortality between intervention and control 0.93 (0.88 to 0.98) In those with baseline CV disease: 0.98 (0.92 to 1.04)		
							All-cause mortality	48	343603 | NA | 28895	In participants without baseline CV disease, for a 5 mm Hg reduction in systolic blood pressure at the end of follow up, hazard ratio of all-cause mortality between intervention and control		

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										0.98 (0.95 to 1.02) In those with baseline CV disease: 0.97 (0.94 to 1.01)		
Katsanos 2017 [41]	SRMA	Secondary stroke prevention after ischemic stroke or TIA	Guanethidine deserpidine/methyclothiazide atenolol ramipril perindopril/indapamide nicardipine nitrendipine candesartan eprosartan telmisartan indapamide	Government	RCT, PROBE, open-label	Systolic blood pressure	Recurrent stroke[2]	11	37835 | NA | 3578	Regression coefficient for achieved SBP and log odds of recurrent stroke 0.02 (0.01 to 0.04), p=0.049	"Our systematic review and metaregression analysis showed that the extent of both SBP and DBP reduction is linearly associated with the magnitude of risk reduction in recurrent cerebrovascular and cardiovascular events."	Across several RCTs in patients with prior ischemic strokes or TIAs, greater reductions in systolic and diastolic blood pressures are associated with improvements in several clinical outcomes including recurrent stroke, MI, all-cause mortality, and CV death.
							MI	5	29129 | NA | 564	Regression coefficient for achieved SBP and log odds of MI 0.022 (0.002 to 0.041), p=0.024		
							All-cause mortality	8	36364 | NA | 2864	Regression coefficient for achieved SBP and log odds of all-cause mortality 0.02 (0.01 to 0.03), p=0.001		
							CV mortality	8	36364 | NA | 1337	Regression coefficient for achieved SBP and log odds of CV		

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										death 0.05 (0.03 to 0.07), p<0.001		
							Disabling or fatal stroke	7	14250 | NA | 493	Regression coefficient for achieved SBP and log odds of disabling or fatal stroke 0.001 (-0.024 to 0.022), p=0.944		
						Diastolic blood pressure	Recurrent stroke	11	37835 | NA | 3578	Regression coefficient for achieved DBP and log odds of recurrent stroke 0.08 (0.01 to 0.15), p=0.026		
							All-cause mortality	8	36364 | NA | 2854	Regression coefficient for achieved DBP and log odds of all-cause mortality 0.08 (0.02 to 0.13), p=0.009		
Ettehad 2016[40]	SRMA	Patients in blood pressure reduction trials	captopril enalapril fosinopril perindopril	Government; University	RCT	Systolic blood pressure	Fatal and non-fatal stroke[4]	54	265323 | NA | 10013	Statistical significance for a greater change in systolic blood pressure between	"In this meta-analysis, blood pressure lowering treatment significantly reduced the risk of	Across many RCTs, greater reductions in systolic BP at the end of trial was

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			quinapril ramipril trandolapril methyldopa candesartan irbesartan losartan olmesartan telmisartan valsartan acebutolol atenolol bucindolol metoprolol nebivolol oxprenolol practolol propranolol timolol bendrofluazide chlorthalidone Co-Amilozide hydrochlorothiazide triamterene amlodipine diltiazem							treatment and control and the relative risk of fatal and non-fatal stroke p<0.0001 For a 10mmHg reduction in SBP, the relative risk of stroke 0.73 (0.68 to 0.77)	cardiovascular disease and death in various populations of patients. Overall, a 10 mm Hg reduction in systolic blood pressure reduced the risk of major cardiovascular disease events by 20%, coronary heart disease by 17%, stroke by 27%, heart failure by 28%, and all-cause mortality by 13%...with similar proportional reductions across various population subgroups, irrespective of starting blood pressure."	associated with improved cardiovascular outcomes including stroke, a composite of MI and sudden cardiac death, and HF, though was not associated with improved risk of renal failure, irrespective of baseline blood pressure and cardiovascular comorbidity.
							Major cardiovascular events[5]	55	265578 | NA | 27277	Statistical significance for a greater change in systolic blood pressure between treatment and control and the relative risk of major cardiovascular events p<0.0001 For a 10mmHg reduction in SBP, the relative risk of major cardiovascular events 0.80 (0.77 to 0.83)		

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			felodipine mibefradil benidipine isradipine lacidipine nifedipine nitrendipine bendrofluazide α-Methyldopa various combinations strict or non-strict BP control				HF[6]	43	222851 | NA | 7044	Statistical significance for a greater change in systolic blood pressure between treatment and control and the relative risk of HF p<0.0001 For a 10mmHg reduction in SBP, the relative risk of HF 0.72 (0.67 to 0.78)		
							All-cause mortality	57	267998 | NA | 19773	Statistical significance for a greater change in systolic blood pressure between treatment and control and the relative risk of all-cause mortality p=0.014 For a 10mmHg reduction in SBP, the relative risk of all-cause mortality		

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										0.87 (0.84 to 0.91)		
							CHD[3]	56	265534 | NA | 10163	Statistical significance for a greater change in systolic blood pressure between treatment and control and the relative risk of CHD p=0.058 For a 10mmHg reduction in SBP, the relative risk of CHD 0.83 (0.78 to 0.88)		
							Kidney failure	16	78931 | NA | 1724	Statistical significance for a greater change in systolic blood pressure between treatment and control and the relative risk of renal failure p=0.09 For a 10mmHg reduction in SBP, the		

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										relative risk of renal failure 0.95 (0.84 to 1.07)		
Lassere 2012[42]	SRM A	Patients in blood pressure reduction trials	candesartan lisinopril perindopril trandolapril pindolol candesartan telmisartan atenolol oxprenolol propranolol amlodipine nifedipine nitrendipine bendroflumethiazide bendrofluazide chlorothiazide chlorthalidone indapamide amiloride hydrochlorothiazide amiloride/ hydrochlorothiazide	None	RCT, open-label	Systolic blood pressure	Fatal and non-fatal stroke	17	96382 | NA | 3240	Regression coefficient for the difference in change of systolic blood pressure between treatment and control and the relative risk reduction of stroke between those arms 0.0196, $p<0.01$; R^2 0.37	"...systolic blood pressure is a Grade B + surrogate endpoint for stroke protection and diastolic blood pressure is a Grade A surrogate endpoint for stroke protection…Our trial-level association for systolic blood pressure may be considered low (R-squared 0.37 assuming no uncertainty). The results for diastolic blood pressure were somewhat better (R-squared 0.58 assuming no uncertainty)."	Across nearly 20 trials, greater decreases in systolic and diastolic blood pressure were associated with lower relative risks of stroke, but not CV or overall mortality. The authors rated systolic and diastolic blood pressure change as a surrogate marker for stroke as a B+ and A using the BSES3, respectively.
						Diastolic blood pressure		18	99809 | NA | 3275	Regression coefficient for the difference in change of diastolic blood pressure between treatment and control and the relative risk reduction of stroke between those arms 0.0453,		

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										$p<0.001$; R^2 0.58		
						Systolic blood pressure	CV mortality	16	95557 | NA | NR	Regression coefficient for the difference in change of systolic blood pressure between treatment and control and the relative risk reduction of CV mortality 0.009, “non-significant;” R^2 0.15		
						Diastolic blood pressure		17	98984 | NA | NR	Regression coefficient for the difference in change of diastolic blood pressure between treatment and control and the relative risk reduction of CV mortality 0.012, “non-significant;” R^2 0.05		

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						Systolic blood pressure	All-cause mortality	17	96382 | NA | NR	Regression coefficient for the difference in change of systolic blood pressure between treatment and control and the relative risk reduction of all-cause mortality 0.005, "non-significant;" R^2 0.06		
						Diastolic blood pressure		18	99809 | NA | NR	Regression coefficient for the difference in change of diastolic blood pressure between treatment and control and the relative risk reduction of all-cause mortality 0.005, "non-significant;" R^2 0.02		
Verdecchia 2010[47]	SRMA	Patients with hypertension or composite features of	ACE inhibitors ACE inhibitor + diuretic ACE inhibitor + CCB	NR	RCT, 1 non-randomized alternate	Systolic blood pressure	MI, stroke, CHF, and CV death	30	221024 | NA | NR	For each 5mmHg greater decrease in systolic blood	"BP reduction is important to reduce the risk of CCEP in clinical trials. A significant	Across several RCTs, greater decreases in systolic

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		high cardiovascular risk	ACE inhibitor + ARB CCBs diuretics ARBs beta blockers		assignment trial					pressure between the treatment arms, odds ratio of the cardiovascular composite endpoint 0.871 (0.824 to 0.921), p<0.0001	difference between two treatment groups in the risk of CCEP may be anticipated for a SBP/DBP reduction differing by 4.6/2.2 mmHg or more.”	and diastolic blood pressures between treatment arms was associated with decreased risks of a composite cardiovascular endpoint.
						Diastolic Blood pressure				For each 2mmHg greater decrease in diastolic blood pressure between the treatment arms, odds ratio of the cardiovascular composite endpoint 0.883 (0.839 to 0.929), p=0.001		
The Blood Pressure Lowering Treatment Trialists’ Collaboration 2014[39]	SRMA	Patients in blood pressure reduction trials	ACE inhibitors CCBs diuretics	None	RCT	Systolic blood pressure	5-year risk of CVD[7]	11	51917 | NA | 4167	For a 5mmHg greater reduction in systolic blood pressure between treatment and control, stratified by baseline risk group, the	“In conclusion, this meta-analysis showed that treatment with blood pressure-lowering drugs resulted in similar relative risk reductions irrespective of the baseline level of absolute	Across 11 RCTs, reductions in systolic blood pressure were associated with decreased risk of adverse cardiovascul

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										risk ratio of 5-year risk of CVD between those groups: Risk <11%: 0.80 (0.72 to 0.88) Risk 11-15%: 0.89 (0.81 to 0.97) Risk 15-21%: 0.90 (0.84 to 0.97) Risk >21%: 0.89 (0.83 to 0.96)	risk, hence greater absolute risk reduction with higher baseline absolute risk."	ar events, regardless of baseline risk.
							5-year risk of stroke[8]		51917 | NA | 1846	For a 5mmHg greater reduction in systolic blood pressure between treatment and control, stratified by baseline risk group, the risk ratio of 5-year risk of stroke between those groups:		

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										Risk <4%: 0.78 (0.66 to 0.91) Risk 4-5.4%: 0.86 (0.76 to 0.97) Risk 5.4-7.2%: 0.87 (0.78 to 0.97) Risk >7.2%: 0.87 (0.76 to 0.98)		
							5-year risk of CHD[9]		52035 | NA | 1659	For a 5mmHg greater reduction in systolic blood pressure between treatment and control, stratified by baseline risk group, the risk ratio of 5-year risk of CHD between those groups Risk <5%: 0.84 (0.70 to 1.01) Risk 5-7%: 0.96 (0.83 to 1.12)		

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										Risk 7-11%: 0.87 (0.75 to 1.00) Risk >11%: 0.90 (0.79 to 1.02)		
							5-year risk of HF[10]		52035 | NA | 885	For a 5mmHg greater reduction in systolic blood pressure between treatment and control, stratified by baseline risk group, the risk ratio of 5-year risk of HF between those groups Risk <2.6%: 0.89 (0.70 to 1.11) Risk 2.6-4.5%: 0.96 (0.77 to 1.19) Risk 4.5-7%: 0.88 (0.73 to 1.06) Risk >7%: 0.80 (0.64 to 1.00)		

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							5-year risk of CV mortality		52035 | NA | 1855	For a 5mmHg greater reduction in systolic blood pressure between treatment and control, stratified by baseline risk group, the risk ratio of 5-year risk of CV mortality between those groups Risk <5%: 0.85 (0.71 to 1.01) Risk 5-8%: 0.85 (0.73 to 0.98) Risk 8-13%: 0.94 (0.84 to 1.05) Risk >13%: 0.93 (0.84 to 1.03)		
							5-year risk of all-cause mortality		48198 | NA | 3055	For a 5mmHg greater reduction in systolic blood pressure between treatment and control,		

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										stratified by baseline risk group, the risk ratio of 5-year risk of all-cause mortality between those groups Risk <6%: 0.88 (0.78 to 0.99) Risk 6-10%: 0.91 (0.82 to 1.01) Risk 10-16%: 0.95 (0.86 to 1.05) Risk >16%: 0.99 (0.91 to 1.08)		
Nazarzadeh 2022[43]	IPD MA	People with and without T2DM	ACE inhibitors ARBs Beta Blockers CCBs diuretics various combinations	None	RCT	Systolic blood pressure	MACE[11] in people with T2D	48	101132 | NA | 16776	For a 5mmHg larger decrease in systolic blood pressure between treatment arms, hazard ratio of MACE in people with T2DM 0.94 (0.91 to 0.98) Regression coefficient for change	"In this individual participant-level data meta-analysis of major pharmacological blood pressure-lowering trials…blood pressure-lowering treatment reduced the risk of major cardiovascular events in those with and without	Across RCTs using individual patient data, greater reductions in systolic blood pressure was associated with decreased rates of MACEs, both in people with and without

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										in systolic blood pressure between treatment arms and hazard ratio of MACE in people with T2DM - 0.007 (-0.036 to 0.0205)	type 2 diabetes.”	type 2 diabetes.
							MACE[11] in people without T2D	44	254146 | NA | 26155	For a 5mmHg larger decrease in systolic blood pressure between treatment arms, HR of MACE in people without T2DM 0.89 (0.87 to 0.92) Regression coefficient for change in systolic blood pressure between treatment arms and hazard ratio of MACE in people without T2DM - 0.014 (-		

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										0.035 to 0.006)		
							Stroke in people with T2D	48	101212 | NR | 5110	For a 5mmHg larger decrease in systolic blood pressure between treatment arms, hazard ratio of stroke in people without T2DM 0.86 (0.81 to 0.91)		
							Stroke in people without T2D	44	254420 | NR | 9658	For a 5mmHg larger decrease in systolic blood pressure between treatment arms, hazard ratio of stroke in people without T2DM 0.87 (0.84 to 0.91)		
							CHD in people with T2D	48	101156 | NR | 8147	For a 5mmHg larger decrease in systolic blood pressure		

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										between treatment arms, hazard ratio of ischemic heart disease in people with T2DM 0.98 (0.94 to 1.03)		
							CHD in people without T2D	44	254284 | NR | 12946	For a 5mmHg larger decrease in systolic blood pressure between treatment arms, hazard ratio of ischemic heart disease in people with T2DM 0.90 (0.87 to 0.94)		
							HF in people with T2D	48	94571 | NR | 3980	For a 5mmHg larger decrease in systolic blood pressure between treatment arms, hazard ratio of HF in people without T2DM 0.92		

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										(0.86 to 0.99)		
							HF in people without T2D	44	222543 | NR | 3928	For a 5mmHg larger decrease in systolic blood pressure between treatment arms, hazard ratio of HF in people without T2DM 0.83 (0.77 to 0.89)		
							CV mortality in people with T2D	48	94993 | NR | 4550	For a 5mmHg larger decrease in systolic blood pressure between treatment arms, hazard ratio of CV death in people without T2DM 1.03 (0.97 to 1.10))		
							CV mortality in people without T2D	44	236970 | NR | 7171	For a 5mmHg larger decrease in systolic blood pressure		

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										between treatment arms, hazard ratio of CV death in people without T2DM 0.90 (0.86 to 0.94)		
							All-cause mortality in people with T2D	48	102984 | NR | 11710	For a 5mmHg larger decrease in systolic blood pressure between treatment arms, hazard ratio of all-cause mortality in people without T2DM 1.00 (0.96 to 1.10)		
							All-cause mortality in people without T2D	44	254431 | NR | 18948	For a 5mmHg larger decrease in systolic blood pressure between treatment arms, hazard ratio of all-cause mortality in people without T2DM 0.95		

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										(0.93 to 0.98)		
Reboldi 2011[44]	SRMA	T2DM	ACE inhibitors ARBs CCBs diuretics beta blockers	Non-profit	RCT, PROBE	Systolic blood pressure	Stroke	29	73913 | NA | NR	For a 5mmHg larger decrease in systolic blood pressure between treatment arms, relative risk of stroke 0.870 (0.797 to 0.950), p=0.002	"One, we found a consistent relationship between BP reduction and prevention of stroke. Two, our analyses did not disclose a significant association between the magnitude of BP reduction and prevention of MI. Three, the relationship between the degree of BP reduction and the risk of MI was not J-shaped, suggesting that a more intensive reduction of BP, whereas not providing additional benefit, does not increase the risk of MI."	Across RCTs and PROBE studies, greater decreases in systolic and diastolic blood pressures were associated with lower relative risks of stroke, but not MI.
						Diastolic blood pressure				For a 2mmHg larger decrease in diastolic blood pressure between treatment arms, relative risk of stroke 0.885 (0.828 to 0.946), p<0.001		
						Systolic blood pressure	MI	24		For a 5mmHg larger decrease in systolic blood pressure between treatment arms,		

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										relative risk of MI 0.982 (0.855 to 1.128), p=0.793		
						Diastolic blood pressure				For a 2mmHg larger decrease in diastolic blood pressure between treatment arms, relative risk of MI 0.990 (0.898 to 1.090), p=0.832		
Salam 2019[45]	SRMA	Patients in blood pressure reduction trials	α-Methyldopa captopril enalapril fosinopril perindopril quinapril ramipril trandolapril candesartan irbesartan losartan olmesartan telmisartan valsartan	NR	RCT	Systolic and diastolic blood pressure	CHD	86	349488 | NR | 22254	For a 6 mmHg SBP and 3 mmHg DBP greater difference between treatment and control across all baseline BP strata, relative risk of CHD 0.86 (0.83 to 0.89)	"Overall, a 6mm Hg reduction in SBP reduced CHD by 14% and stroke by 18%...Benefits were apparent in numerous high-risk patient groups with baseline SBP less than 140mmHg, with more evidence of benefit in the SBP 130–139mmHg group than for any other."	Across 86 RCTs, treatment was associated with either greater reductions in SBP and DBP and lower increases in SBP (at lower baseline BP strata) and lower rates of CHD, stroke, or the composite endpoint.
							Stroke			For a 6 mmHg SBP and 3 mmHg DBP greater difference between treatment		

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			atenolol bisoprolol bucindolol carvedilol metoprolol nebivolol oxprenolol practolol propranolol timolol amlodipine diltiazem felodipine mibefradil nifedipine nisoldipine nitrendipine verapamil bendrofluazide chlorothiazide chlorthalidone hydrochlorothiazide indapamide triamterene; ramipril + HCTZ candesartan + HCTZ							and control across all baseline BP strata, relative risk of stroke 0.82 (0.79-0.86)		
						Systolic blood pressure	CHD and stroke	17	18022 | NR | 1013	For patients with baseline SBPs <120 mmHg, when compared to the control group treatment was associated with a 4.6 mmHg lower increase in SBP at follow-up and a relative risk of the combined CHD and stroke endpoint of 0.81 (0.72 to 0.91)		
								28	41358 | NR | 1859	For patients with baseline SBPs between 120-129 mmHg, when compared to		

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			nitrendipine ± captopril ± HCTZ nitrendipine ± enalapril ± HCTZ						the control group treatment was associated with a 3.7 mmHg lower increase in SBP at follow-up and a relative risk of the combined CHD and stroke endpoint of 0.83 (0.76 to 0.90)		
								33	112879 | NR | 6082	For patients with baseline SBPs between 130-139 mmHg, when compared to the control group treatment was associated with a 5.3 mmHg greater decrease in SBP at follow-up and a relative risk of the combined CHD and		

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										stroke endpoint of 0.85 (0.81 to 0.89)		
Thomopoulos 2014[46]	SRMA	Patients in blood pressure reduction trials	Anti-hypertensive agents	Government	RCT, 1 alternate assignment	Systolic and diastolic blood pressure	Fatal and non-fatal stroke[2]	54	235385 | NA | 9513	For a 10 mmHg reduction in SBP and 5 mmHg reduction in DBP, risk reduction of fatal and non-fatal stroke 0.64 (0.57 to 0.71)	"Our primary meta-analysis…confirms that stroke and heart failure were the events most effectively prevented by BP lowering (heart failure to an even larger extent than stroke), but also CHD and cardiovascular and all-cause deaths were significantly prevented though to a smaller extent. Our secondary meta-analysis, comprehensive of intentional and nonintentional BP-lowering RCTs…is entirely consistent with the conclusion of the primary analysis."	Across many RCTs involving both intentional and non-intentional blood pressure lowering trials, reductions in systolic and diastolic blood pressures were associated with lower risks of several clinical outcomes, including stroke, CHD, HF, and CV & all-cause mortality.
							CHD[7]	58	236064 | NA | 8512	For a 10 mmHg reduction in SBP and 5 mmHg reduction in DBP, risk reduction of CHD 0.82 (0.57 to 0.71)		
							HF hospitalization[2]	36	147921 | NA | 5787	For a 10 mmHg reduction in SBP and 5 mmHg reduction in DBP, risk reduction of hospitalization for HF 0.62 (0.51 to 0.75)		

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							Fatal and non-fatal stroke[2] + CHD[7]	56	234575 | NA | 17861	For a 10 mmHg reduction in SBP and 5 mmHg reduction in DBP, risk reduction of fatal and non-fatal stroke and CHD 0.74 (0.70 to 0.80)		
							Stroke[2] + CHD[7] + HF hospitalization	38	168680 | NA | 19461	For a 10 mmHg reduction in SBP and 5 mmHg reduction in DBP, risk reduction of stroke, CHD, and hospitalization for HF: 0.73 (0.68 to 0.79)		
							CV mortality	58	236022 | NA | 9543	For a 10 mmHg reduction in SBP and 5 mmHg reduction in DBP, risk reduction of CV mortality: 0.84 (0.77 to 0.92)		
							All-cause mortality	66	243764 | NA | 18031	For a 10 mmHg reduction in		

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										SBP and 5 mmHg reduction in DBP, risk reduction of all-cause mortality 0.90 (0.85 to 0.95)		

CCEP: Composite cardiovascular endpoint

1: Defined as fatal and non-fatal stroke, fatal and non-fatal MI, ischemic heart disease, HF causing hospitalization or death

2: Defined individually by study

3: Fatal and non-fatal MI excluding silent MI, sudden cardiac death

4: Excluding TIA

5: Fatal and non-fatal MI sudden cardiac death, fatal and non-fatal stroke, revascularization, fatal and non-fatal HF

6: New HF diagnosis, hospitalization for HF, or HF-related death

7: Coronary death and non-fatal MI

8: Fatal and non-fatal stroke, or death from cerebrovascular disease

9: Fatal and non-fatal MI excluding silent MI, sudden cardiac death

10: Hospitalization for HF or HF-related death

11: Defined as fatal or non-fatal stroke or cerebrovascular disease, fatal or non-fatal ischemic heart disease, HF requiring hospitalization or causing death

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eTable 11. Hypertriglyceridemia												
Author, Year	**Study design**	**Indication**	**Interventions**	**Funding source**	**Design of included studies**	**Surrogate marker**	**Clinical outcome**	**No. studies**	**Sample size | number of outcomes**	**Evidence**	**Author's conclusion**	**Plaintext Summary**
Marston 2019[33]	SRMA	Hypertriglyceridemia	unspecified fibrates niacin omega-3 fatty acid unspecified statins	None; industry competing interests	RCT, open-label	Serum triglycerides	Major vascular events[2]	44	374358 | NR | 46180	For a 1 mmol/L reduction in triglycerides, relative risk for major vascular events 0.84, (0.75 to 0.94), p=0.0026 With the REDUCE-IT trial removed: For a 1 mmol/L reduction in triglycerid	"In randomized controlled trials, triglyceride lowering is associated with a lower risk of major vascular events, even after adjusting for LDL-C lowering, although the effect is attenuated when REDUCE-IT is excluded."	In 44 RCTs, reductions in triglycerides were independently associated with decreased risk of major vascular events, though this was heavily influenced by the presence of one large trial.

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										es, relative risk for major vascular events 0.91, (0.81 to 1.006), p=0.06		
Stauffer 2013[35]	SRMA	Hypertriglyceridemia	atorvastatin lovastatin pravastatin simvastatin simvastatin/ezetimibe rosuvastatin bezafibrate fenofibrate gemfibrozil niacin niacin/gemfibrozil/cholestyramine simvastatin/niacin estrogen-progestin omega-3 fatty acids cholestyramine diet	Industry	RCT	Serum triglycerides	Major vascular events[3]	40	200593 | NR | 16843	The proportional change of triglycerides between treatment in control arms and the log ratio of event rates between treatment and control arms of major vascular events across all studies has a slope of 0.488, p=0.005	"Changes in triglyceride levels were predictive of cardiovascular events in RCTs. This relationship was significant in primary prevention populations but not in secondary prevention populations."	Across 40 RCTs, reductions in triglycerides were associated with decreased risk of major vascular events, which in this meta-analysis were mostly cardiovascular, even when taking into account lipoprotein levels known to be involved with atherosclerosis. The triglyceride-vascular event relationship was statistically significant in primary prevention studies, but not secondary prevention studies.
								11	NR | NR | NR	The proportional change of triglycerides between treatment		

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										in control arms and the log ratio of event rates between treatment and control arms of major vascular events in primary prevention studies has a slope of 1.031, p=0.010		
								25	NR | NR | NR	The proportional change of triglycerides between treatment in control arms and the log ratio of event rates between treatment and control arms of major vascular events in secondary prevention		

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										studies has a slope of 0.373, p=0.114		
Labreuche 2010[32]	SRMA	Hypertriglyceridemia	atorvastatin cerivastatin fluvastatin lovastatin pravastatin simvastatin bezafibrate clofibrate fenofibrate gemfibrozil niacin pioglitazone rosiglitazone troglitazone metformin glimepiride glyburide clofibrate + niacin colestipol + niacin gemfibrozil + niacin + cholestyramine simvastatin + ezetimibe statin + ezetimibe + fibrate or niacin	Non-profit	RCT	Serum triglycerides	Stroke	64	165,792 | NR | >5929[1]	For a 10 mg/dL greater decrease in absolute triglyceride between active and control groups and adjusted for baseline triglyceride levels, log relative risk of stroke: 0.4, (-3.8 to 4.8), p=0.84	"Despite the analysis of lipid-modifying randomized trials including >190,000 patients, the present meta-regression analysis failed to detect a positive impact of triglyceride reduction on stroke risk."	Despite evidence of association of baseline triglyceride levels with stroke in the analysis of 64 RCTs, there was no evidence of association between greater decreases in triglyceride levels between treatment and control arms, when adjusted for baseline values, and decreased incidence of stroke.

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			statin + niacin									

1: Data not reported in 12 studies

2: Defined by each study, but often including stroke, coronary heart disease-related death, myocardial infarction, coronary revascularization; sometimes as all-cause mortality, any acute coronary syndrome

3: Defined by each study, but most often coronary heart disease-related death, myocardial infarction; sometimes as coronary revascularization, stroke, angina, or acute coronary syndrome

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eTable 12. Osteoporosis												
Author, Year	**Study design**	**Indication**	**Interventions**	**Funding source**	**Design of included studies**	**Surrogate marker**	**Clinical outcome**	**No. studies**	**Overall sample size | No. surrogate measures | No. clinical outcomes**	**Evidence**	**Author's conclusion**	**Plaintext Summary**
Black 2020[48]	IPD MA	Osteoporosis	alendronate arzoxifene bazedoxifene denosumab equine estrogen equine estrogen + medroxyprogesterone ibandronate lasofoxifene odanacatib PTH(1-34) PRH(1-84) raloxifene risedronate zoledronic acid	Government	RCT	Hip BMD[3]	Vertebral fractures [1, 2]	14	53410 | NR | 4402	Odds ratio of vertebral fracture risk reduction between treatment and placebo arms versus difference in mean percentage change in hip BMD between those arms after 24 months: R^2 0.73 (0.41 to 0.83), p<0.0001	"...we found strong and significant associations between treatment induced changes in BMD and reductions in vertebral, hip, and non-vertebral fractures. These results confirm that larger net increases in BMD with treatment are associated with larger fracture risk reductions. "	Across placebo controlled trials, differences in bone mineral density between treatment arms and placebo controls were significantly and consistently associated with decreased odds of fracture (for vertebral fracture) and increased time to fracture from trial initiation. These associations were directional and scalable, and changes in bone mineral density explain
							Hip fractures	15	61415 | NR | 841	Hazard ratio of time to first hip fracture between treatment and placebo arms		

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										versus difference in mean percentage change in hip BMD between those arms after 24 months: R^2 0.41 (0.06 to 0.62), p=0.014		statistically significant proportions of the treatment effects. However, it is worth noting that definitions of vertebral fracture varied across the component studies. Some of the studies used quantitative morphometry. According to FDA's surrogate endpoint table, new morphometric vertebral fractures are considered are a surrogate marker for postmenopausal women with osteoporosis.
							Non-vertebral fractures	15	66703 | NR | 6440	Hazard ratio of time to first non-vertebral fracture between treatment and placebo arms versus difference in mean percentage change in hip BMD between those arms after 24 months: R^2 0.53 (0.16 to 0.69), p=0.0021		
						Femoral neck BMD	Vertebral fractures	16	53410 | NR | 5065	Odds ratio of vertebral fracture risk reduction between treatment and placebo		

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										arms versus difference in mean percentage change in femoral neck BMD between those arms after 24 months: R^2 0.59 (0.25 to 0.73), p=0.0005		
							Hip fractures	17	61415 | NR | 1063	Hazard ratio of time to first hip fracture between treatment and placebo arms versus difference in mean percentage change in femoral neck BMD between those arms after 24 months: R^2 0.41 (0.08 to 0.61), p=0.0074		
							Non-vertebral fractures	17	66703 | NR | 7453	Hazard ratio of time to first non-vertebral fracture between		

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										treatment and placebo arms versus difference in mean percentage change in femoral neck BMD between those arms after 24 months: R^2 0.65 (0.33 to 0.77), p<0.0001		
						Spine BMD	Vertebral fractures	16	53410 | NR | 5065	Odds ratio of vertebral fracture risk reduction between treatment and placebo arms versus difference in mean percentage change in spine BMD between those arms after 24 months: R^2 0.61 (0.27 to 0.74), p=0.0003		
							Hip fractures	16	61415 | NR | 1007	Hazard ratio of time to first hip fracture		

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										between treatment and placebo arms versus difference in mean percentage change in spine BMD between those arms after 24 months: R^2 0.34 (0.03 to 0.56), p=0.023		
							Non-vertebral fractures	16	66703 | NR | 7267	Hazard ratio of time to first non-vertebral fracture between treatment and placebo arms versus difference in mean percentage change in spine BMD between those arms after 24 months: R^2 0.51 (0.16 to 0.68), p=0.0019		
Bouxsein 2019[49]	SRMA	Osteoporosis	abaloparatide	Government; industry	RCT	Hip BMD	Vertebral	20	91340 | NR | 3174	Relative risk of vertebral	"We found that change in BMD across all	Across placebo-controlled

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			alendronate arzoxifene bazedoxifene calcitonin clodronate denosumab etidronate estrogen estrogen + progestin ibandronate lasofoxifene odanacatib PTH(1-34) PTH(1-84) raloxifene risedronate romosozumab tibolone zoledronic acid				fractures [4]			fracture, as confirmed by radiograph, between treatment and placebo arms versus difference in mean percentage change in hip BMD between those arms: R^2 0.56 (0.26 to 0.70), p=0.0002	published randomized trials is strongly predictive of hip and vertebral fracture reduction…In contrast, lumbar spine BMD changes were predictive only of vertebral fracture risk…very weakly associated with reductions in nonvertebral fracture in these analyses…Although these results cannot be directly applied to predict the treatment benefit in an individual patient, they provide compelling evidence that improvements in BMD with osteoporosis therapies may be useful as surrogate endpoints for fracture in trials of new therapeutic agents.”	trials, differences in changes in hip bone mineral density between treatment and placebo were associated with decreases in relative risk of vertebral and hip fractures, with larger improvements in BMD associated with greater reductions in hip fractures specifically. A similar association was seen between decreased relative risk of vertebral fractures with improvements in femoral neck and spine BMD. However, there was no statistical evidence of decreased risk of non-vertebral fractures.
							Hip fractures	12	85010 | NR | 882	Relative risk of hip fracture between treatment and placebo arms versus difference in mean percentage change in hip BMD between those arms: R^2 0.48 (0.07 to 0.67), p=0.013		
							Non-vertebral fractures	22	74513 | NR | 4999	Relative risk of non-vertebral		

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										fracture between treatment and placebo arms versus difference in mean percentage change in hip BMD between those arms: R^2 0.12 (0.00 to 0.34), p=0.11		
						Femoral neck BMD	Vertebral fractures	24	73904 | NR | 3630	Relative risk of vertebral fracture, as confirmed by radiograph, between treatment and placebo arms versus difference in mean percentage change in hip BMD between those arms: R^2 0.54 (0.27 to 0.68), p<0.0001		
							Hip fractures	13	69557 | NR | 816	Relative risk of hip		

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										fracture between treatment and placebo arms versus difference in mean percentage change in hip BMD between those arms: R^2 0.42 (0.05 to 0.63), p=0.17		
							Non-vertebral fractures	28	84981 | NR | 6383	Relative risk of non-vertebral fracture between treatment and placebo arms versus difference in mean percentage change in hip BMD between those arms: R^2 0.12 (0.00 to 0.31), p=0.07		

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						Spine BMD	Vertebral fractures	30	111183 | NR | 4557	Relative risk of vertebral fracture, as confirmed by radiograph, between treatment and placebo arms versus difference in mean percentage change in hip BMD between those arms: R^2 0.63 (0.41 to 0.73), p<0.0001		
							Hip fractures	15	94469 | NR | 863	Relative risk of hip fracture between treatment and placebo arms versus difference in mean percentage change in hip BMD between those arms: R^2 0.22 (0.00 to 0.46), p=0.08		

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							Non-vertebral fractures	32	92556 | NR | 6340	Relative risk of non-vertebral fracture between treatment and placebo arms versus difference in mean percentage change in hip BMD between those arms: R^2 0.12 (0.00 to 0.30), p=0.05		
Cummings 2002[50]	SRMA	Osteoporosis in postmenopausal women	alendronate calcitonin estradiol etidronate raloxifene risedronate tiludronate	Unclear; industry competing interests	RCT	Spine BMD	Vertebral fractures	12	17746 (according to table) | NR | NR	A 1% improvement in spine bone mineral density in the treatment over placebo arms was associated with a decrease in the relative risk of vertebral fractures of 0.03 (0.02 to 0.05), p=0.002	"Our analyses indicate that improvement in spine bone mineral density…accounts for a part of the reduction in risk of vertebral fractures observed with antiresorptive drugs."	Across 12 RCTs using several drug classes, improvements in spine bone mineral density were associated with decreased risks of vertebral fractures in postmenopausal women
Hochberg 2002[51]	SRMA	Osteoporosis in	alendronate	Industry	RCT	Spine BMD	Non-vertebral	17	26494 | NR | 1916	A 1% greater change in	"..changes in BMD…appeared to explain a	In several RCTs, improvements

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		postmenopausal women	alendronate + estrogen calcitonin etidronate estrogen risedronate raloxifene tiludronate				fractures [4]			spine bone mineral density in the treatment arm vs placebo at 1 year was associated with an 8.2% (SE 0.0349) reduction in non-vertebral fracture risk, p=0.02	significant part of the risk reduction and indicate that there is no significant effect of treatment on fracture risk for treatments that were not associated with increases in BMD…the antifracture efficacy of antiresorptive agents is associated with changes in BMD for both nonvertebral and vertebral fractures.	in spine and hip bone mineral density in the treatment arms over placebo were consistently associated with decreases in the risk of non-vertebral fractures.
						Hip BMD		14	24477 | NR | 2190	A 1% greater change in spine bone mineral density in the treatment arm vs placebo at 1 year was associated with a 27% (SE 0.0976) reduction in non-vertebral fracture risk.		
Watts 2005[53]	Pooled analysis	Osteoporosis in postmenopausal women	risedronate	Industry	RCT	Spine BMD	Non-vertebral fractures [6]	3	3979 | 3290 | <307 Risedronate only: 2087 | NR | 123	Hazard ratio of non-vertebral fracture for those patients treated with risedronate with	"The results of this analysis of data from the risedronate clinical trial phase III fracture programs show that greater increases in BMD	In a pooled analysis of 3 RCTs with patients treated with risedronate and using individual patient data,

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										increases in spinal BMD to those risedronate-treated patients with decreases in spinal BMD: 0.79 (0.50 to 1.25) Hazard ratio of non-vertebral fracture versus change in spinal BMD as a continuous covariate in risedronate-treated patients 1.02 (0.97, 1.06)	are not associated with greater decreases in nonvertebral fracture incidence…Our findings…indicate that the magnitude of change in BMD associated with antiresorptive treatment is not a valid surrogate for reduction in the risk of nonvertebral fractures.	there was no observable change in relative risk of non-vertebral fractures in those risedronate-treated patients who gained BMD in either the spine or femoral neck versus those risedronate-treated patients who lost BMD in those areas. Further analysis did not indicate that increases in BMD in patients given risedronate were associated with decreases in non-vertebral fracture risk in these groups.
						Femoral neck BMD		3	Risedronate only: 2504 | NR | 162	Hazard ratio of non-vertebral fracture for those patients treated with risedronate with increases in spinal BMD to those risedronate-treated patients with decreases in spinal		

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										BMD: 0.93 (0.68 to 1.28) Hazard ratio of non-vertebral fracture versus change in femoral neck BMD as a continuous covariate in risedronate-treated patients: 1.01 (0.98, 1.05)		
Wasnich 2000[52]	MA	Osteoporosis in postmenopausal women	alendronate calcitonin etidronate HRT raloxifene tiludronate	NR	RCT	Spine BMD	Vertebral fractures[4]	13	NR | NR | 1577	An 8% increase in spine BMD in the treatment arm vs placebo was associated with a relative risk of vertebral fracture of 0.59 (0.43-0.80)	"Our finding that larger increases in BMD are associated with greater antifracture efficacy is concordant with our conceptual model…the results support the theory that clinically important degrees of antifracture efficacy cannot be attained without an adequate, concomitant increase in BMD."	In several placebo-controlled RCTs, increases in spine and hip BMD were associated with, and thought to be causative of, decreased relative risks of vertebral fracture.
						Hip BMD[5]		9	NR | NR | 1350	An 5% increase in hip BMD in the treatment arm vs placebo was associated with a		

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										relative risk of vertebral fracture of 0.62 (0.46-0.83)		

BMD: Bone mineral density

1: Fracture was often defined by individual study, though attempts were made to exclude fractures from major trauma, if reported

2: L1-L4 preferentially, L2-L4 if not differentiated within the study

3: Interconverted measurements to create standardized values

4: Defined by each study individually

5: Measured either as total hip or femoral neck

6: Confirmed radiographically

eTable 13. Pulmonary fibrosis

Author, Year	Study design	Indication	Interventions	Funding source	Design of included studies	Surrogate marker	Clinical outcome	No. studies	Overall sample size | No. surrogate measures | No. clinical outcomes	Evidence	Author's conclusion	Plaintext Summary

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Khan 2022[54]	IPD MA	Idiopathic pulmonary fibrosis	azathioprine mycophenolate nintedanib pirfenidone prednisolone	Government	RCT	Δ 3-month FVC	Mortality (placebo arms)	12	1729 | NR | 159	Per 2.5% relative decline in FVC over 3 months, hazard ratio for mortality in the placebo arms 1.15 (1.06 to 1.24)	"IPD meta-analysis demonstrated that 3-month changes in physiological variables, particularly FVC, were associated with mortality among individuals with IPF. FVC change over 3 months may hold potential as a surrogate endpoint in IPF adaptive trials."	Across the placebo arms of 12 RCTs and treatment arms of 2 medications, changes in FVC at 3 months was associated with differences in mortality and disease progression.
							Mortality (treatment arms)	6	1602 | NR | 135	Per 2.5% relative decline in FVC over 3 months, hazard ratio for mortality in the treatment arms 1.20 (1.12 to 1.28)		
							Disease progression[1] (placebo arms)	12	1551 | NR | 591	Per 2.5% relative decline in FVC over 3 months, odds ratio for disease progression in the placebo arms 1.30 (1.19 to 1.41)		
							Disease progression (treatment arms)	6	1602 | NR | 406	Per 2.5% relative decline in FVC over 3 months, odds ratio for disease progression in the treatment arms 1.46 (1.36 to 1.57)		

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1: Death within 12 months of baseline or 10% relative decline from baseline

eTable 14. Secondary hyperparathyroidism

Author, Year	Study design	Indication	Interventions	Funding source	Design of included studies	Surrogate marker	Clinical outcome	No. studies	Sample size | number of outcomes	Evidence	Author's conclusion	Plaintext Summary

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Palmer, 2015[37]	SRMA	Secondary hyperparathyroidism in CKD	Phosphate binders cinacalcet vitamin D bisphosphonates calcitonin	Government	RCT	Target serum PTH	All-cause mortality	12	3410 | NA | NR	Pearson's correlation coefficient of the log relative risk of achieving a study-specific serum PTH target value between treatment and control arms and the log relative risk of all-cause mortality between those treatment arms: 0.12 (-0.61 to 0.73)	"We found that the effects of a broad range of drugs used widely in CKD to correct perturbed serum PTH…generally do not correlate with cardiovascular and all-cause mortality in randomized trials…drug effects on serum PTH…are weakly and imprecisely correlated with mortality in CKD at best…On the basis of these findings, the central role of surrogate biochemical markers of bone disease in the drug management of CKD appears to be of uncertain clinical value."	When looking across several studies, decreases in serum PTH was weakly and inconsistently associated with improvements in all-cause and cardiovascular mortality, though the trial length was generally short.
							Cardiovascular mortality	6	1637 | NA | NR	Pearson's correlation coefficient of the log relative risk of achieving a study-specific serum PTH target value		

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										between treatment and control arms and the log relative risk of all-cause mortality between those treatment arms: -0.03 (-0.91 to 0.91)		
						Continuous serum PTH	All-cause mortality	17	2845 | NA | NR	Pearson's correlation coefficient of the ratio of mean serum PTH between treatment arms at trial end and the log relative risk of all-cause mortality between those treatment arms: -0.69 (-0.88 to -0.18)		

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							Cardiovascular mortality	5	796 | NA | NR	Pearson's correlation coefficient of the ratio of mean serum PTH between treatment arms at trial end and the log relative risk of all-cause mortality between those treatment arms: -0.28 (-0.98 to 0.96)		

eTable 15. Type 2 diabetes

Author, Year	Study design	Indication	Interventions	Funding source	Design of included studies	Surrogate marker	Clinical outcome	No. studies	Overall sample size | No. surrogate measur	Evidence	Author's conclusion	Plaintext Summary

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									es | No. clinical outcomes			
Baechle 2022[56]	SRMA (secondary analysis of SRMA data)	T2DM	α-glucosidase inhibitors basal insulin DPP-4 inhibitors GLP-1 receptor agonists meglitinide metformin SGLT2 inhibitors sulfonylureas thiazolidinediones	None	RCT	HbA1c	All-cause mortality	205	122245 | NR | 361	Regression coefficient for the estimation of the absolute change in HgA1c between treatment and control and risk difference in all-cause mortality between those arms -0.031% (-0.179% to 0.117%) Pearson's correlation coefficient: -0.089 (-0.232 to 0.060) Regression coefficient for the estimation of the absolute change in HgA1c between treatment and control and the change in log relative risk of all-cause mortality between those arms 0.129 (-0.043 to 0.302)	"Based on the results of more than 200 randomized trials, HbA1c is not a valid surrogate marker for all-cause mortality in people with type 2 diabetes."	Using results from 205 RCTs, differences in HgA1c between treatment arms were not associated with risk ratio differences or changes in relative risk for all-cause mortality, though the number of events was low.

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										Pearson's correlation coefficient - 0.010 (-0.145 to 0.134)		
Huang 2022[60]	SRMA	T2DM	Alogliptin Linagliptin Omarigliptin Saxagliptin Sitagliptin Albiglutide Dulaglutide Efpeglenatide Exenatide Liraglutide Lixisenatide Semaglutide Canagliflozin Dapagliflozin Empagliflozin Ertugliflozin Pioglitazone	Governm ent	RCT		MACE[1]	18	155610 | NA | 15868	Regression coefficient for the difference in change in HgA1c between treatment and placebo-control arms and the natural log relative risk of a major adverse cardiovascular events between those groups - 0.3911 (-0.5676 to -0.2147) p<0.0001 A 1% greater reduction in HgA1c between treatment and placebo control reduced the relative risk of MACE to 0.75 (0.68 to 0.83), p<0.0001	"Risk reduction in MACE was proportional to the magnitude of HbA1c decrease conferred by antidiabetic agents with less hypoglycemic hazard…	Across 18 placebo-controlled RCTs examining antidiabetic medications with lower risk of hypoglycemia, increased reductions in HgA1c were associated with lower chances of MACEs and various other clinical outcomes even when adjusted for the non-HbA1c beneficial effects of antidiabetic medications.
							Stroke[1]	18	155610 | NA | 4041	Regression coefficient for the difference in change in HgA1c between		

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										treatment and placebo-control arms and the natural log relative risk of stroke between those groups -0.5706 (-0.9395 to -0.2018) p=0.0024		
							MI[1]	18	155610 | NA | 7595	Regression coefficient for the difference in change in HgA1c between treatment and placebo-control arms and the natural log relative risk of MI between those groups -0.2869 (-0.5586 to -0.0152) p=0.0385		
							Hospitalization for HF[1]	18	155610 | NA | 5137	Regression coefficient for the difference in change in HgA1c between treatment and placebo-control arms and the natural log relative risk of hospitalization due to heart failure between those groups -0.2145 (-		

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										0.7575 to 0.3286) p=0.4390		
							CV mortality	18	155610 | NA | 6861	Regression coefficient for the difference in change in HgA1c between treatment and placebo-control arms and the natural log relative risk of cardiovascular death between those groups -0.2810 (-0.5948 to 0.0327) p=0.0791		
							Composite kidney Outcome[1]	14	133524 | NA | 8857	Regression coefficient for the difference in change in HgA1c between treatment and placebo-control arms and the natural log relative risk of composite renal outcome between those groups -0.3405 (-0.7026 to 0.0216) p=0.0653		
							Retinopathy[1]	10	82682 | NA | 1927	Regression coefficient for the difference in change in		

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										HgA1c between treatment and placebo-control arms and the natural log relative risk of retinopathy between those groups 0.0558 (-0.5724 to 0.6839) p=0.8619		
							All-cause mortality[1]	18	155610 | NA | 10647	Regression coefficient for the difference in change in HgA1c between treatment and placebo-control arms and the natural log relative risk of all-cause death between those groups -0.2751 (-0.5376 to -0.0126), p=0.0400		
							Hypoglycemia[1]	18	155610 | NA | 19074	Regression coefficient for the difference in change in HgA1c between treatment and placebo-control arms and the natural log relative risk of hypoglycemia between those groups 0.0202		

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										(-0.3654 to 0.4059) p=0.9181		
							Severe hypoglycemia[1]	16	142171 | NA | 2810	Regression coefficient for the difference in change in HgA1c between treatment and placebo-control arms and the natural log relative risk of severe hypoglycemia between those groups -0.0608 (-0.7767 to 0.6550) p = 0.8677		
de Carvalho 2022[58]	SRMA	T2DM	DPP-4 inhibitors DPP-4 inhibitor + pioglitazone GLP-1 agonists GLP-1 agonist + insulin GLP-1 agonist + SGLT-2 inhibitor GLP-1 agonist + Thiazolidinedione insulin	Government	RCT		MACE[2]	126	270874 | NA | 20724	Hazard ratio of MACE between those treatment arms achieving a HbA1c ≤ 7.0% and those arms ending with a HbA1c >7.0% in a bivariate analysis: 0.9579 (0.8117 to 1.1097), p=0.256 In a multivariate analysis adjusted for drug type, time since diagnosis, and trial length: 0.8785 (0.6471	"...the absolute change in HbA1c and the target ≤ 7.0% were associated with reduced risk of MACE in therapies based on SGLT2i, DPP4i, pioglitazone, or GLP1-RA, with no evidence of increasing all-cause mortality"	Across 126 RCTs, treatment arms that achieved a HbA1c of ≤7.0% were associated with lower risks of MACE only when including data from trials on SGLT-2 inhibitors, DPP-4 inhibitors, pioglitazone, and GLP-1 agonists, with minimal supporting evidence to show that greater reductions in HgA1c across all antidiabetic drugs were associated with decreased rates of MACEs.

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			metformin SGLT-2 inhibitors SGLT-2 inhibitor + sulfonylureas sulfonylurea + insulin thiazolidinediones							to 1.0820), p=0.162 For a 1% greater reduction in HbA1c in the active arm compared to control, hazard ratio of MACE in a bivariate analysis 0.8979 (0.7249 to 1.0171), p=0.109 In a multivariate analysis adjusted for drug type, time since diagnosis, and trial length 0.8837 (0.7019 to 0.9991), p=0.049		
Rivera 2021[62]	SRMA	T2DM	pioglitazone alogliptin linagliptin omarigliptin saxagliptin sitagliptin canagliflozin dapagliflozin empagliflozin		RCT		All-cause mortality	19	163170 | NA | 11111	Pearson's correlation coefficient for the mean difference in HbA1c between treatment and placebo control and relative risk of mortality 0.339 (-0.136 to 0.687), p=0.156; R^2 0.115	"Using data from placebo-controlled RCTs (*n* = 19) and trial-level linear regression analysis, the findings of this study show that a reduction in HbA1c does not reliably predict a reduction in the relative risk of mortality, myocardial infarction, stroke, heart failure, and	Across 19 placebo-controlled RCTs, differences in HbA1c between treatment and control did not reliably correlate with changes in the risk of mortality, MI, stroke, HF, or kidney injury, though there was a statistically significant

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			ertugliflozin albiglutide dulaglutide exenatide liraglutide lixisenatide semaglutide aleglitazar							Regression coefficient for the mean difference in HbA1c between treatment and placebo control and log relative risk of mortality 0.320 (-0.151 to 0.791)	kidney injury in type 2 DM (DM2) trials. Even though a statistically significant association was found between stroke and HbA1c, the strength of the association did not reach the cut-off point established for HbA1c to be considered a valid surrogate (lower limit of 95 percent CI of *R* greater than or equal to .85)."	correlation between HbA1c and stroke.
							MI[1]	18	158769 | NA | 7956	Pearson's correlation coefficient for the mean difference in HbA1c between treatment and placebo control and relative risk of MI 0.199 (-0.295 to 0.609), p=0.892; R^2 0.040 Regression coefficient for the mean difference in HbA1c between treatment and placebo control and log relative risk of MI 0.142 (-0.209 to 0.493)		
							Stroke[1]	17	155586 | NA | 4075	Pearson's correlation coefficient for the mean difference in HbA1c		

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										between treatment and placebo control and relative risk of stroke 0.811 (0.541 to 0.929), p<0.001; R^2 0.657 Regression coefficient for the mean difference in HbA1c between treatment and placebo control and log relative risk of stroke 0.789 (0.494 to 1.083)		
							HF events[1]	18	153707 | NA | 5248	Pearson's correlation coefficient for the mean difference in HbA1c between treatment and placebo control and relative risk of heart failure 0.079 (-0.403 to 0.526), p=0.755; R^2 0.006 Regression coefficient for the mean difference in HbA1c between treatment and placebo control		

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										and log relative risk of heart failure 0.094 (-0.744 to 0.933)		
							Kidney injury[3]	16	147662 | NA | 6432	Pearson's correlation coefficient for the mean difference in HbA1c between treatment and placebo control and relative risk of kidney injury -0.037 (-0.523 to 0.467), p=0.892; R^2 0.001 Regression coefficient for the mean difference in HbA1c between treatment and placebo control and log relative risk of kidney injury 0.160 (-1.244 to 1.563)		
Maiorino 2021[61]	SRMA	T2DM	alogliptin linagliptin saxagliptin sitagliptin albiglutide dulaglutide exenatide	None	RCT		MACE[2]	18	161156 | NA | NR	Regression coefficient for the difference in achieved HbA1c at trial end between treatment and control and log hazard ratio of MACE -0.298, p=0.007; R^2 0.97	"The results of the meta-regression analysis of the 18 CVOTs in 161,156 patients with type 2 diabetes show that the reduction of HbA1c during treatment with DPP-4i, GLP-1RA or SGLT-2i is associated with	Across 18 placebo-controlled RCTs, greater reductions in end-treatment HbA1c were associated with improved outcomes for MACE, driven nearly entirely by non-fatal stroke risk reduction.

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			liraglutide lixisenatide semaglutide canagliflozin empagliflozin ertugliflozin Ssotagliflozin							For every 1% greater difference in HbA1c at trial end between treatment and control, the risk of MACE decreased by 0.26	reduction of MACE, explaining almost all (R^2 = 97%) of the between-study variance. The risk reduction of MACE was almost completely driven by the reduction of non-fatal stroke, whose association explains 100% of between-study variance, and is unique in holding this relationship among MACE components"	
							CV mortality			Regression coefficient for the difference in achieved HbA1c at trial end between treatment and control and log hazard ratio of CV death -0.176, p=0.311; R^2 .04		
							Non-fatal MI			Regression coefficient for the difference in achieved HbA1c at trial end between treatment and control and log hazard ratio of non-fatal MI -0.181, p=0.256; R^2 .03		
							Non-fatal stroke			Regression coefficient for the difference in achieved HbA1c at trial end between treatment and control and log hazard ratio of non-fatal stroke		

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										-0.531, p=0.008; R^2 1.00 For every 1% greater difference in HbA1c at trial end between treatment and control, the risk of non-fatal stroke decreased by .41		
							Hospitalization for HF			Regression coefficient for the difference in achieved HbA1c at trial end between treatment and control and log hazard ratio of hospitalization for HF -0.186, p=0.474; R^2 0.00		
							All-cause mortality			Regression coefficient for the difference in achieved HbA1c at trial end between treatment and control and log hazard ratio of all-cause mortality -0.196, p=0.192; R^2 0.24		

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Ambrosi 2020[55]	SRMA		alogliptin linagliptin omarigliptin saxagliptin sitagliptin albiglutide exenatide liraglutide lixisenatide semaglutide canagliflozin eapagliflozin empagliflozin	None	RCT		MACE[2]	14	128149 | NA | 12114	In a univariate analysis, Pearson's correlation coefficient between mean difference in HbA1c reduction between treatment and placebo control and relative difference in MACE between those arms r=0.88 (0.67 to 0.97), p<0.001 In a bivariate analysis adjusting for weight loss in 13 of those trials: p=0.019	"Our analysis finds an association between HbA1c reduction and MACE decrease across CVOT and this association is still significant when taking into account weight loss. This result supports the usefulness of HbA1c as a surrogate marker for the prevention of cardiovascular outcomes."	Across 14 placebo-controlled RCTs examining cardiovascular outcomes, greater reductions in HgA1c between treatment and control were associated with lower rates of MACEs.
Fralick 2020[59]	SRMA		dapagliflozin linagliptin alogliptin sitagliptin saxagliptin albiglutide lixisenatide liraglutide semaglutide dulaglutide exenatide	None	RCT		Composite CV events[4]	14	"Over 130000"	For a 0.5% greater reduction in HbA1c in the treatment vs. placebo control arm, the hazard ratio between those arms 0.83 (0.72 to 0.94)	"Our study provides further support that reducing the risk of cardiovascular events for adults with diabetes is only partly associated with changes in HbA1c"	Across 14 placebo -controlled RCTs, greater reductions in HbA1c at end of trial were associated with decreased rates of cardiovascular events, but not all-cause mortality.
							All-cause mortality			For a 0.5% greater reduction in HbA1c in the treatment vs. placebo control arm, the hazard ratio between those arms		

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										0.92 (0.73 to 1.17)		
Thomopoulos 2019[63]	SRMA	T2DM	insulin metformin GLP-1 agonists DPP-4 inhibitors PPAR antagonists SGLT2 inhibitors	None; industry competing interests	RCT		CHD events[5]	≤25	174235 | NA | 8619	Regression coefficient for the end-trial HbA1c between treatment and control and the natural log of the risk ratio of CHD events between those groups -0.012, p=0.063 For a 0.52% reduction in HbA1c, risk ratio of CHD events in 20 trials after controlling for BP change 0.92 (0.88 to 0.95)	"Treatment to lower glucose levels is associated with reduced risk of CHD, major cardiovascular events and increased risk of treatment-related discontinuations after adjustment for the ongoing BP difference. No reduction in mortality was noticed in the same setting. Risk change of the composite of CHD and stroke, as well as treatment-related discontinuations is linearly related to the extent of HBA1c-lowering."	Across 25 placebo-controlled RCTs, greater reductions in HbA1c were associated with decreased risks of major cardiovascular events and stroke, as well as increased risk of treatment discontinuation even when accounting for changes in BP over that same time. However, there was no statistical association between changes in HbA1c between those arms and all-cause mortality, CV mortality, or hospitalization for HF.
							Fatal and non-fatal stroke		174235 | NA | 4714	Regression coefficient for the end-trial HbA1c between treatment and control and the natural log of the risk ratio of fatal and non-fatal stroke between those groups -0.040, p=0.68 For a 0.52% reduction in HbA1c, risk ratio of fatal		

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										and non-fatal stroke in 21 trials after controlling for BP change 0.95 (0.90 to 1.01)		
							Hospitalization for HF		174235 | NA | 6477	Regression coefficient for the end-trial HbA1c between treatment and control and the natural log of the risk ratio of hospitalization for HF between those groups -0.086, p=0.61 For a 0.52% reduction in HbA1c, risk ratio of hospitalization for HF in 23 trials after controlling for BP change 1.00 (0.90 to 1.11)		
							CHD events[5] and fatal or non-fatal stroke		174235 | NA | 15343	Regression coefficient for the end-trial HbA1c between treatment and control and the natural log of the risk ratio of CHD or stroke between those		

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										groups 0.006, p=0.049 For a 0.52% reduction in HbA1c, risk ratio of CHD events or fatal or non-fatal stroke in 22 trials after controlling for BP change 0.95 (0.91 to 0.98)		
							CHD events[5], fatal or non-fatal stroke, and hospitalization for HF		174235 | NA | 19452	Regression coefficient for the end-trial HbA1c between treatment and control and the natural log of the risk ratio of CHD events, stroke, or hospitalization for HF between those groups 0.042, p=0.43 For a 0.52% reduction in HbA1c, risk ratio of CHD events, fatal or non-fatal stroke or hospitalization for HF after controlling for BP change 0.95 (0.90 to 0.99)		

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							CV mortality		174235 | NA | 7755	Regression coefficient for the end-trial HbA1c between treatment and control and the natural log of the risk ratio of CV mortality between those groups 0.014, p=0.35 For a 0.52% reduction in HbA1c, risk ratio of CV mortality after controlling for BP change 0.94 (0.88 to 1.02)		
							All-cause mortality		174235 | NA | 13852	Regression coefficient for the end-trial HbA1c between treatment and control and the natural log of the risk ratio of all-cause mortality between those groups -0.12, p=0.31 For a 0.52% reduction in HbA1c, risk ratio of all-cause mortality after controlling for BP change		

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										0.95 (0.90 to 1.01)		
Bejan-Angoulvant 2015[57]	SMRA	T2DM	insulin metformin saxagliptin alogliptin aleglitazar gliclazide pioglitazone rosiglitazone sulphonylureas.	None	RCT		All-cause mortality	7	NR | NA | NR	Regression coefficient for the difference in HbA1c between treatment and control at trial end and log odds ratio of mortality between those arms 0.222 (SE 0.168), p=0.242	"However, our analysis could find no significant relationship between the decrease in HbA1c, observed in RCTs evaluating glucose-lowering regimens and rates of total or cardiovascular mortality, or any cardiovascular or microvascular complications in T2D patients."	Across several RCTs on more intensive versus less intensive antidiabetic regimens, greater improvement in HbA1c was not associated with improved clinical outcomes, though the number of studies included in the analysis was not large.
							CV mortality	8	33396 | NA | NR	Regression coefficient for the difference in HbA1c between treatment and control at trial end and log odds ratio of mortality between those arms 0.367 (SE 0.231), p=0.164		
							MI[1]	7	NR | NA | NR	Regression coefficient for the difference in HbA1c between treatment and control at trial end and log odds ratio of mortality between those arms -0.098		

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										(SE 0.142), p=0.518		
							Fatal and non-fatal stroke	7	NR | NA | NR	Regression coefficient for the difference in HbA1c between treatment and control at trial end and log odds ratio of mortality between those arms 0.114 (SE 0.194), p=0.584		
							HF	8	33396 | NA | NR	Regression coefficient for the difference in HbA1c between treatment and control at trial end and log odds ratio of mortality between those arms 0.020 (SE 0.274), p=0.945		
							Microalbuminuria	6	NR | NA | NR	Regression coefficient for the difference in HbA1c between treatment and control at trial end and log odds ratio of mortality between those arms -0.307		

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										(SE 0.138), p=0.091		
							Neuropathy	6	NR | NA | NR	Regression coefficient for the difference in HbA1c between treatment and control at trial end and log odds ratio of mortality between those arms -0.135 (SE 0.085), p=0.188		
							Peripheral vascular events[6]	6	NR | NA | NR	Regression coefficient for the difference in HbA1c between treatment and control at trial end and log odds ratio of mortality between those arms -0.189 (SE 0.241), p=0.477		
							Severe hypoglycemia	5	NR | NA | NR	Regression coefficient for the difference in HbA1c between treatment and control at trial end and log odds ratio of mortality between those arms 0.606 (SE		

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										0.307), p=0.143		

MACE: Major adverse cardiovascular event; HF: Heart Failure

1: Defined individually by each study

2: Defined as non-fatal MI, non-fatal stroke, cardiovascular death

3: Defined variably by each study as a composite outcome including various parameters, including persistent macroalbuminuria, doubling of creatinine level, initiation of dialysis, kidney transplantation, initiation of renal replacement therapy, reduction of estimated glomerular filtration rate ≥30%, ESRD, and death from kidney disease

4: Defined as non-fatal MI, non-fatal stroke, cardiovascular death in 12 of those studies

5: Defined as non-fatal MI, coronary death

6: Defined as leg revascularization, peripheral arterial disease or intermittent claudication

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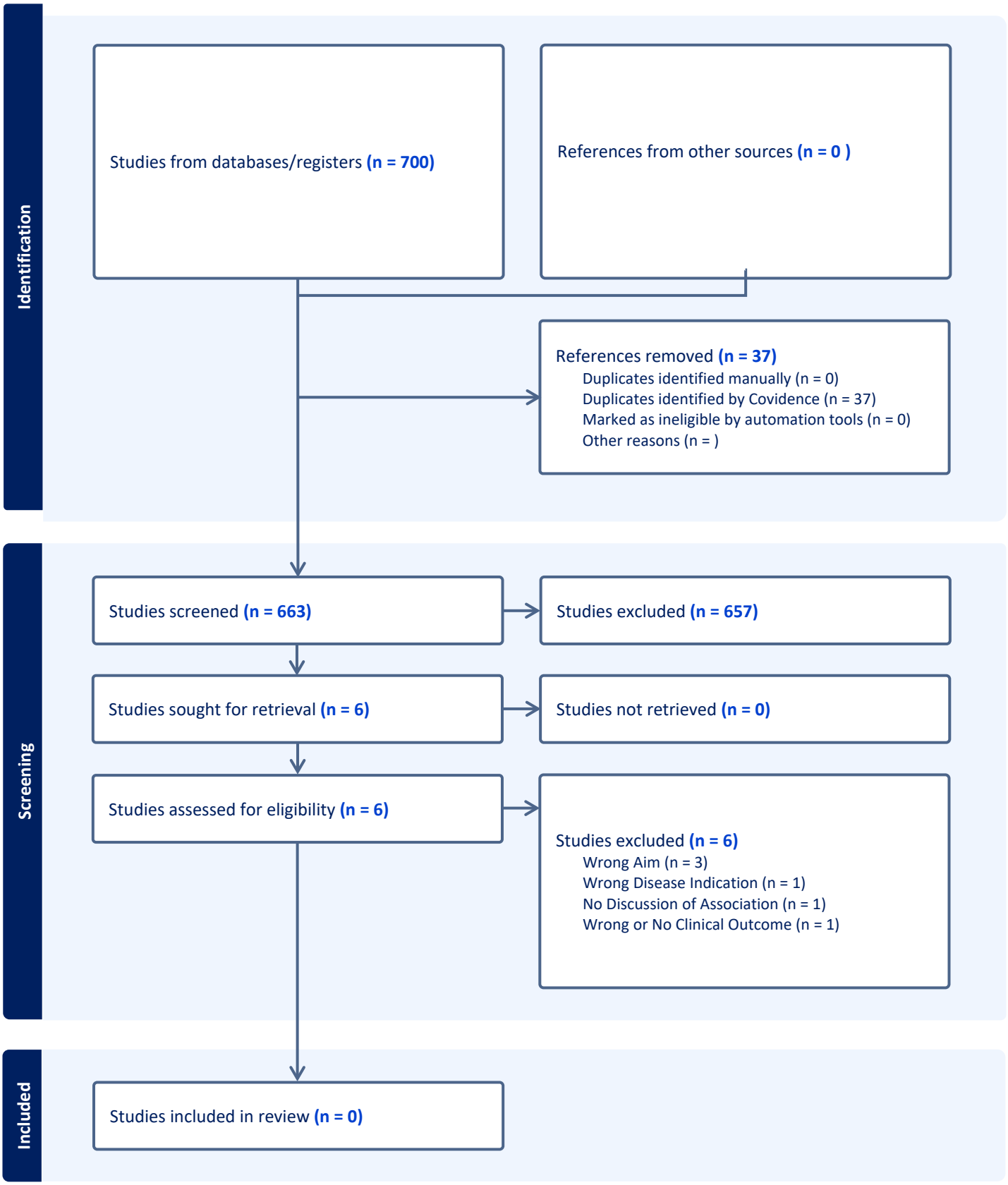
eFigure 1. Asthma



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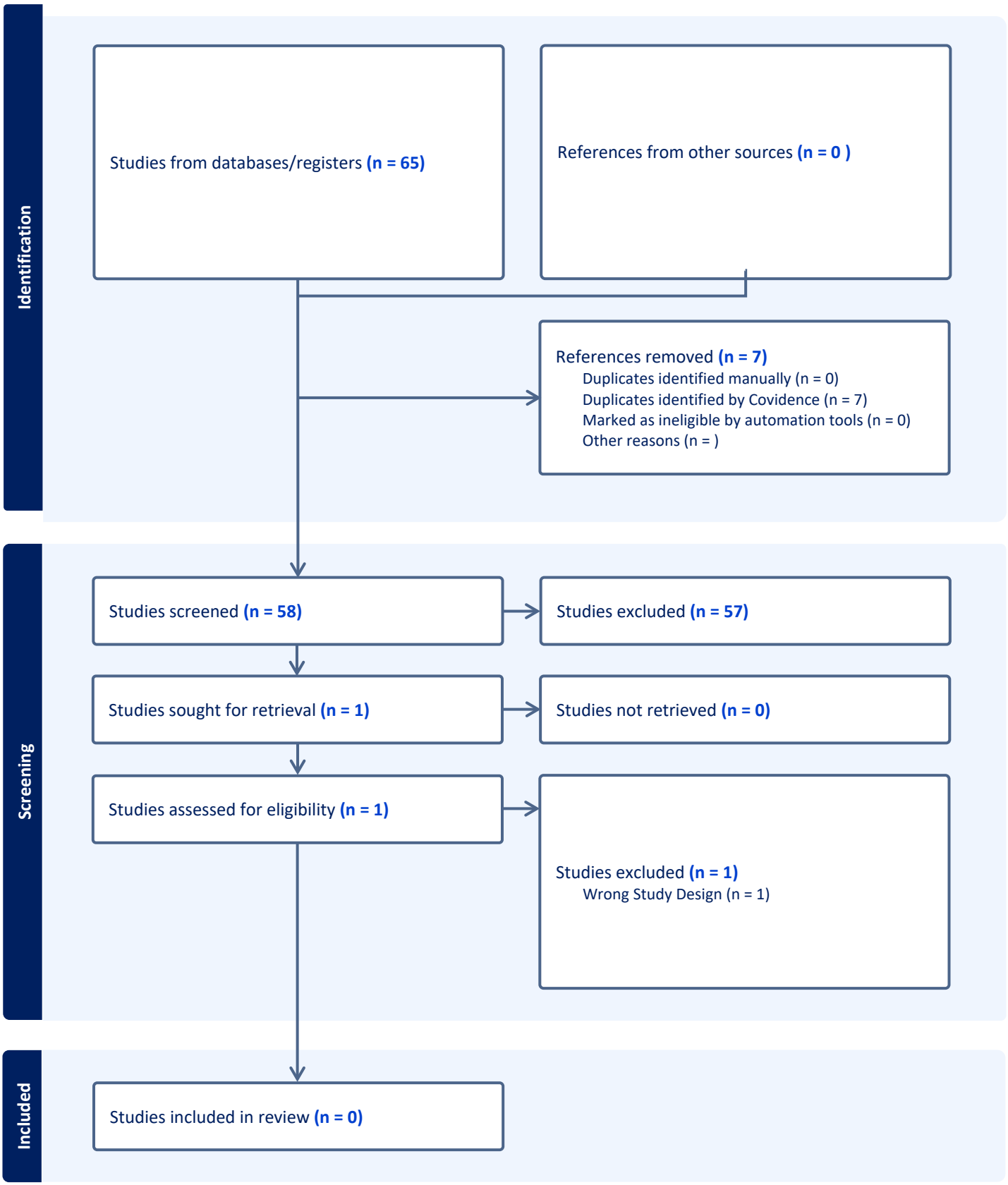
eFigure 2. Cushing's Disease / Cushing's Syndrome



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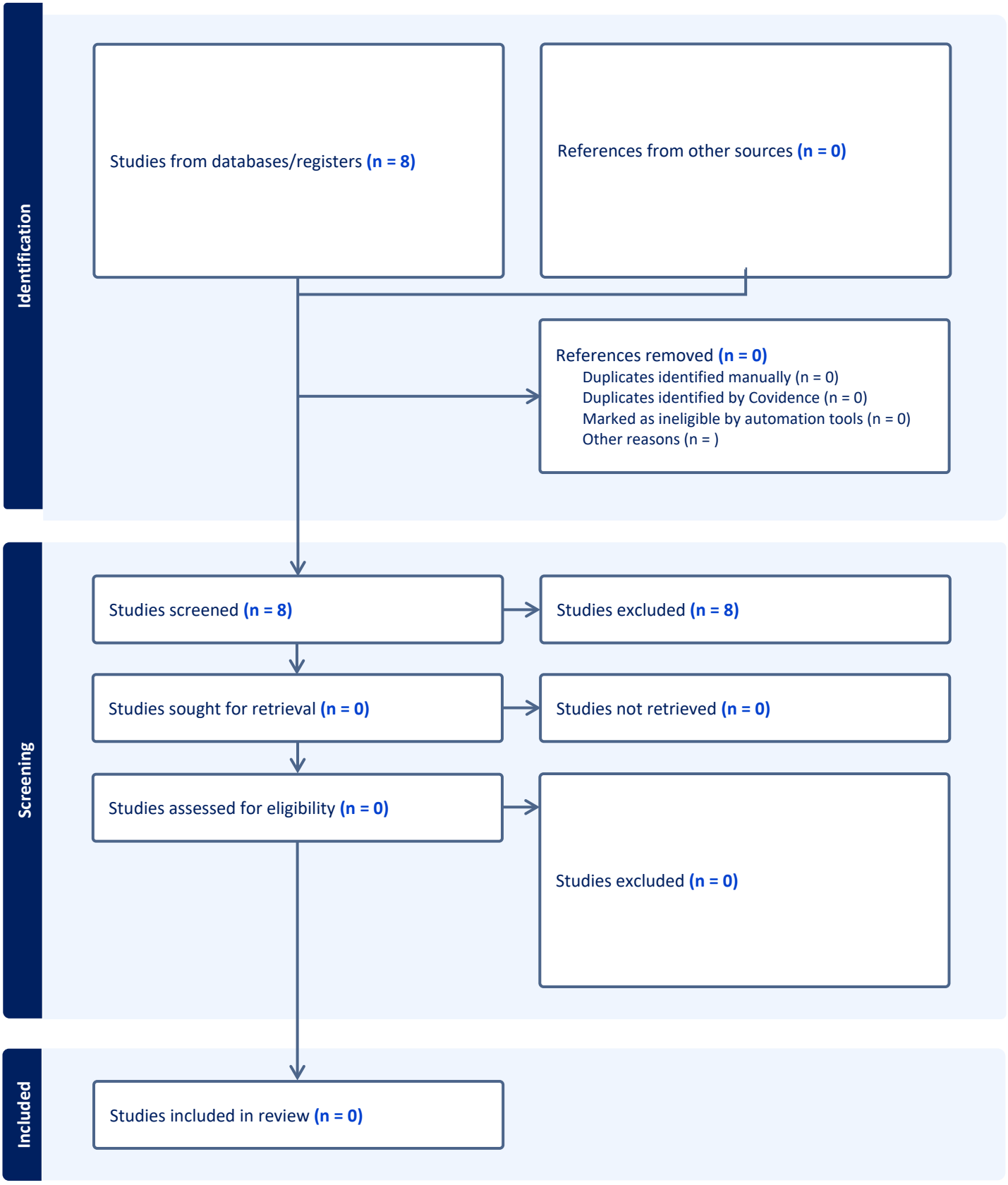
eFigure 3. Exocrine Pancreatic Insufficiency



eFigure 4. Hepatitis B

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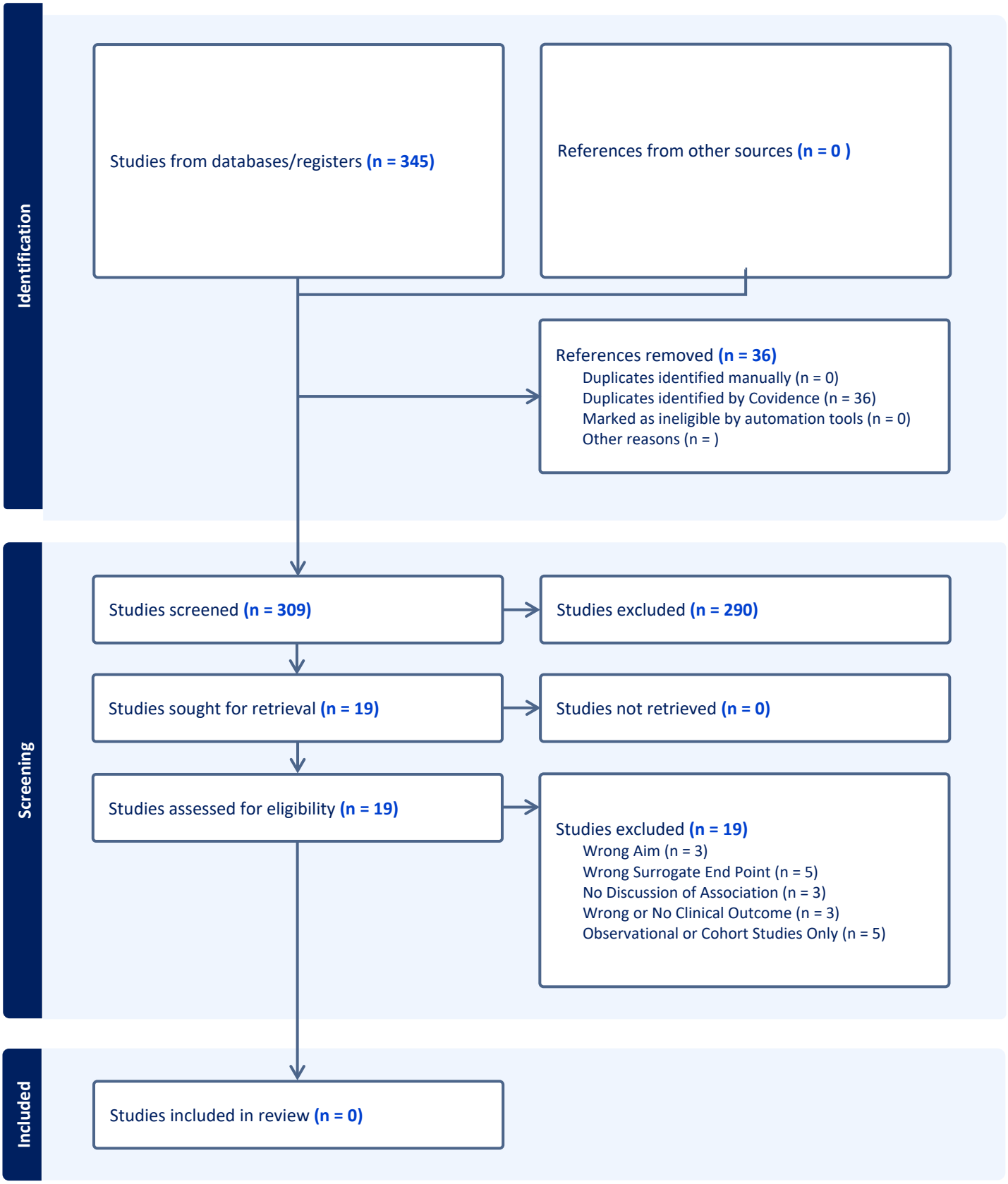

eFigure 5. Hepatitis C

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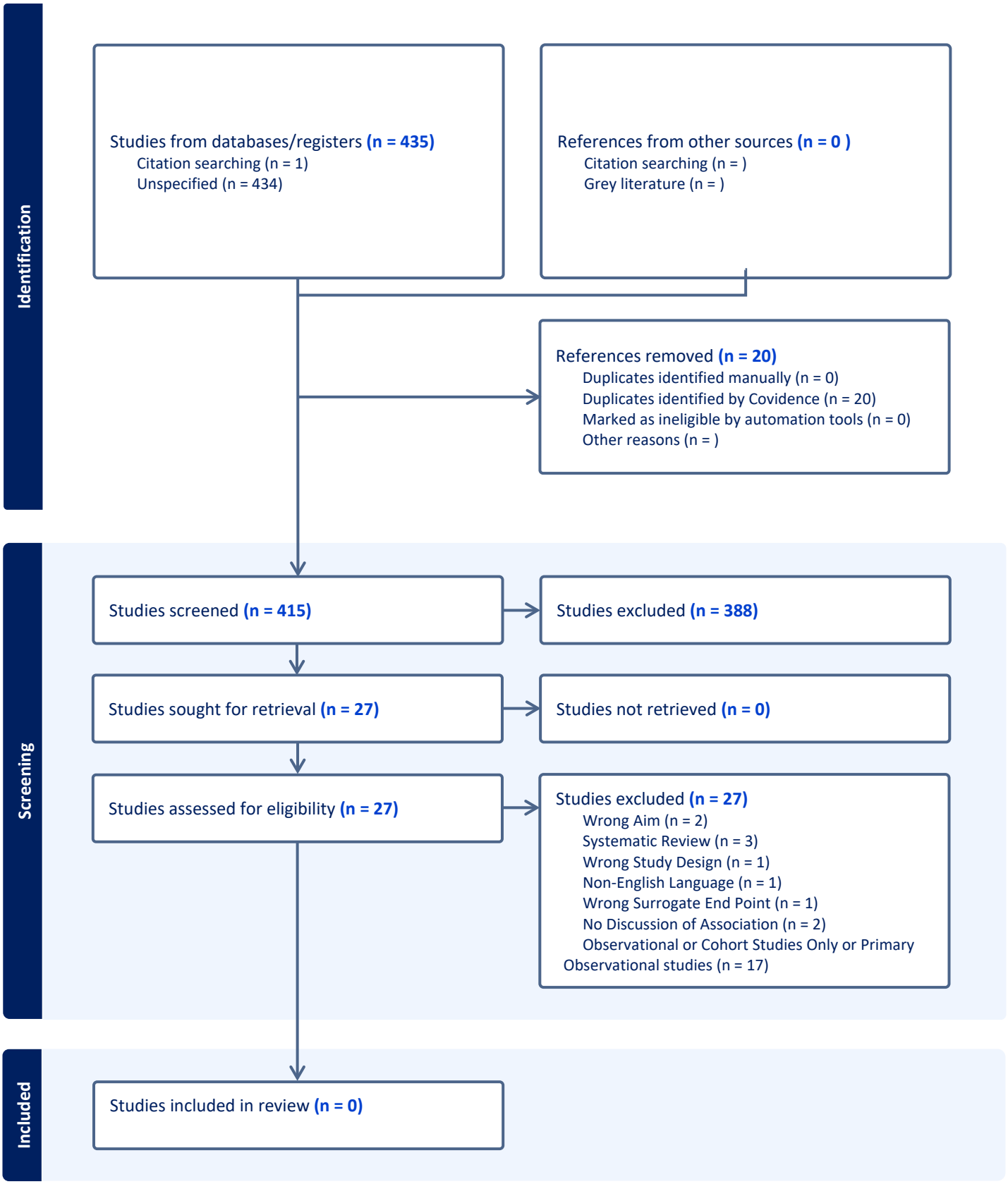

eFigure 6. Hepatitis D

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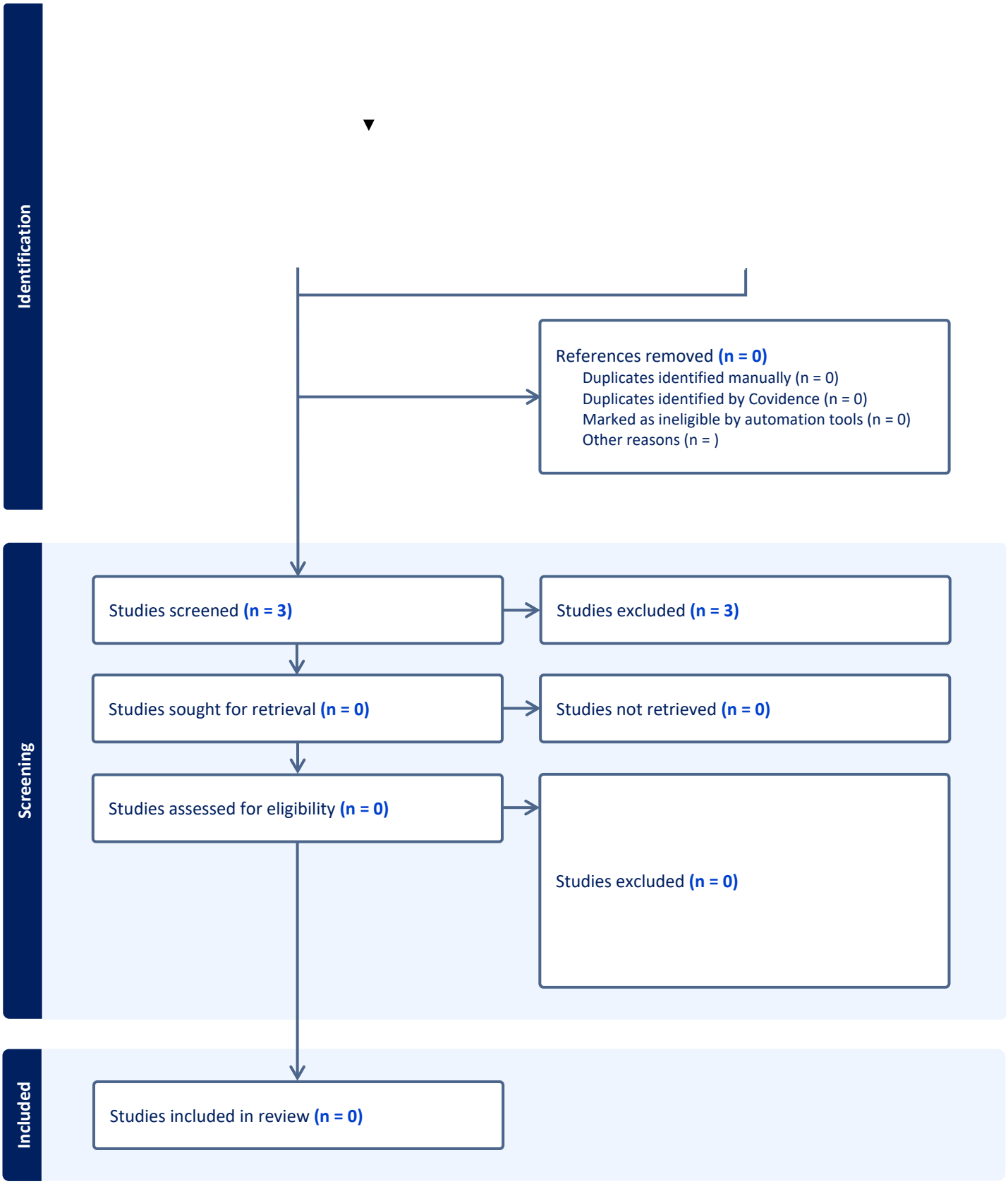

eFigure 7. Hypothyroidism

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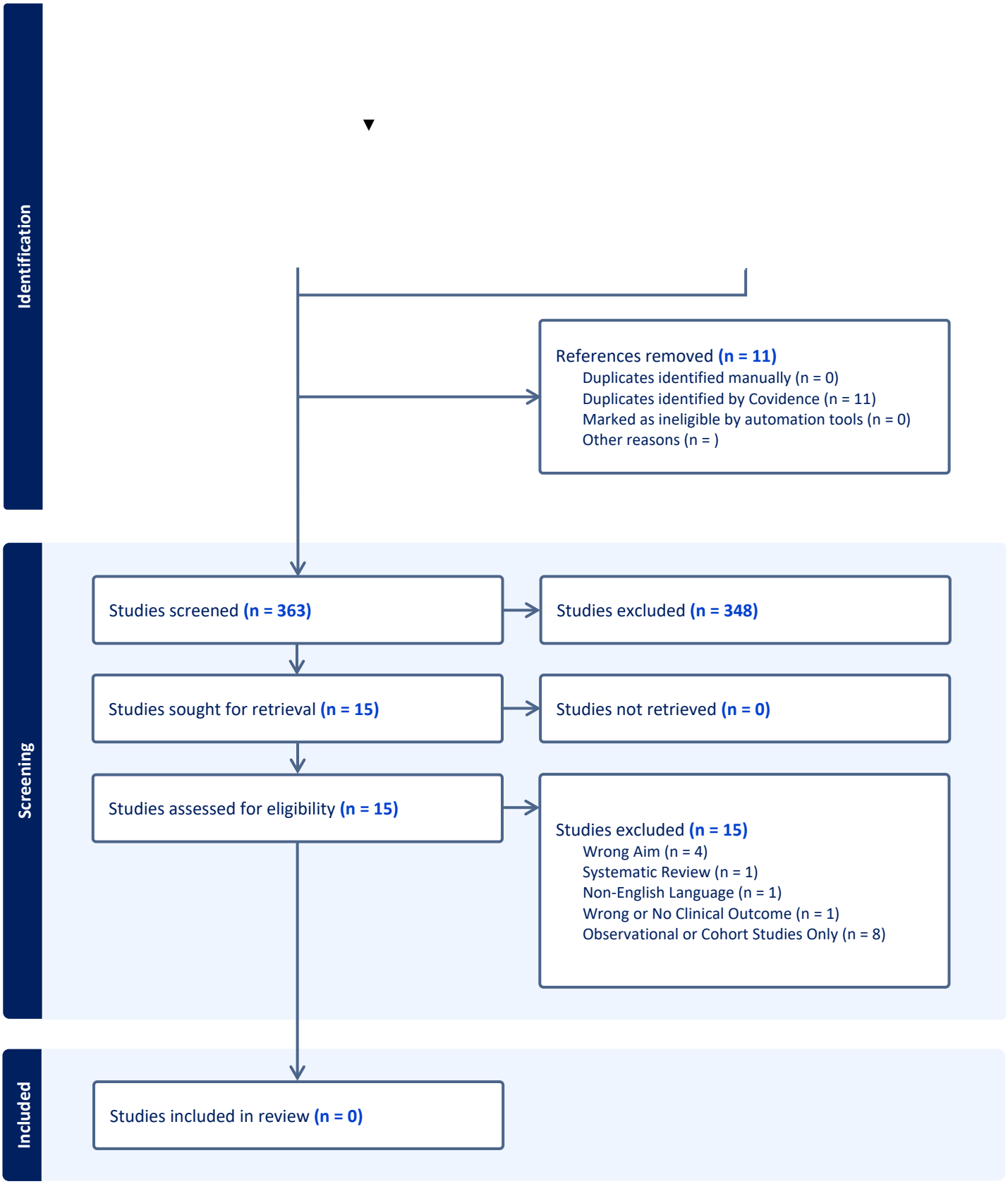
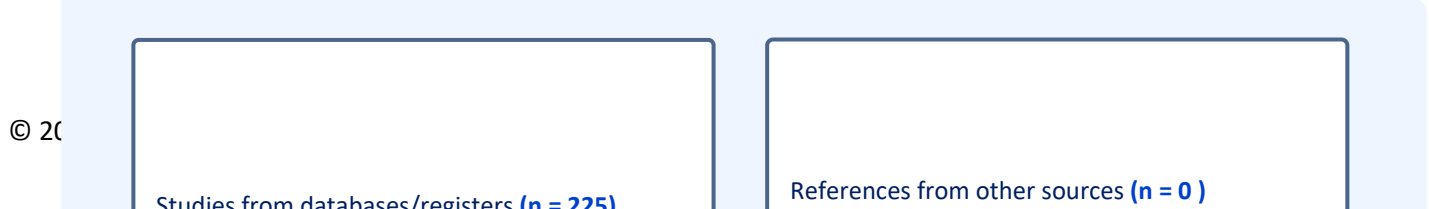


eFigure 8. Lupus nephritis



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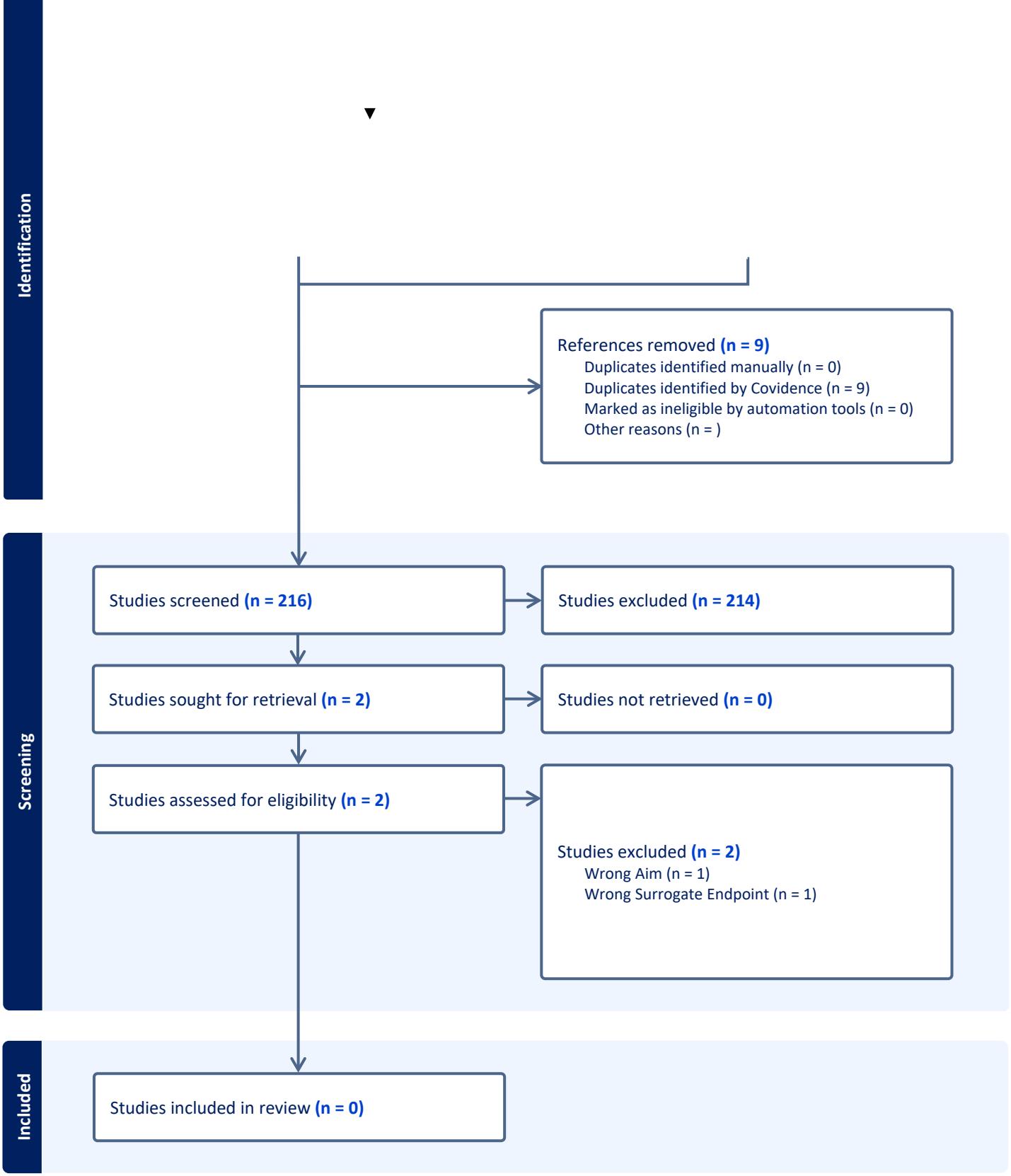
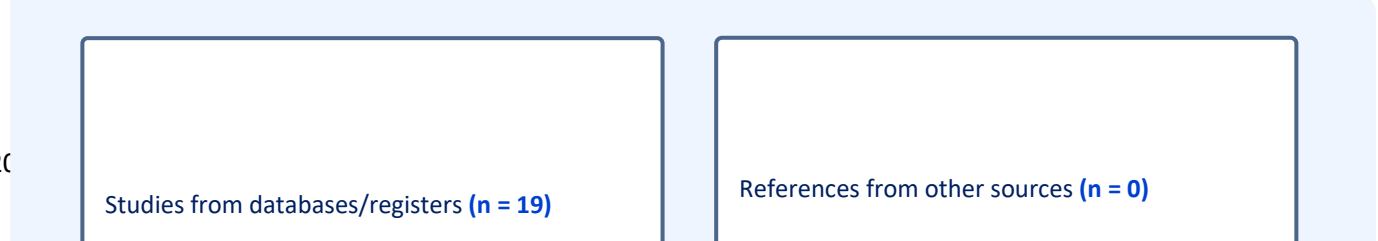


eFigure 9. Mycobacterium avium complex (MAC) lung disease



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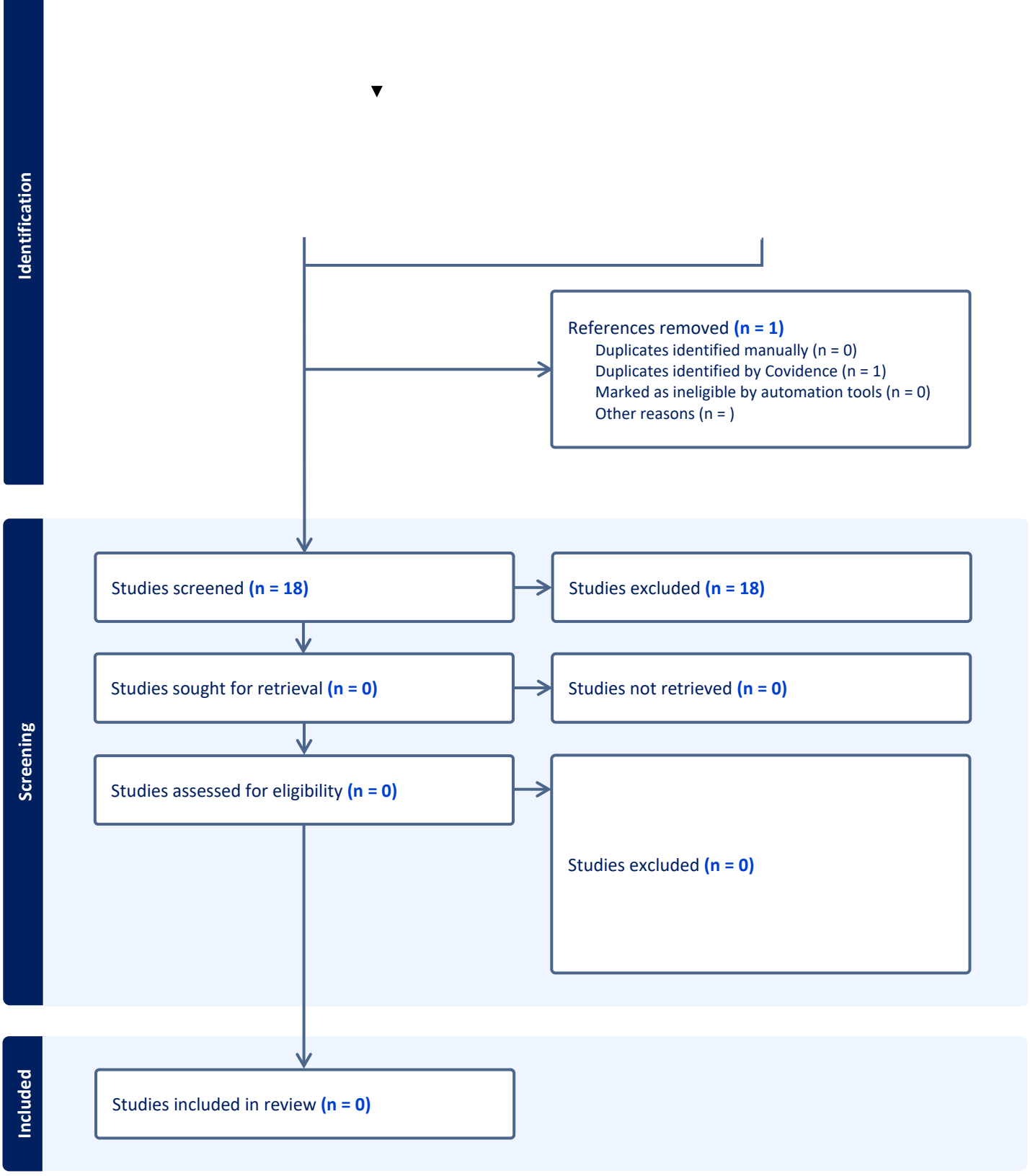
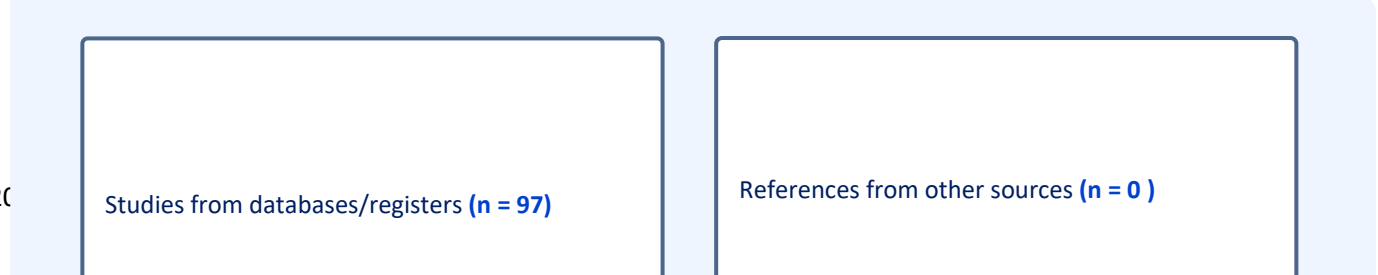


Supplementary Figure 10. Non-alcoholic steatohepatitis (NASH)



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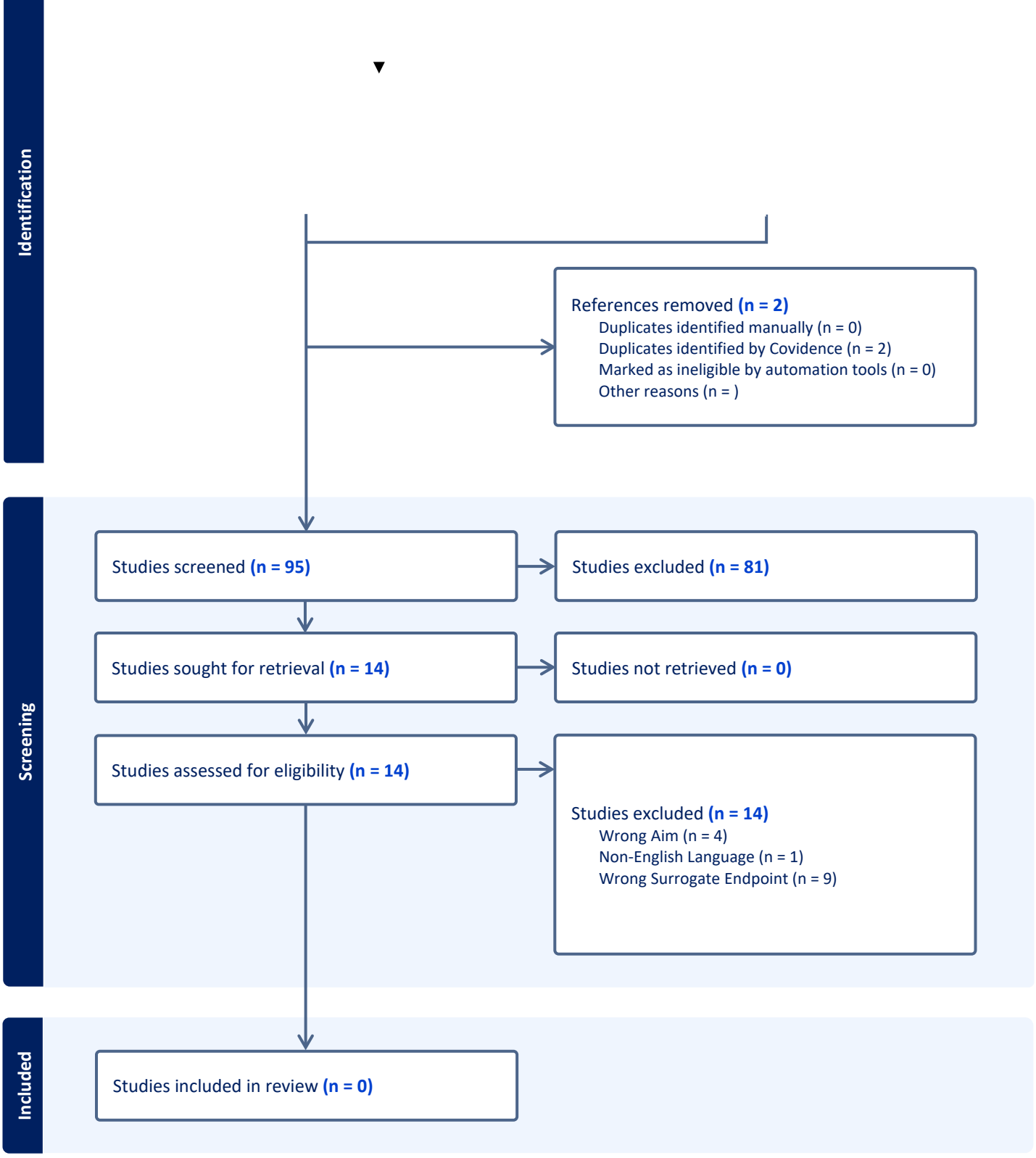
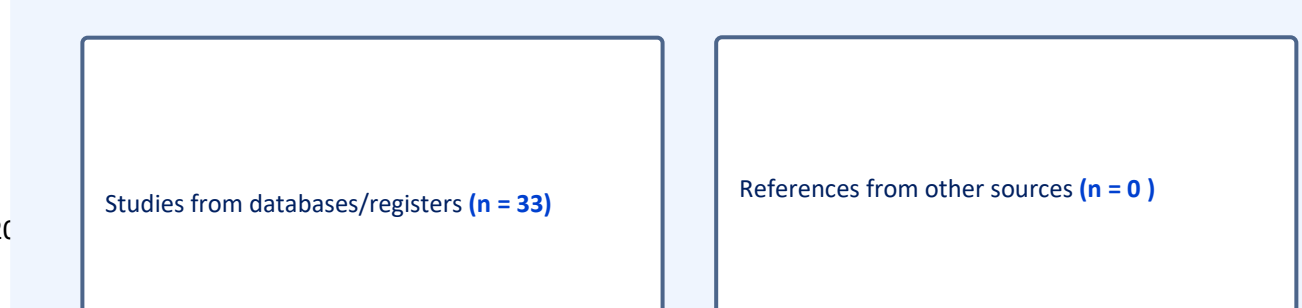


eFigure 11. Opioid use disorder



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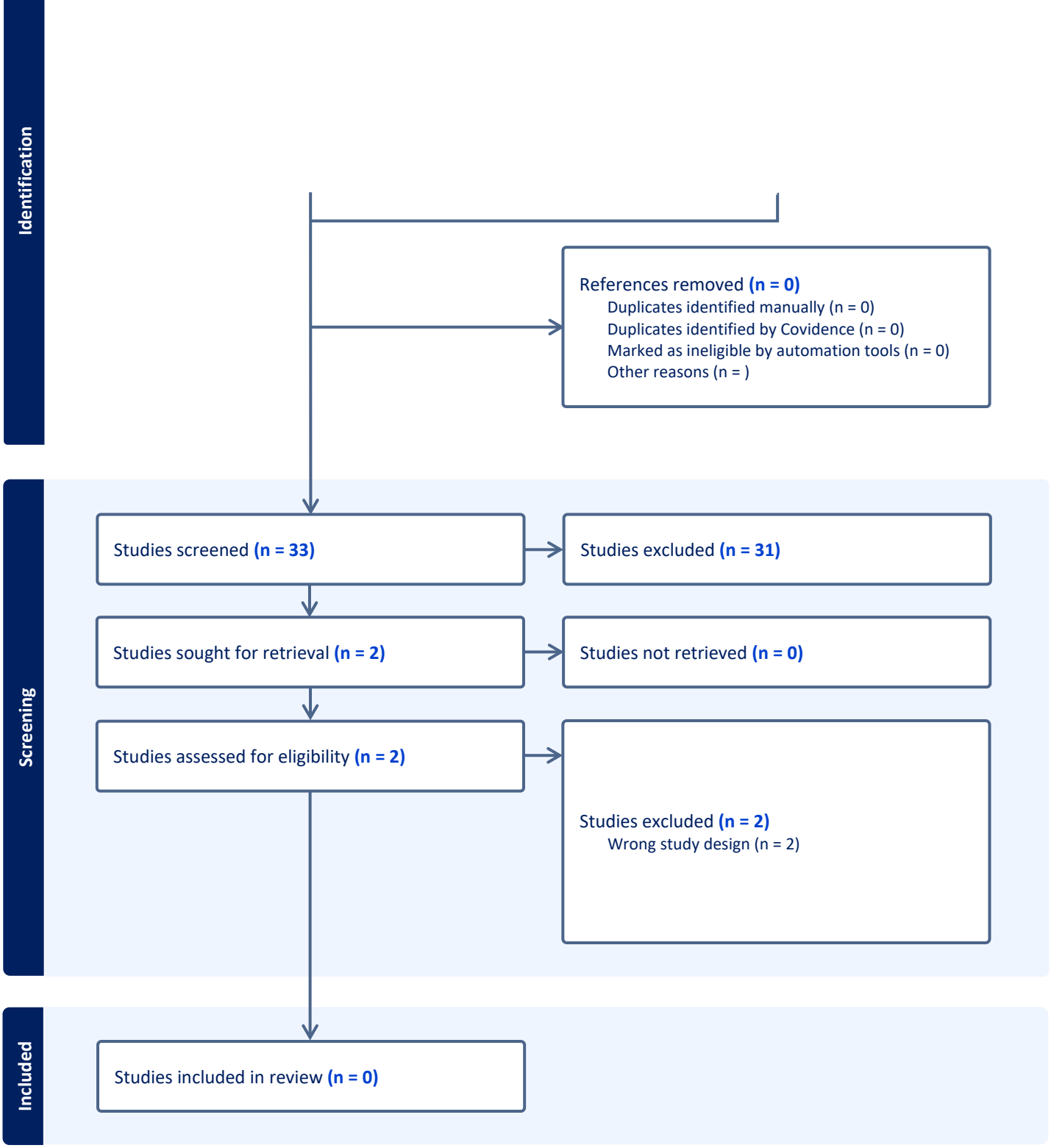
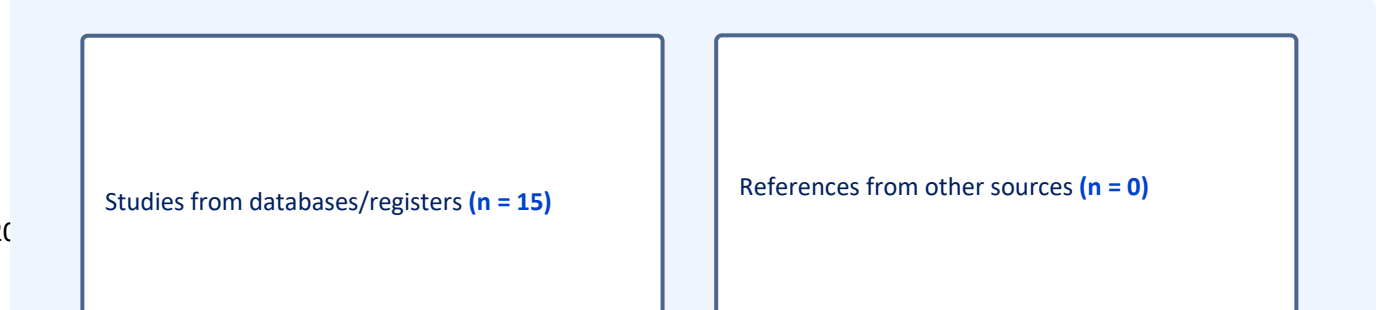


eFigure 12. Paget's Disease



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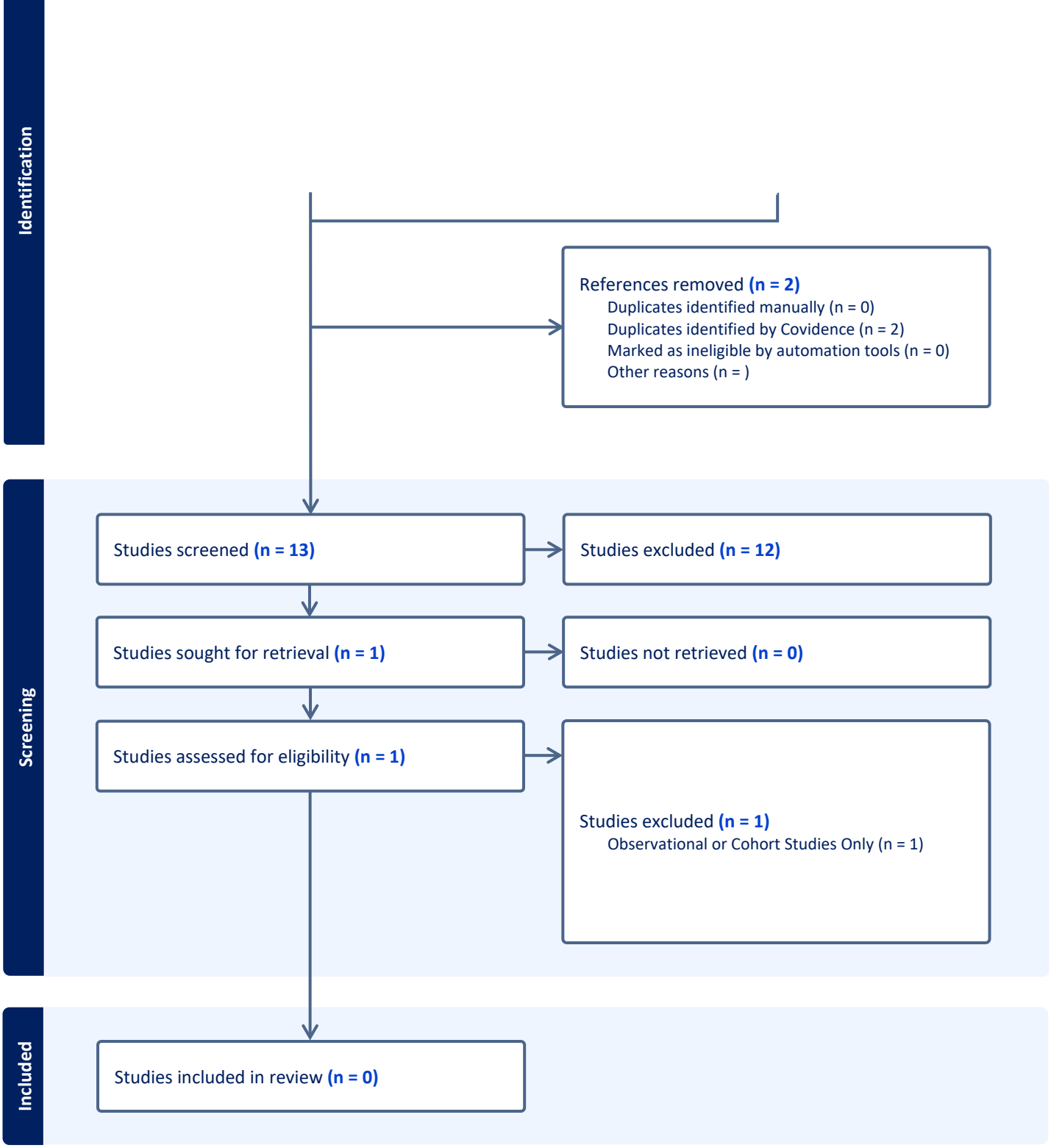
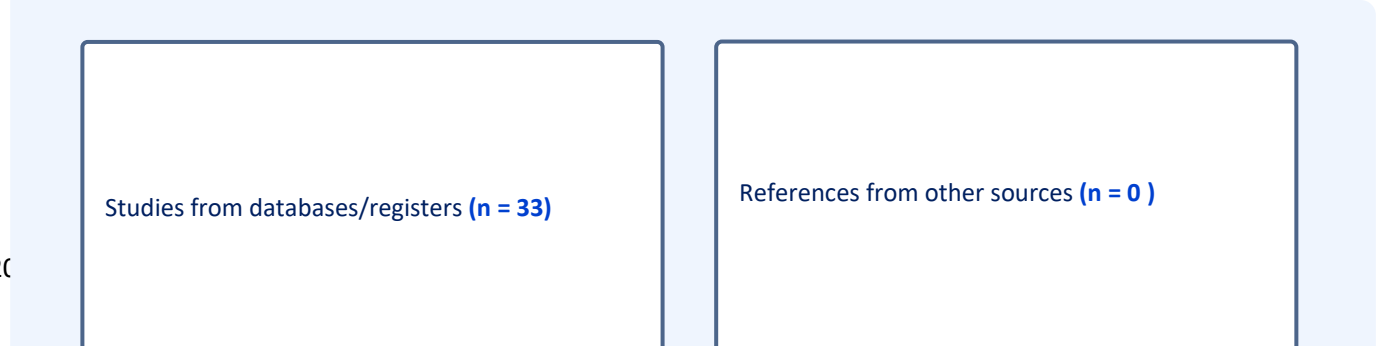


eFigure 13. Primary biliary cholangitis



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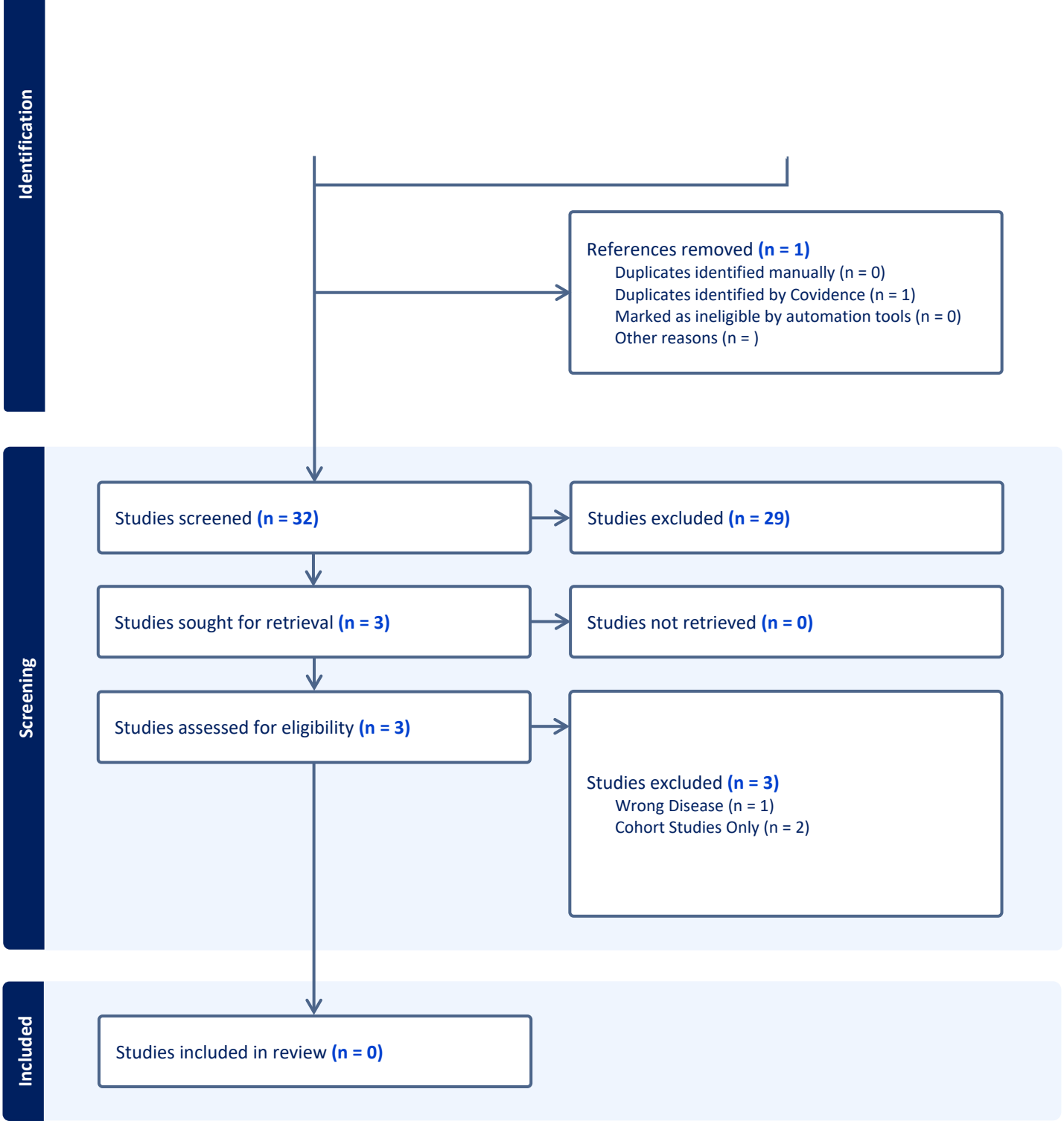
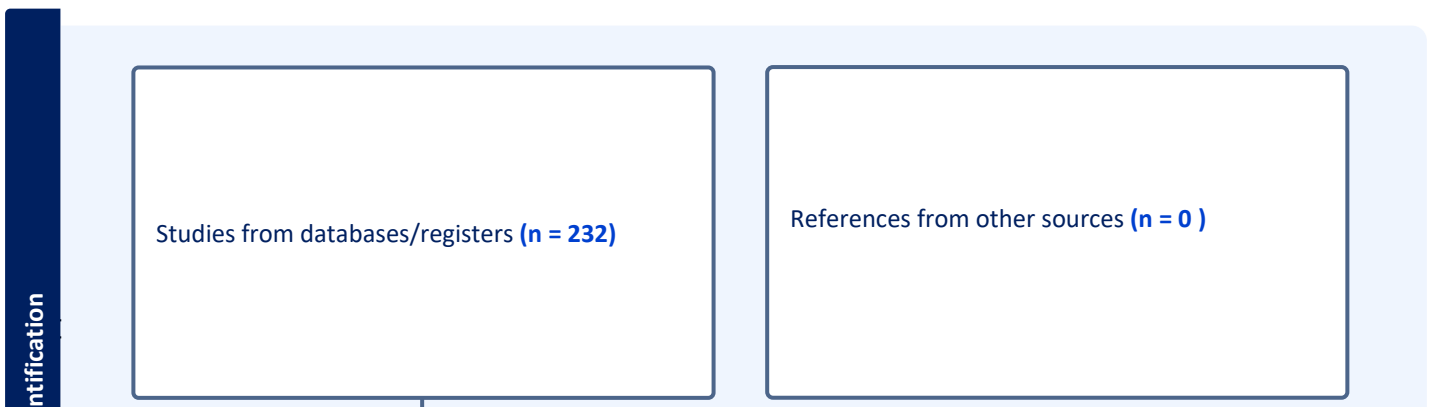
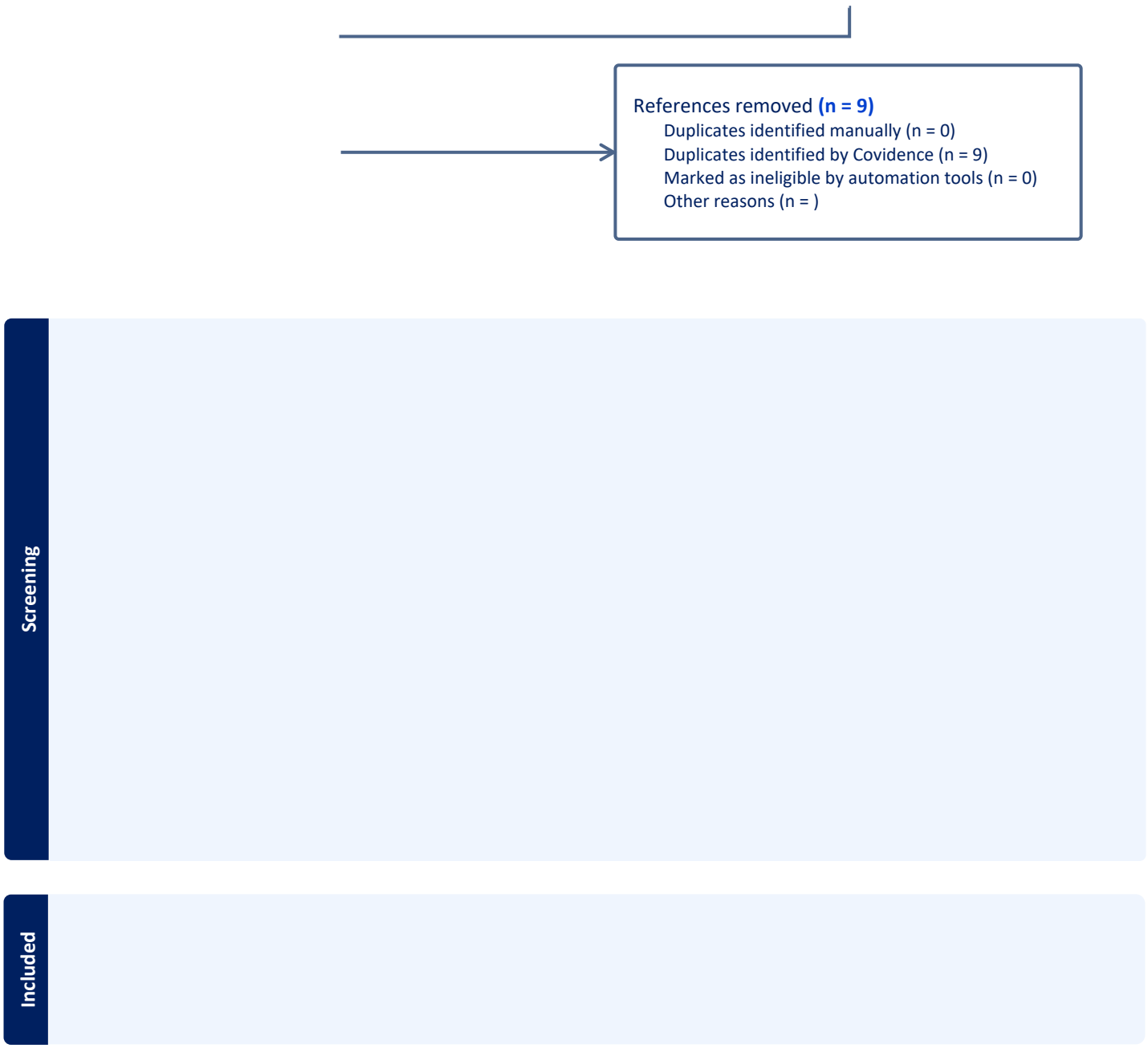
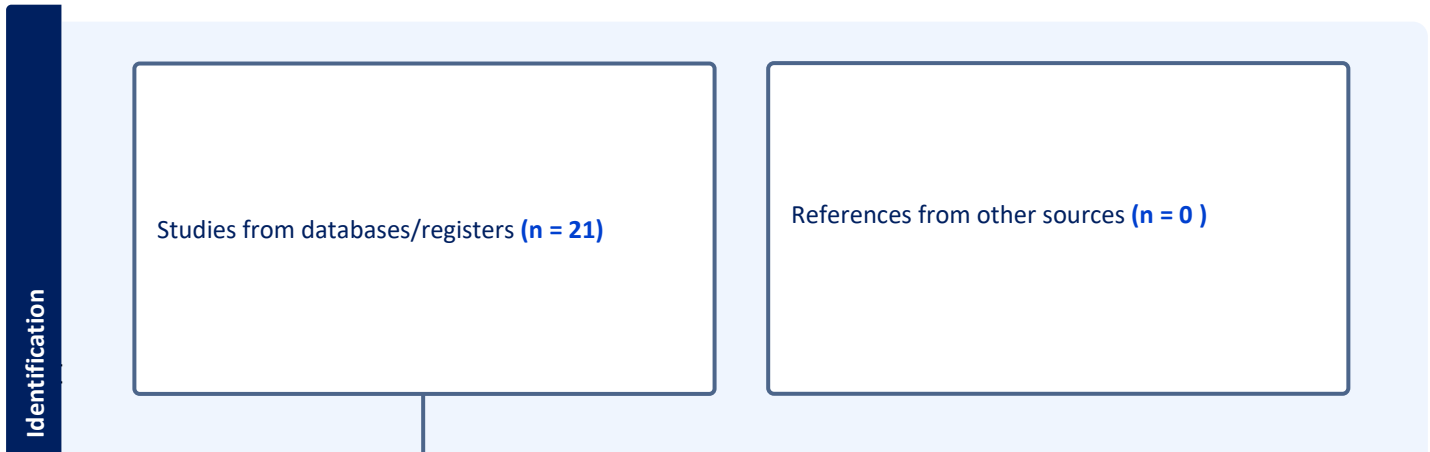


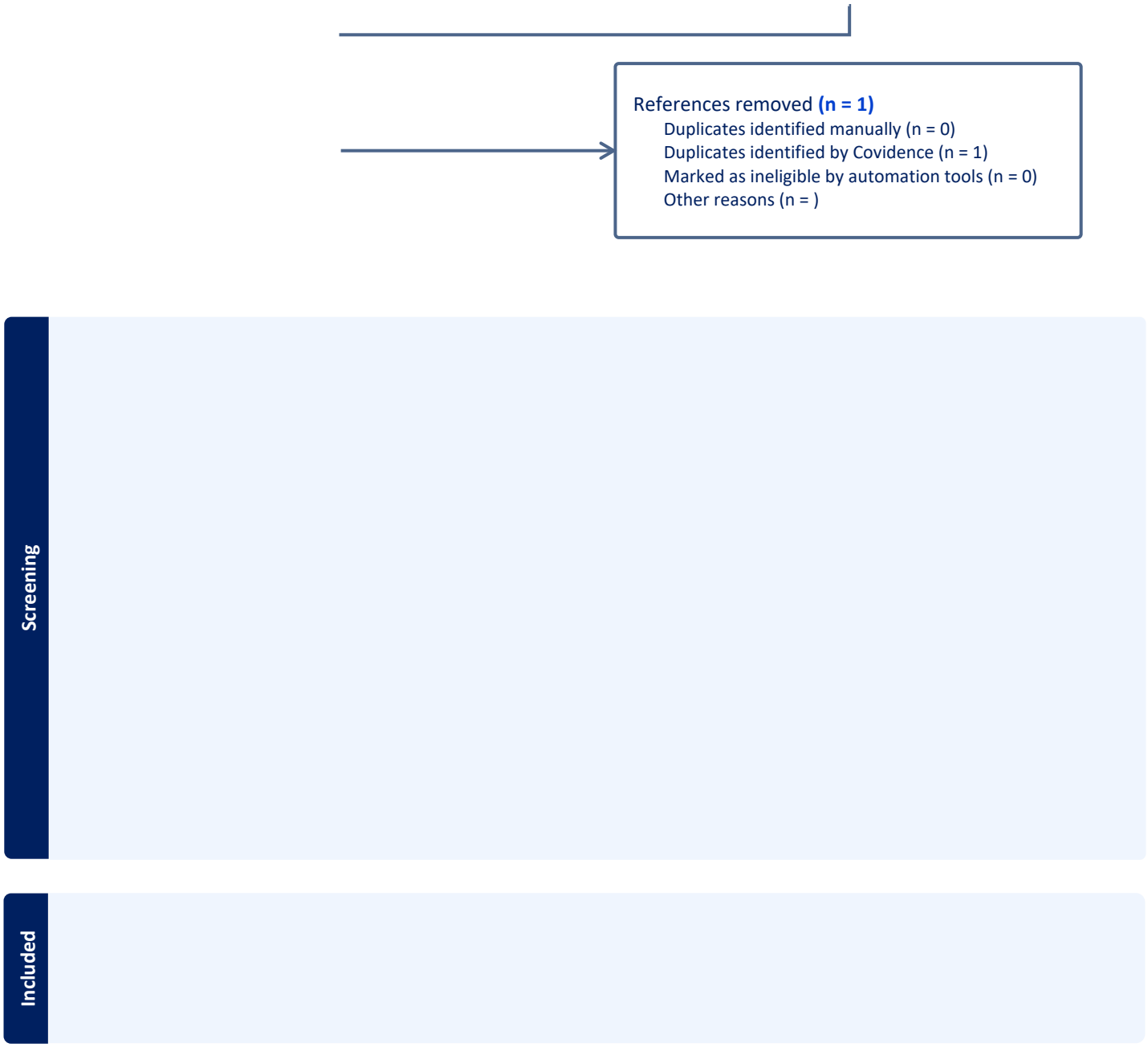
eFigure 14. Primary hyperparathyroidism



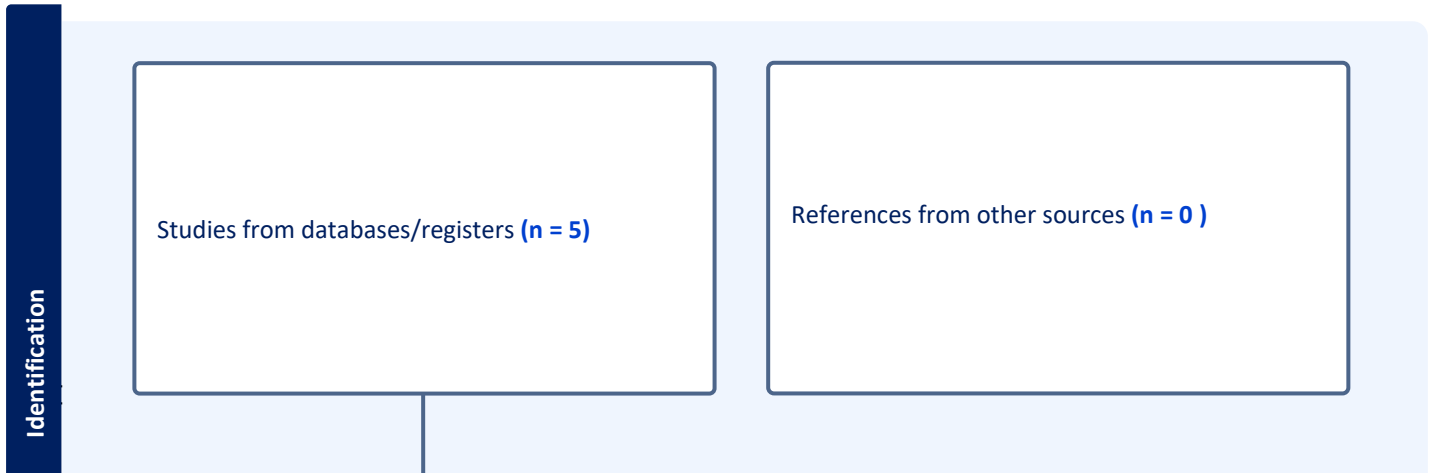


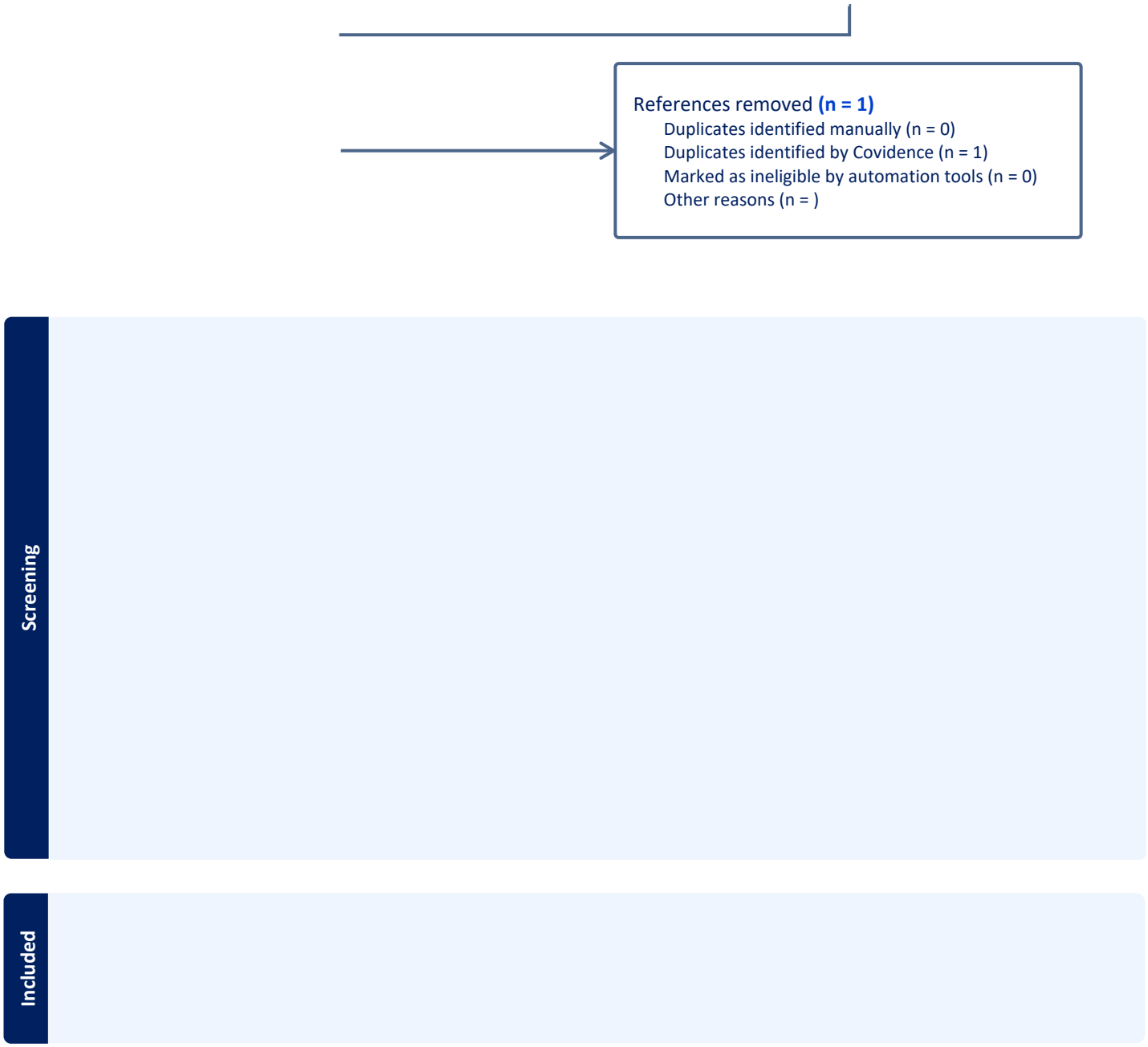
eFigure 15. Pulmonary tuberculosis



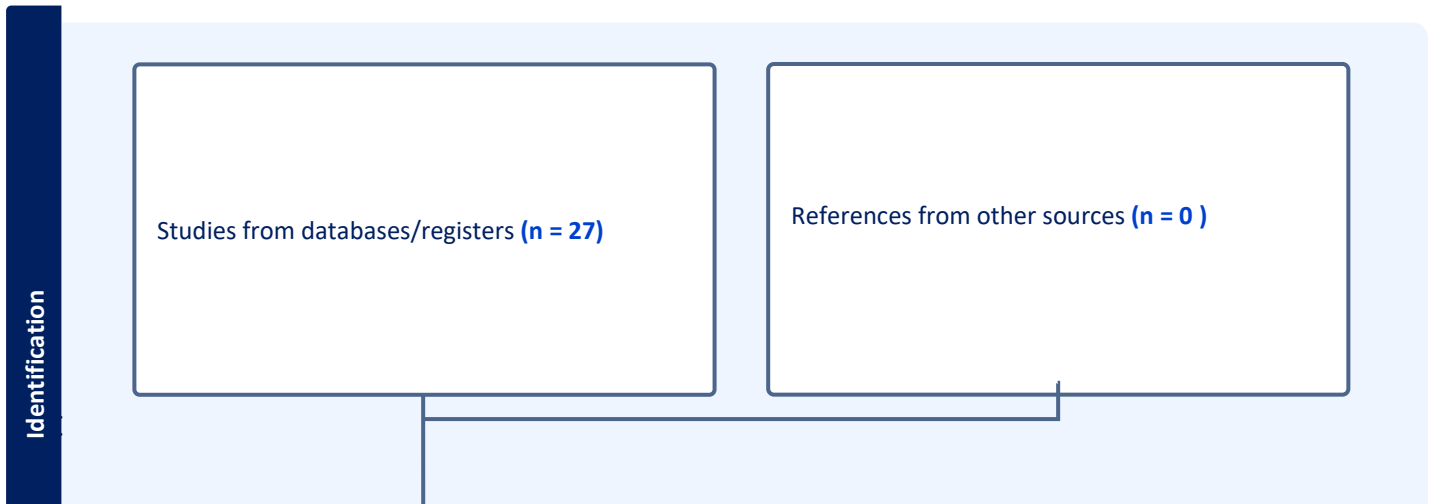


eFigure 16. Systemic sclerosis-interstitial lung disease



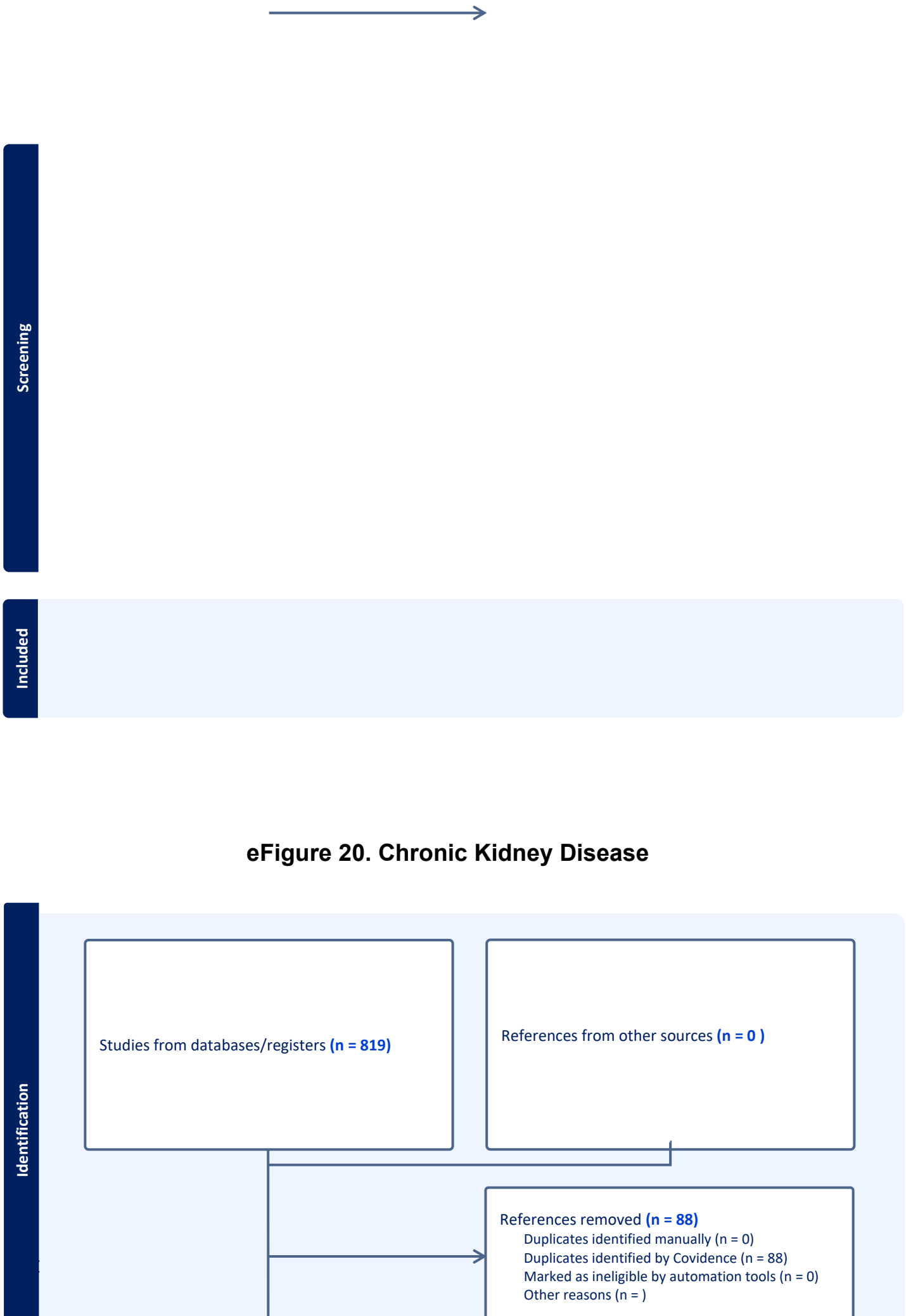


eFigure 17. Tobacco dependence



eFigure 18. Alzheimer's Disease

eFigure 19. Primary glomerular diseases associated with significant proteinuria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eFigure 20. Chronic Kidney Disease
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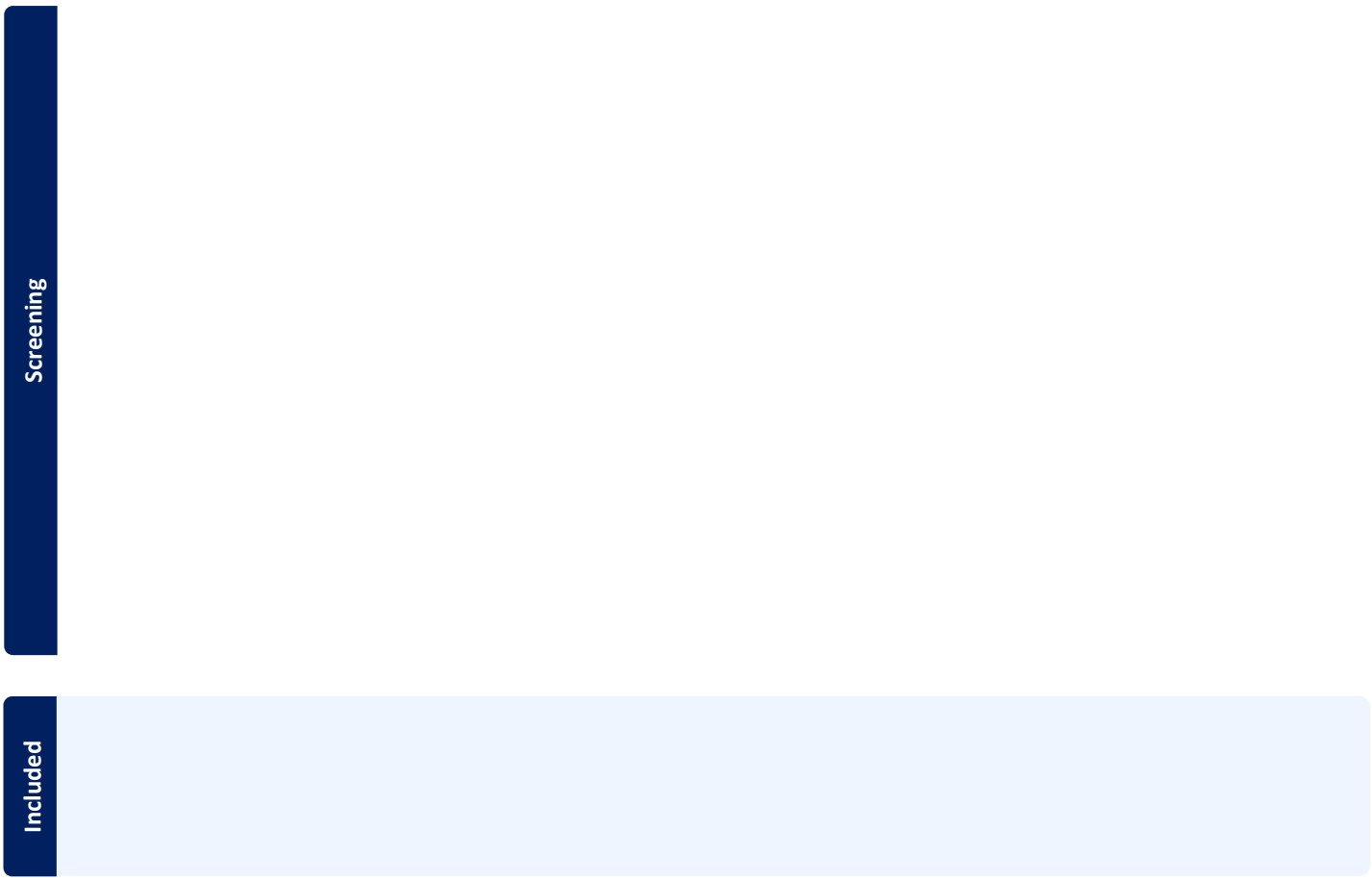
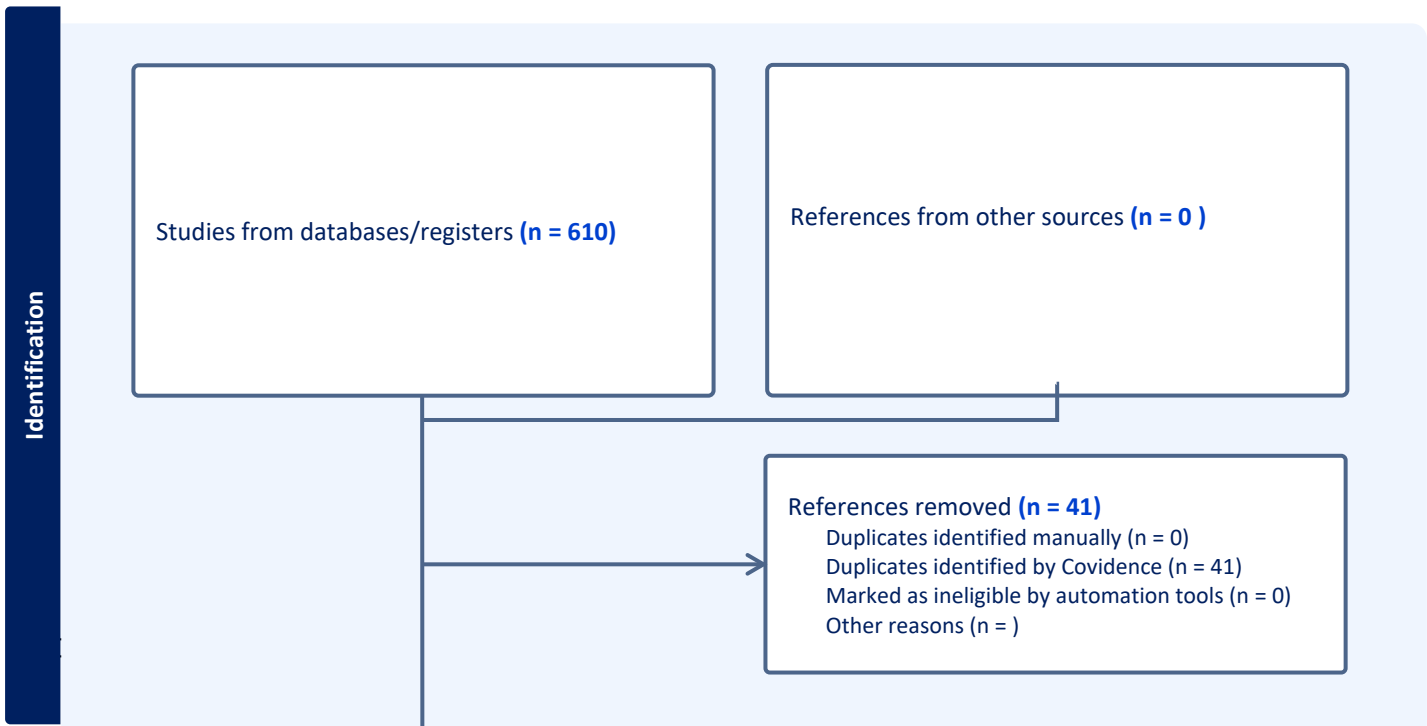


eFigure 21. Chronic Obstructive Pulmonary Disease



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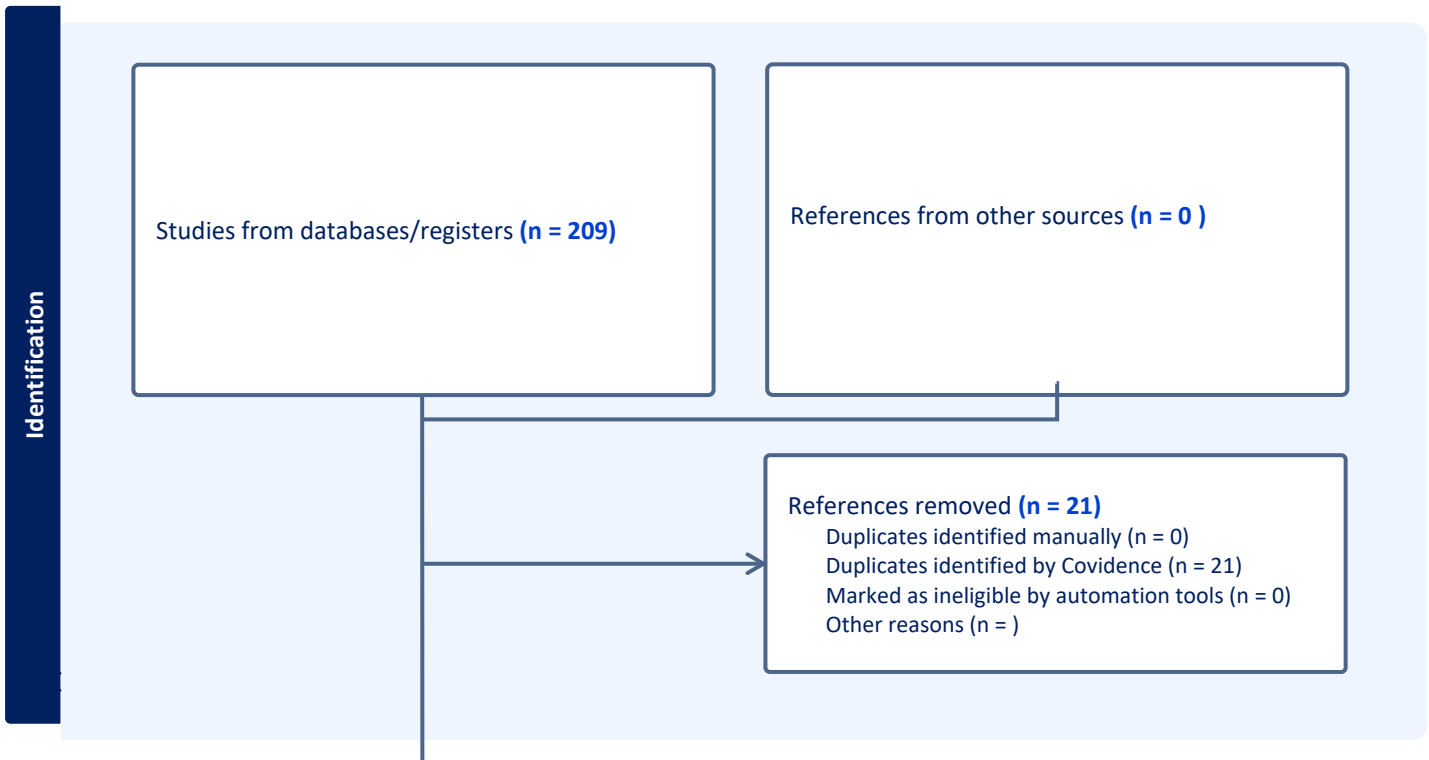
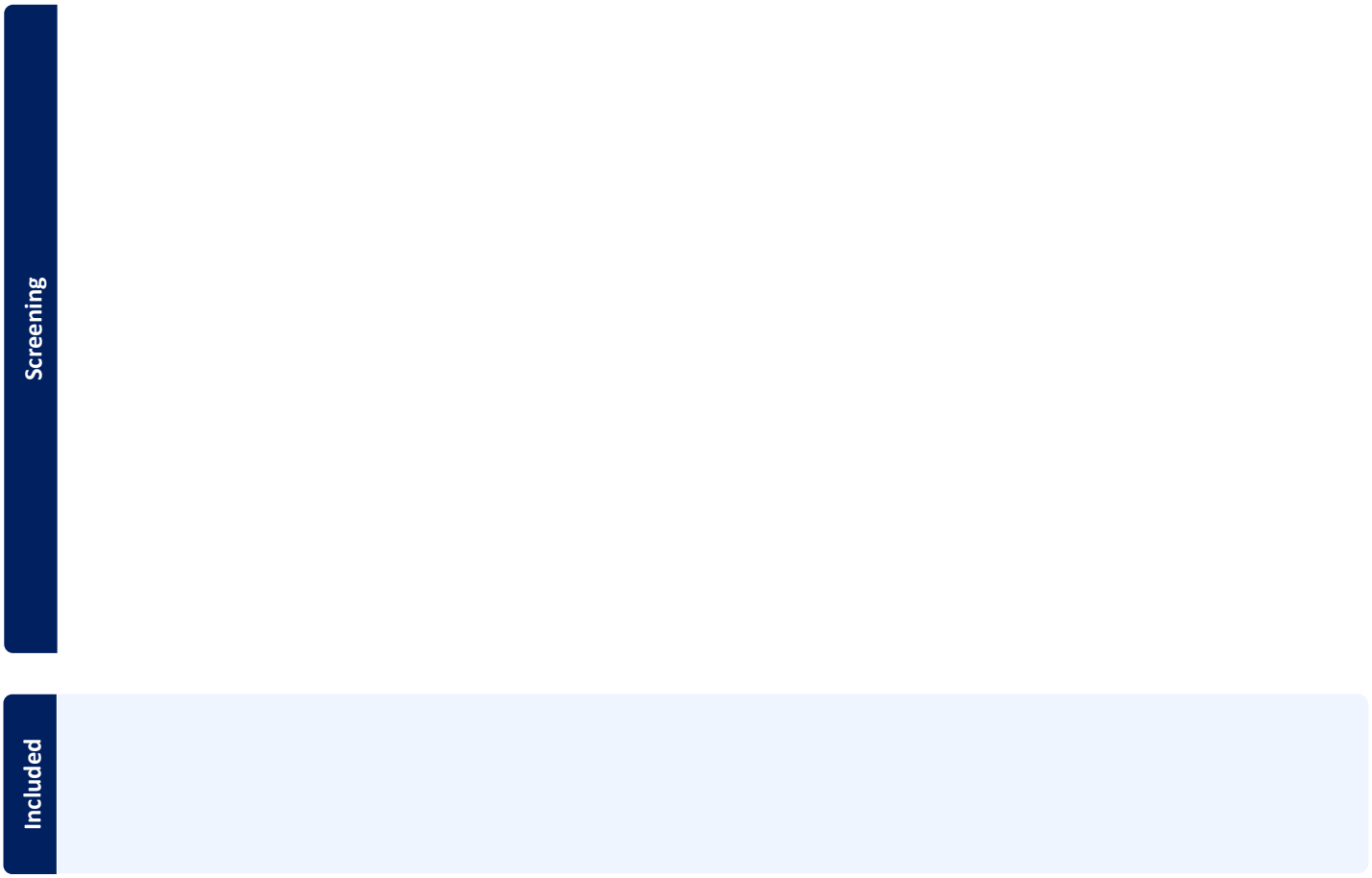
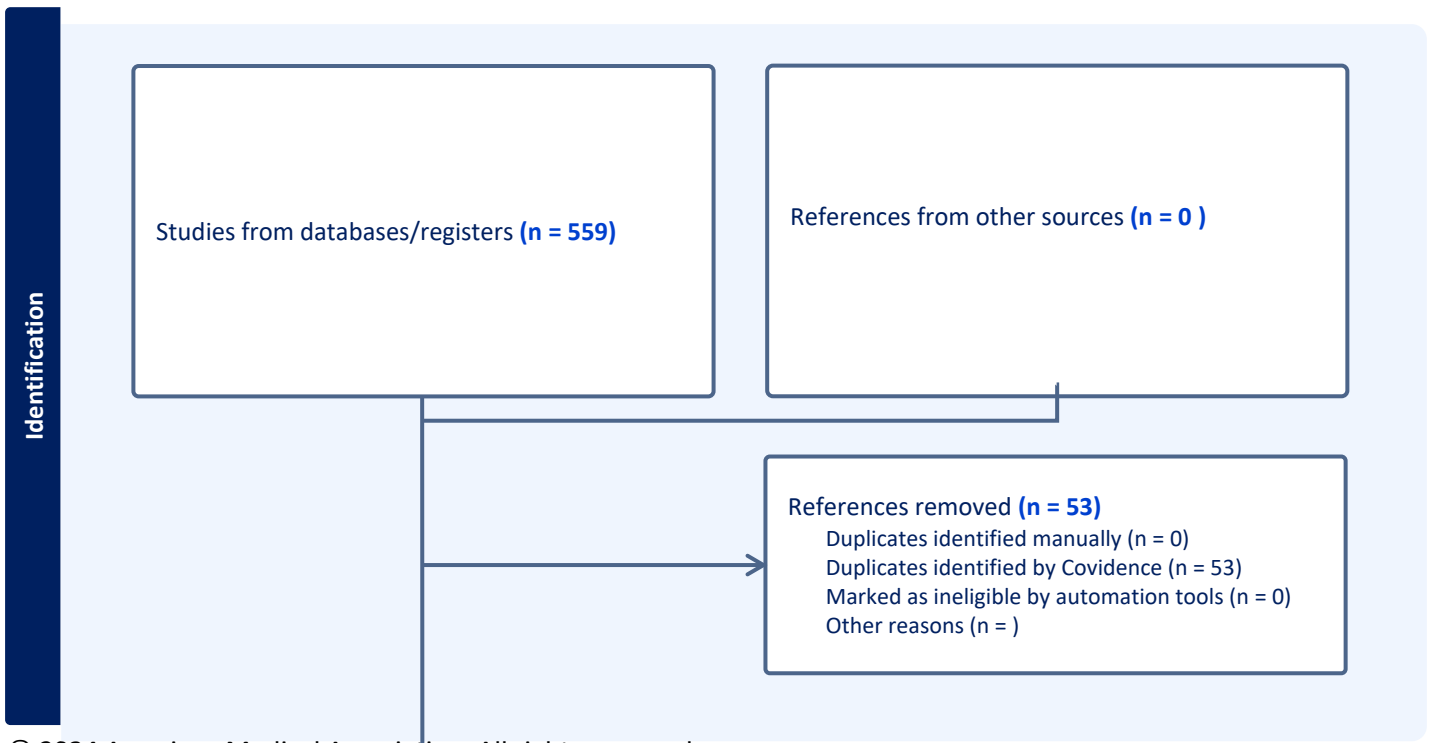
eFigure 22. Gout





eFigure 23. Human Immunodeficiency Virus (HIV)



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Screening

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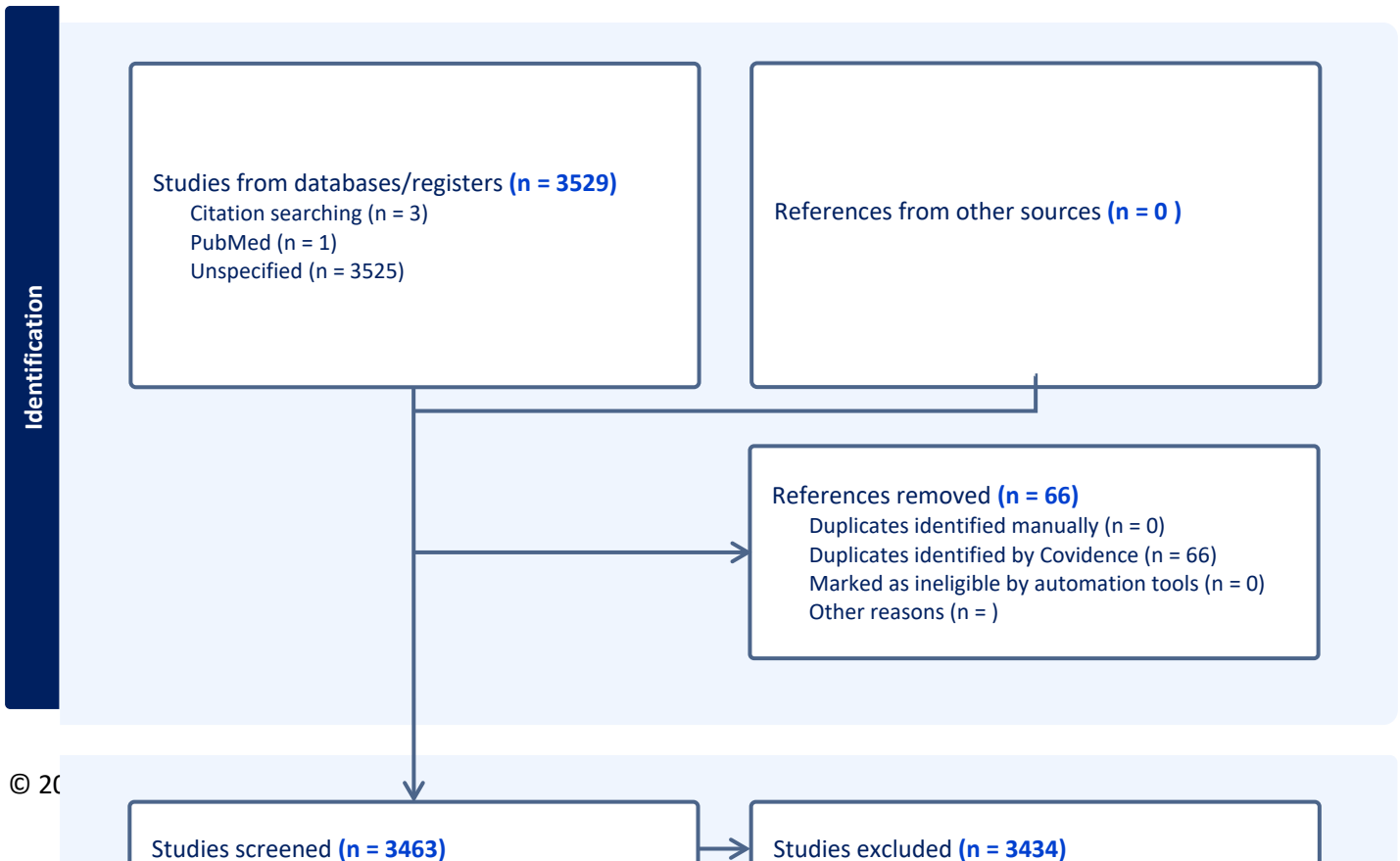
eFigure 24. Hypercholesterolemia



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Screening

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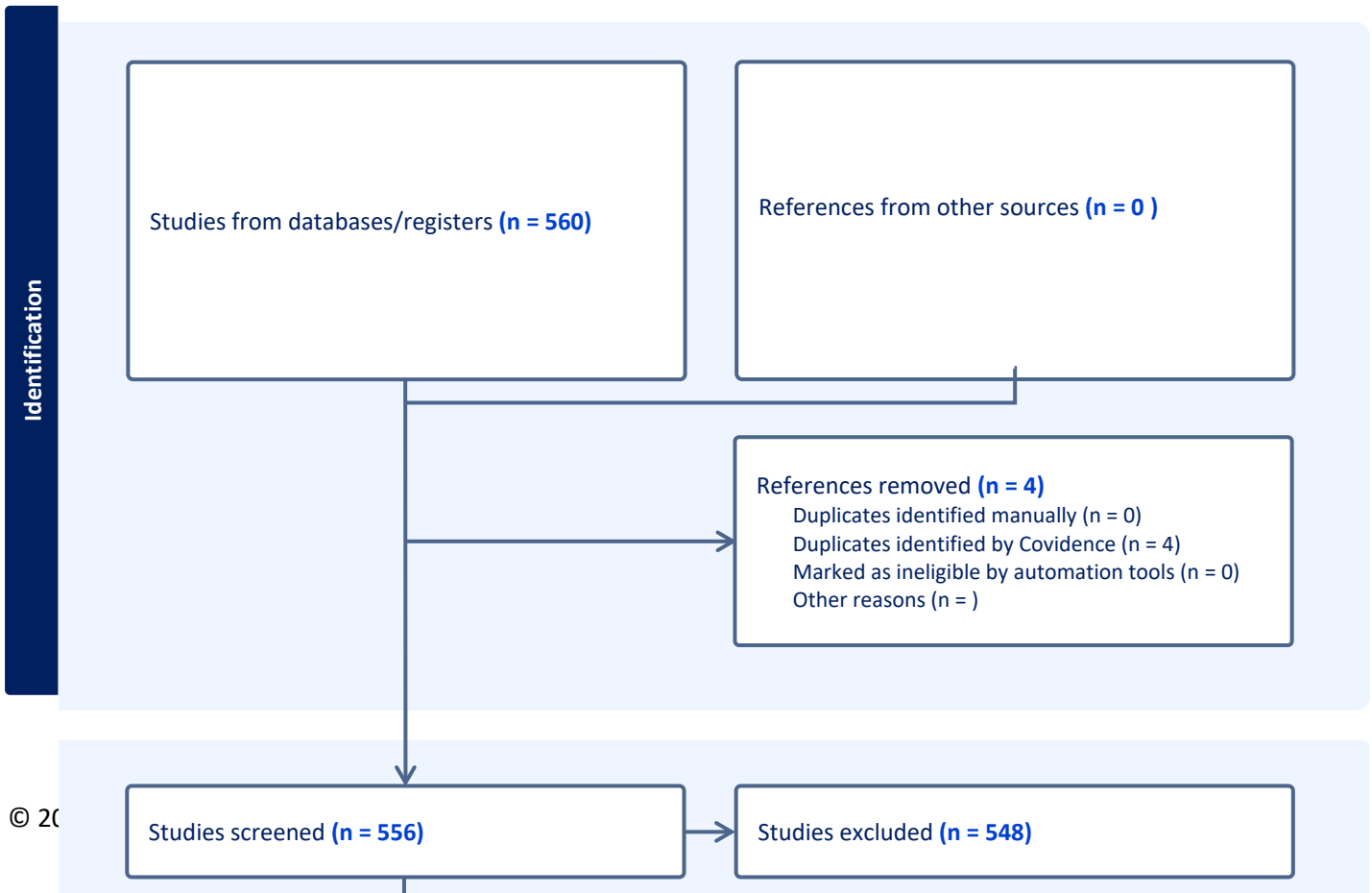
eFigure 25. Hyperphosphatemia



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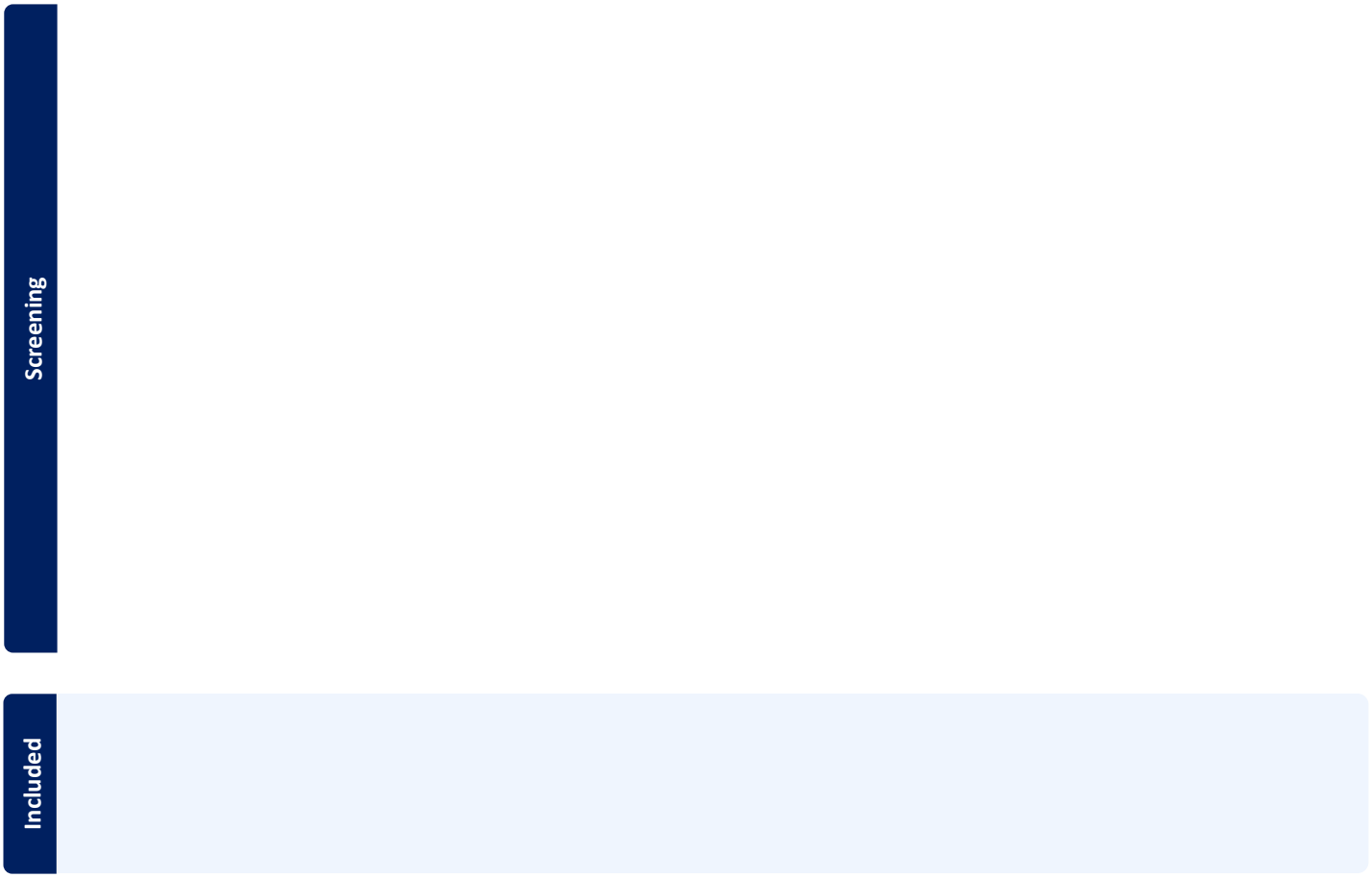

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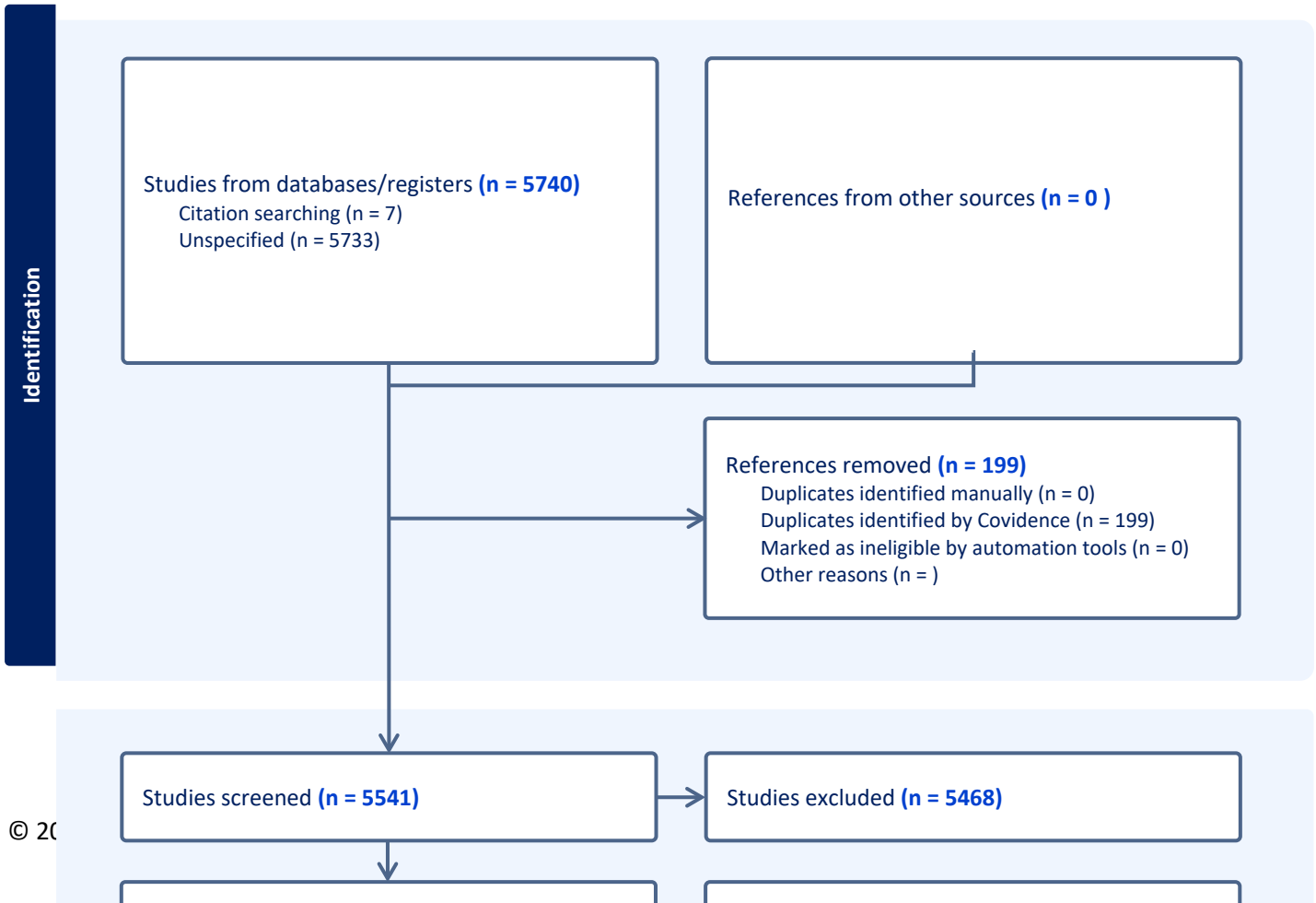

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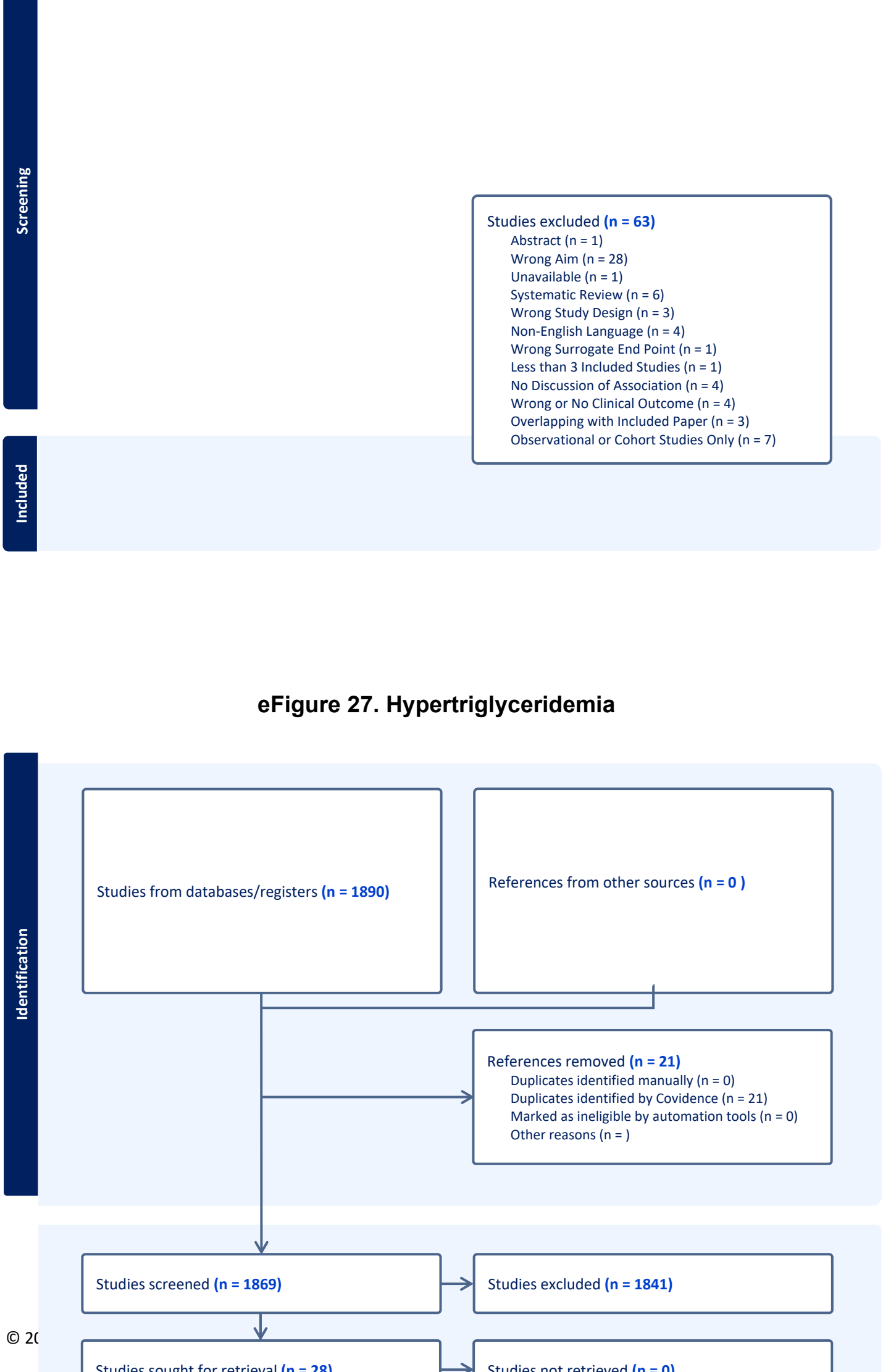

eFigure 27. Hypertriglyceridemia

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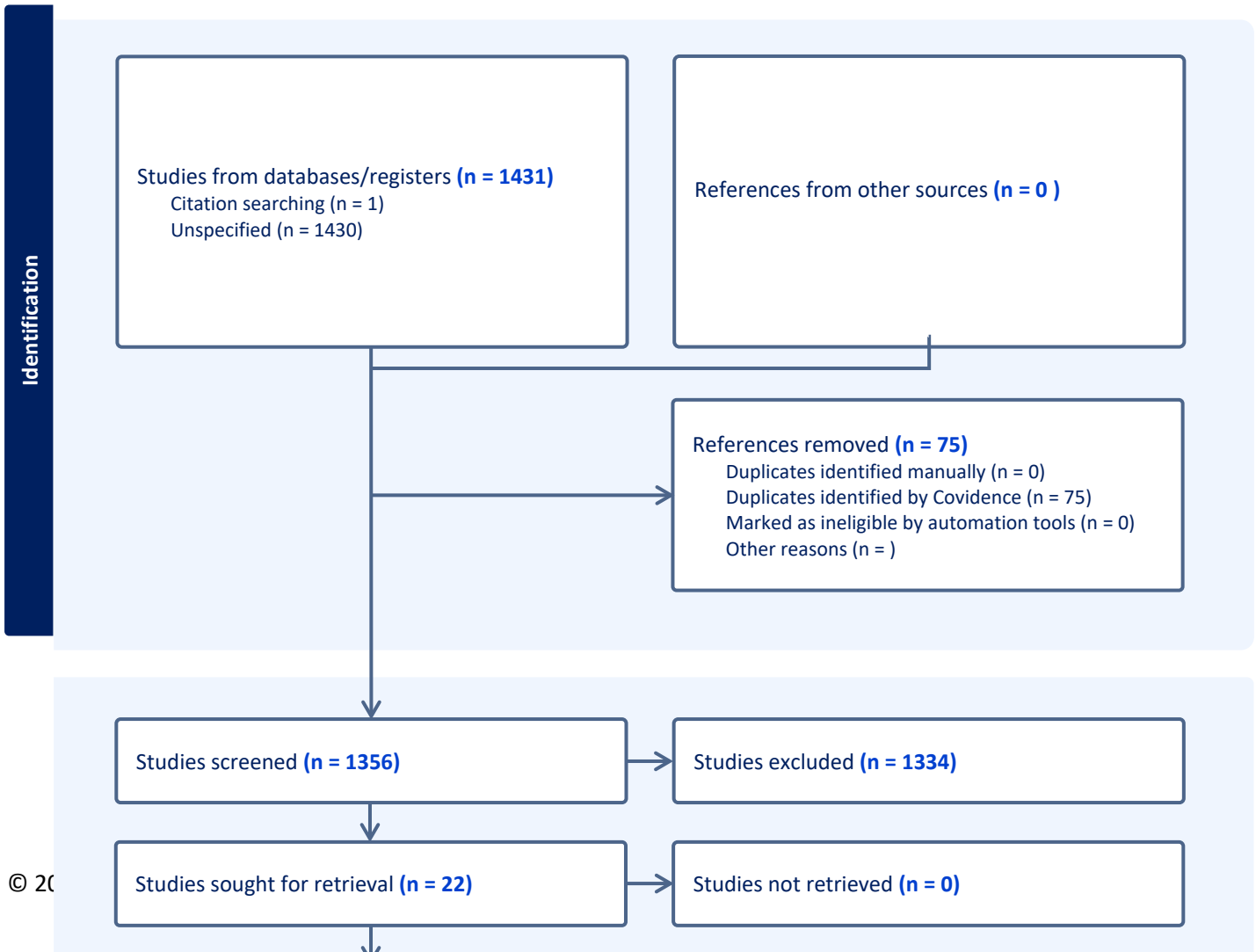
eFigure 28. Osteoporosis



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Screening

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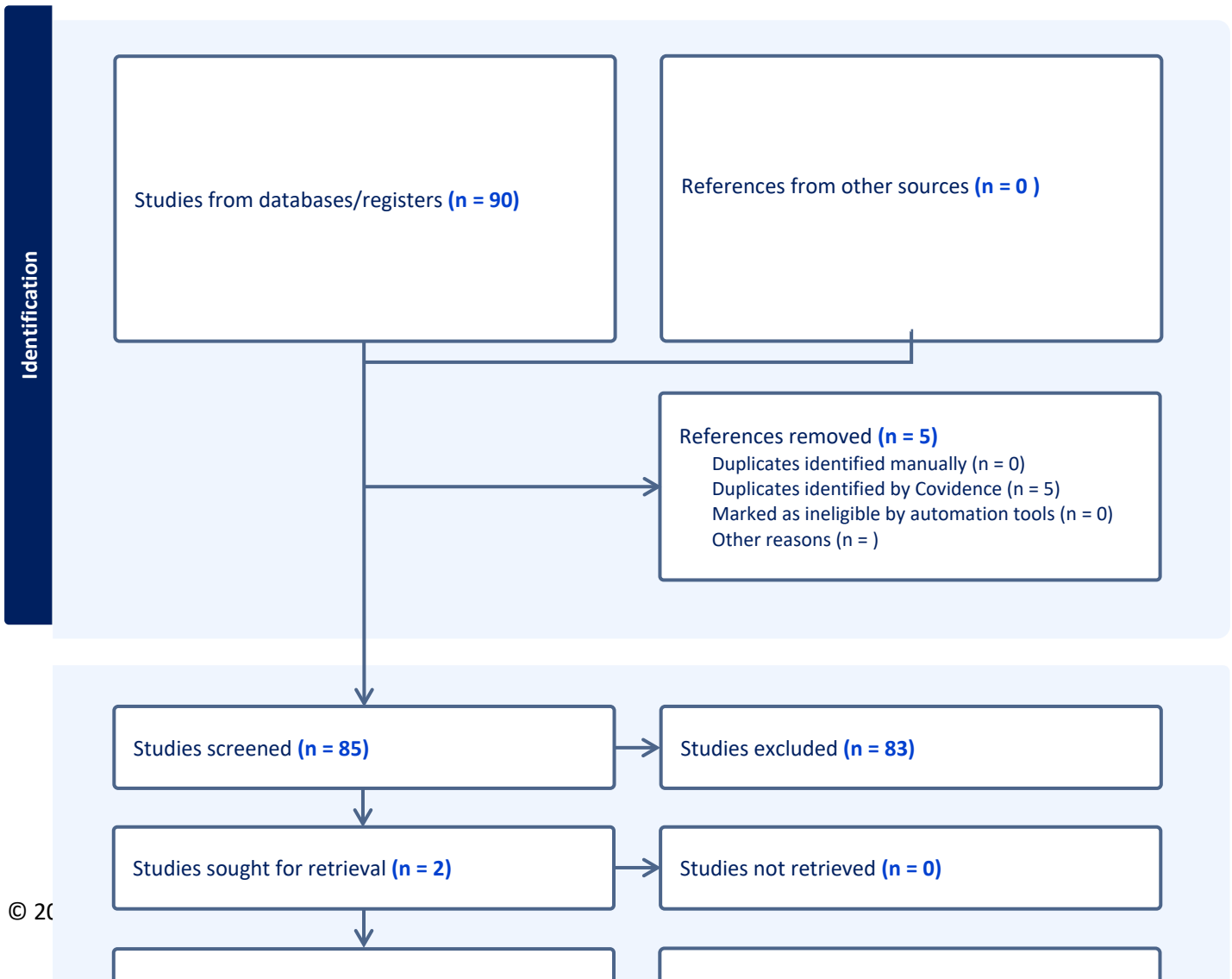
eFigure 29. Pulmonary fibrosis



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Screening

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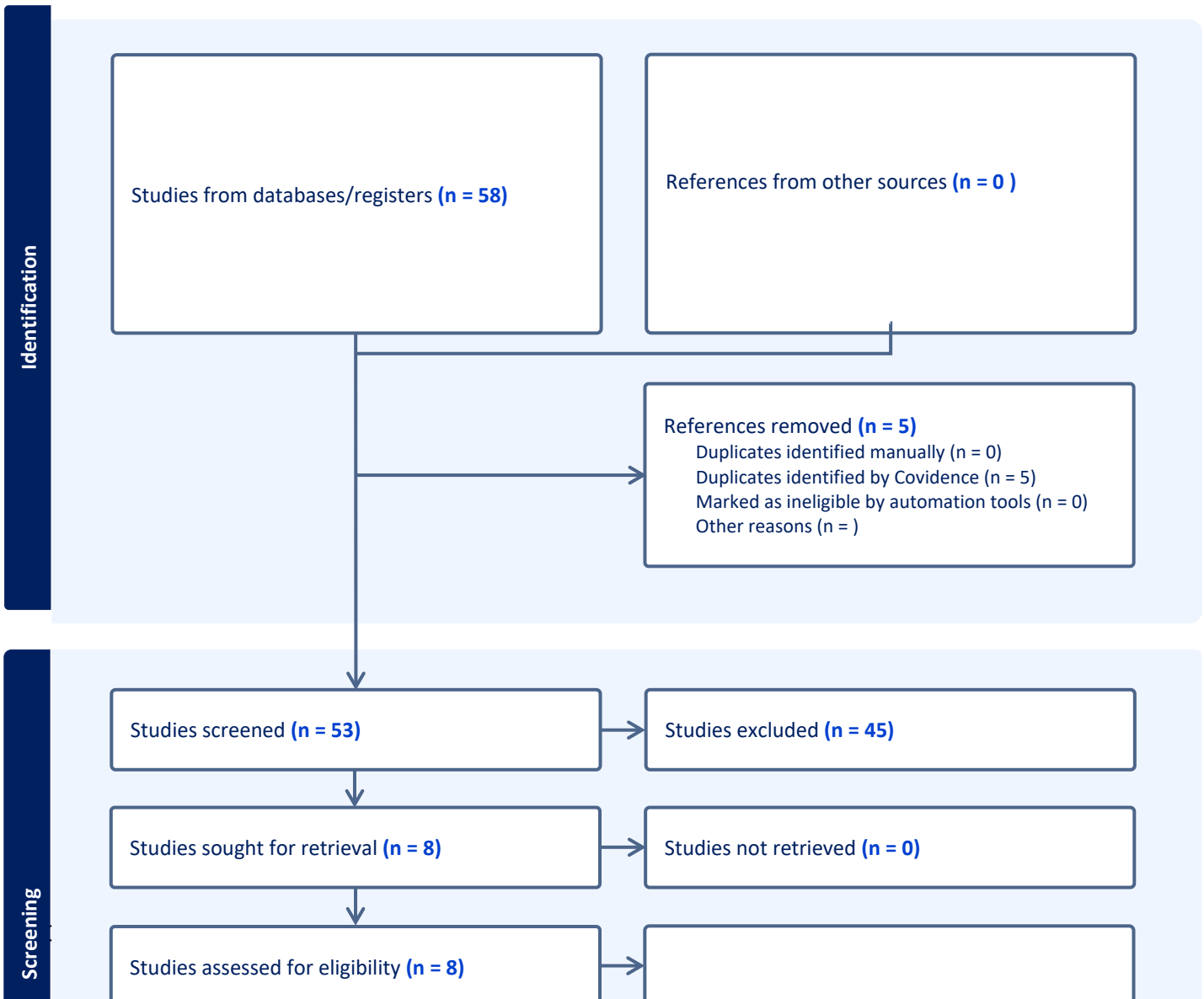
eFigure 30. Secondary hyperparathyroidism



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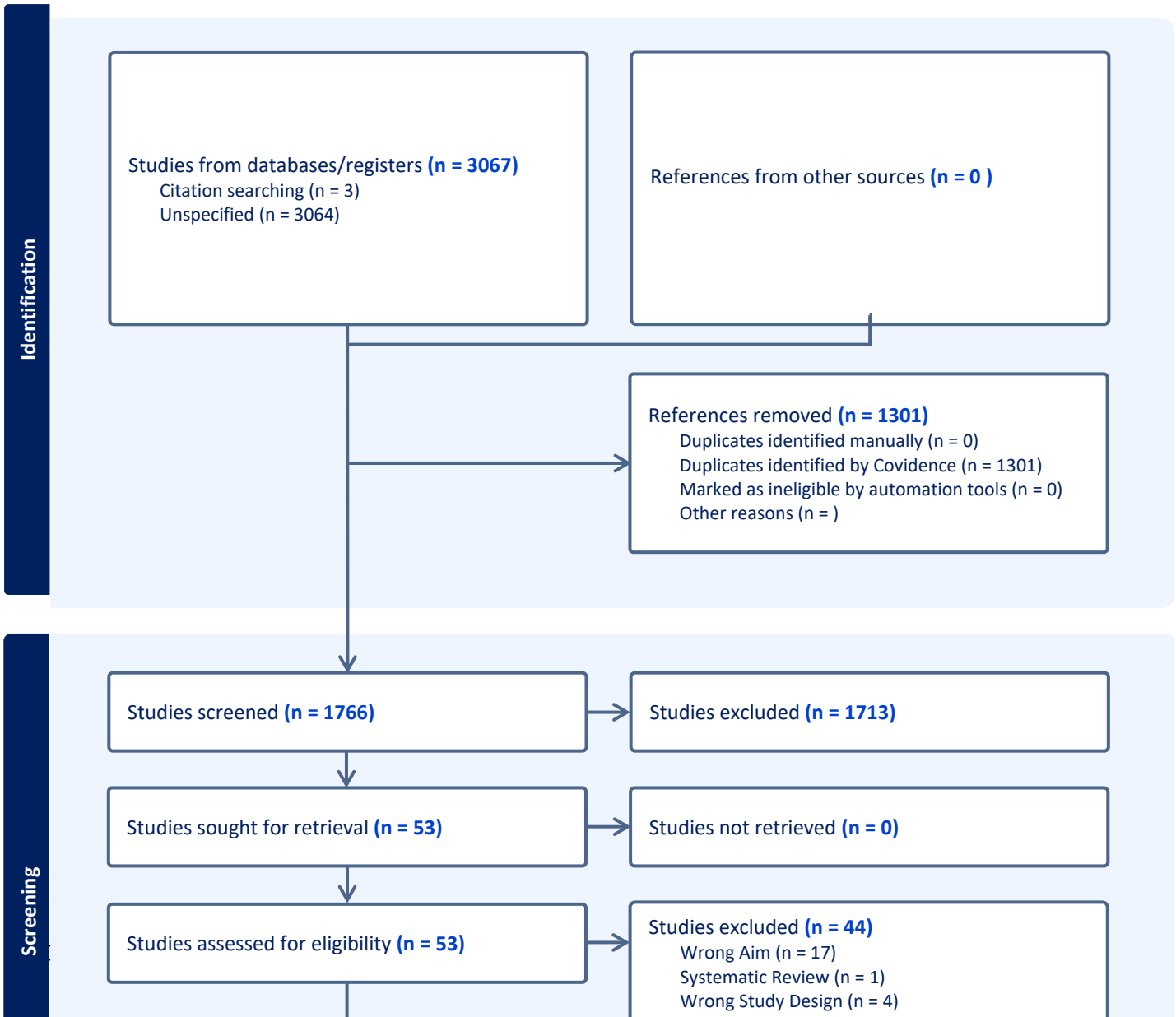
eFigure 31. Type 2 diabetes mellitus



Included

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