List of Supplements

Supplement 1. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract page
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Part 1. Paragraph 1&2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Part 1. Paragraph 3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Part 2. Paragraph 2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Part 2. Paragraph 1
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Part 2. Paragraph 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Part 2. Paragraph 2
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Part 2. Paragraph 2
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Part 2. Paragraph 2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Part 2. Paragraph 2
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Part 2. Paragraph 3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	NA
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Part 2. Paragraph 2
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Part 2. Paragraph 2

Section and Topic	Item #	Checklist item	Location where item is reported
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Part 2. Paragraph 3
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Part 3.1 & Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Part 3.1 & Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Part 3.2-3.8 & Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Part 3.9 & Supplement table 1-5
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Part 3.2-3.8 & Table 1&2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Part 3.9 & Supplement table 1-5
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Part 5
	23b	Discuss any limitations of the evidence included in the review.	Part 4.2
	23c	Discuss any limitations of the review processes used.	NA
	23d	Discuss implications of the results for practice, policy, and future research.	Part 5
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Part 2. Paragraph 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Part 2. Paragraph 2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	No
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funding

Section and Topic	Item #	Checklist item	Location where item is reported
Competing interests	26	Declare any competing interests of review authors.	Competing interests
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Availability of data

Abbreviations: NA, not applicable

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

Supplement 2. The detailed literature search strategy for each database

Date: From the earliest accessible publication to Feb 27th, 2022.
Databases searched: Web of Science (WOS), PubMed, Embase, and the Cochrane Library
Other resources: Drugs.com, Google Scholar, UpToDate and the prescribing information of commercial formulations
Settings: No restriction on language, publication date or article type. The lists of references will also be screened in case of any missed articles.

Search sentence for each database (advanced search):
WOS: (TS=levothyroxine OR TS=thyroxine OR TS= L-T4 OR TS=LT4) AND (TS=malabsorption OR TS=interaction)
PubMed: (levothyroxine OR thyroxine OR L-T4 OR LT4) AND (malabsorption OR interaction)
Embase: (levothyroxine OR thyroxine OR L-T4 OR LT4) AND (malabsorption OR interaction)
The Cochrane Library: All text = (levothyroxine OR thyroxine OR L-T4 OR LT4) AND (malabsorption OR interaction)

Supplement 3. Summary of included studies evaluating the effects of drugs or food on the pharmacokinetics and pharmacodynamics of levothyroxine

Reference	Country	Study type	Participants and concomitant diseases	LT4 formulation and dose [a]	Interfering substances	Effects [b]	Possible mechanisms
Medications							
Irving, 2015 [1]	UK	Retrospective, pre-post, self-control	744 from database	Form NA, dose NA but constant	Calcium	TSH were 1.39 at baseline and 1.64 mU/L after interferants, p=0.005	Affecting the absorption of thyroxine
Schneyer, 1998 [2]	USA	Case report	3 hypothyroid	Tablet, 125-325μg/d	Calcium carbonate	TSH rose to 7.3-13.3 mU/L	-
Butner, 2000 [3]	USA	Case report	1 hypothyroid after gastric bypass surgery	Tablet, 150μg/d	Calcium carbonate	TSH rose to 21.85 IU/mL	Chelation with calcium carbonate
Singh, 2000 [4]	USA	Prospective, pre-post, self-control	20 hypothyroid	Tablet, dose NA	Calcium carbonate	FT4 decreased from 1.34±0.04 to 1.22±0.05 ng/dL, TSH increased from 1.60±0.22 to 2.71±0.43 mU/L, TT4 decreased from 9.21±0.46 to 8.55±0.41 μg/dL	Binding of LT4 to calcium at low pH
Csako, 2001 [5]	USA	Case report	1 hypothyroid with lupus erythematosus, celiac disease, after pancreaticoduodenectomy	Form NA, 175μg/d	Calcium carbonate	TSH rose to 41.4 mU/L	Binding of LT4 to calcium
Singh, 2001 [6]	USA	Randomized, single-blind, crossover	7 euthyroid	Tablet, 1000μg once	Calcium carbonate	T4-absorption dropped by 25.8%, TT4 increases were 7.04±0.91 vs. 4.36±0.97μg/dL with or without calcium, respectively, TT3 increases were 12.82±4.35 vs. 4.93±7.12ng/dL, FT4 increases were 1.79±0.24 vs. 1.44±0.21ng/dL	Adsorption of T4 to calcium carbonate occurred at acidic pH levels

Diskin, 2007 [7]	USA	Retrospective, pre-post, self-control	19 hypothyroid	Tablet, 98.68 ± 45.24μg/d	Calcium carbonate	TSH increased to 23.80 ± 19.50 mU/L	Binding of LT4 to calcium
Mazokopakis, 2008 [8]	Greece	Case report	1 hypothyroid with osteopenia	Form NA, 88 μg/d	Calcium carbonate	FT4 decreased to 0.2 ng/dL, TSH rose to 9.8 mU/L	-
Zamfirescu, 2011 [9]	USA	Prospective, pre-post, self-control	8 euthyroid	Tablet, 1000μg once	Calcium carbonate	AUC for LT4 alone was 1696±96 (SE) μg-min/dL AUC for LT4 plus calcium carbonate was 1344±160 (SE) μg-min/dL	Binding of LT4 to calcium
Morini, 2019 [10]	Italy	Retrospective, pre-post, self-control	50 hypothyroid	Tablet, mean dose of 1.43±0.24 μg/kg/d	Calcium carbonate	TSH were 3.33 ± 1.93 mU/L in LT4 group versus 1.93 ± 0.51 in LT4+Calcium group	Nonspecific adsorption (complexing)
Morini, 2019 [11]	Italy	Retrospective, cohort	50 hypothyroid	Tablet, liquid solution and capsule, mean dose of 1.43±0.24 μg/kg/d	Calcium carbonate	TSH decreased in the liquid group (1.23 ± 0.49 vs. 1.80 ± 0.37 mU/L, $P < 0.01$)	-
Diskin, 2007 [7]	USA	Retrospective, pre-post, self-control	35 hypothyroid	Tablet, 95.00 ± 83.75μg/d	Calcium acetate	No positive results	-
Zamfirescu, 2011 [9]	USA	Prospective, pre-post, self-control	8 euthyroid	Tablet, 1000μg once	Calcium acetate	AUC for LT4 alone was 1696±96 (SE) μg-min/dL AUC for LT4 plus calcium acetate was 1274±137 (SE) μg-min/dL	Binding of LT4 to calcium
Zamfirescu, 2011 [9]	USA	Prospective, pre-post, self-control	8 euthyroid	Tablet, 1000μg once	Calcium citrate	AUC for LT4 alone was 1696±96 (SE) μg-min/dL AUC for LT4 plus calcium citrate was 1381±151 (SE) μg-min/dL	Binding of LT4 to calcium

Benvenga, 2017 [12]	Italy	Prospective, pre-post, self-control	19 hypothyroid	Tablet and liquid solution, mean dose of 1.9 ± 0.4 μg/kg/d	Calcium, iron	TSH were 7.48±5.8 mU/L in tablet group and 1.95±1.3 mU/L in liquid solution group	Liquid formulation reduces the binding of LT4 to sequestrants
Irving, 2015 [1]	UK	Retrospective, pre-post, self-control	723 from database	Form NA, dose NA but constant	Iron	TSH were 1.29 at baseline and 1.65 mU/L with interferants, p<0.001	Affecting the absorption of thyroxine
Campbell, 1992 [13]	Canada	Prospective, pre-post, self-control	14 hypothyroid	Tablet, dose NA	Ferrous sulfate	TSH rose from 1.6±0.4 to 5.4±2.8 mU/L	Binding of LT4 to iron, proved by *in vitro* study
Shakir, 1997 [14]	USA	Case report	1 hypothyroid with pregnancy	Tablet, 150μg/d	Ferrous sulfate	TSH rose to 56 mU/L	Binding of LT4 to iron
Leger, 1999 [15]	Canada	Case report	1 hypothyroid with hypertension and congestive heart failure	Form NA, 250μg/d	Ferrous sulfate	TSH increased to 243 mU/L, FT4 decreased to <0.52 pmol/L	Binding of LT4 to iron
Vita, 2014 [16]	Italy	Prospective, pre-post, self-control	24 hypothyroid	Tablet and liquid solution, 1.5μg/kg/d	PPIs	TSH were 1.7±1.0 mU/L in solution group and 5.4±4.3 mU/L in tablet group	PPIs increase the gastric pH and impair tablet LT4 dissolution
Irving, 2015 [1]	UK	Retrospective, pre-post, self-control	1491 from database	Form NA, dose NA but constant	PPIs	TSH were 1.51 at baseline and 1.69 mU/L with interferants, p=0.001	Dissolution of thyroxine decreased with an increase in pH
Trifiro, 2015 [17]	Italy	Retrospective, pre-post, self-control	3787 hypothyroid from database	Form NS, Dose NA	PPIs	TSH levels increase at the beginning of PPI exposure	-
Ananthakrishnan, 2008 [18]	USA	Prospective, pre-post, self-control	10 euthyroid	Tablet, 600μg once	Esomeprazole	No positive results onT4, T3 and TSH	-
Yue, 2015 [19]	Switzerland	Prospective, pre-post, self-control,	32 euthyroid	Tablet and capsule, 600μg once	Esomeprazole (PPI)	C_{max} and AUC_{0-12} decreased by 12.7% and 14.8% respectively in tablet plus PPI group compared to tablet alone,	Soft gel capsules may be less sensitive to the influence of pH increases than tablets

		randomized, crossover				C_{max} and AUC_{0-12} decreased by 16.1% and 14.8% respectively in tablet group compared to capsule group	
Dietrich, 2006 [20]	Germany	Randomized, crossover, two-arm	21 euthyroid	Tablet, 4μg/kg once	Pantoprazole	No positive results on T4 and TSH	-
Vita, 2014 [21]	Italy	Case report	1 hypothyroid	Tablet and softgel capsule, 150μg/d for tablet and 125μg/d for capsule	Pantoprazole (PPI)	TSH decreased from 4.4-6.5 to 2.4 mU/L after switching to capsule, and rose to 3.2-4.7 mU/L after switching back.	Soft gel capsule showed more complete dissolution than the tablet
Centanni, 2006 [22]	Italy	Retrospective, cohort	10 euthyroid with multinodular goiter and gastroesophageal reflux disease	Form NA, 1.58 μg/kg/d	Omeprazole	TSH level was 1.70 mU/L in patients with omeprazole than 0.1 mU/L in those without omeprazole	Alkalization
Abi-Abib, 2014 [23]	Brazil	Prospective, pre-post, self-control	19 hypothyroid	Tablet, dose NA	Omeprazole	No positive results on TSH	-
Sachmechi, 2007 [24]	USA	Retrospective cohort, pre-post, self-control	92 hypothyroid	Form NA, 82.8 ± 40.3 μg/d	Lansoprazole	TSH increased by 0.69±1.9 mU/L	Increasing metabolic clearance of LT4 (increasing the biliary clearance of LT4 through induction of UGT enzymes), or reducing gastrointestinal absorption of LT4 (reduction of gastric acidity)
Vita, 2017 [25]	Italy	Prospective, pre-post, self-control	11 hypothyroid	Tablet and liquid solution, 1.6-1.7 μg/kg/d	PPIs, calcium, iron, sevelamer, aluminum/magnesium hydroxide and sodium alginate	Mean TSH levels under tablet L-T4 were 4-fold higher than those under liquid L-T4	Liquid formulation does not need a dissolution phase, it is refractory to sequesters, ethanol may enhance LT4 absorption by increasing intestinal blood flow

Benvenga, 2019 [26]	Italy	Prospective, open-labeled, pre-post	20 hypothyroid	Tablet, liquid solution and soft gel capsule, dose NA	PPIs, calcium and iron supplements	TSH in tablet, liquid solution and capsule groups were 7.53±2.82, 2.74±0.98 2.70±0.79 mU/L, respectively (p<0.001)	Greater bioavailability of soft gel capsule when the intestinal absorption of LT4 is challenged by the ingestion of certain medications
Sperber, 1992 [27]	USA	Case report	1 hypothyroid	Form NA, 150μg/d	Aluminum hydroxide	TSH increased to 4.63 mU/L	Direct complexing
Liel, 1994 [28]	Israel	Prospective, pre-post, self-control	5 hypothyroid	Form NA, dose NA	Aluminum hydroxide	TSH rose from 2.62±0.8 to 7.19±1.3 mU/L	Nonspecific adsorption (binding of LT4 to aluminum hydroxide), proved by *in vitro* study
Mersebach, 1999 [29]	Denmark	Case report	2 hypothyroid	Tablet, 50-200μg/d	Aluminum hydroxide, magnesium oxide	A: TSH 64.3 mU/, TT4 50 nmol/L, TT3 0.8 nmol/L B: TSH 48.9 mU/, TT4 33 nmol/L, TT3 1.1 nmol/L	Direct complexing, proved by *in vitro* study, alkalinization of gastric contents, slowing of gastric emptying
Havrankova, 1992 [30]	Canada	Case report	1 hypothyroid	Form NA, 150-200μg/d	Sucralfate	TSH increased to 76.8 mU/L	Binding of LT4 to sucralfate, proved by *in vitro* study
Khan, 1993 [31]	USA	Retrospective, pre-post, self-control	10 hypothyroid	Form NA, Dose NA	Sucralfate	No positive results on T4 and TSH	-
Campbell, 1994 [32]	USA	Randomized, single-blinded, two-arm	9 hypothyroid	Tablet, mean dose of 133μg/d	Sucralfate	T4 index decreased (7.4 ± 0.8 vs. 8.3 ± 0.6, p = 0.038), TSH increased (4.63 ± 3.20 vs. 2.69 ± 1.93, p = 0.097)	Binding of L-thyroxine by sucralfate
Sherman, 1994 [33]	USA	Case report	1 hypothyroid with dyspepsia	Form NA, 150μg/d	Sucralfate	TSH increased to 30.5 mu/L, TT4 decreased to 57 nmol/L, T3 resin dropped to 0.21, FT4 index dropped to 0.9	Binding of LT4 to sucralfate
Sherman, 1994 [33]	USA	Prospective, pre-post, self-control	5 euthyroid	Tablet, 1000μg once	Sucralfate	L-T4 absorption decreased by 57.1% when co-ingested with sucralfate, T_{max} was delay by 2 hours	Binding of LT4 to sucralfate

Irving, 2015 [1]	UK	Retrospective, pre-post, self-control	530 from database	Form NA, dose NA but constant	H2 antagonist	No positive results on TSH	-
Jonderko, 1992 [34]	Poland	Randomized, double-blind, crossover	10 hypothyroid	Gelatin capsule, dose NA but stable	Cimetidine	$AUC_{0\text{-}240min}$ were 371±72 with cimetidine vs. 467±82 with placebo	Complexion
Jonderko, 1992 [34]	Poland	Randomized, double-blind, crossover	10 hypothyroid	Gelatin capsule, dose NA but stable	Ranitidine	No positive results on AUC	Delaying the emptying of stomach
Ananthakrishnan, 2008 [18]	USA	Prospective, pre-post, self-control	10 euthyroid	Tablet, 600μg once	Famotidine	No positive results on T4, T3 and TSH	-
Irving, 2015 [1]	UK	Retrospective, pre-post, self-control	1944 from database	Form NA, dose NA but constant	Statins	TSH were 1.65 at baseline and 1.44 mU/L after interferants, $p<0.001$	-
Demke, 1989 [35]	USA	Case report	1 hypothyroid with diabetes mellitus type 1	Tablet, 125μg/d	Lovastatin	TSH rose to >100 mU/L	Inhibition of LT4 absorption, acceleration of LT4 clearance
Gormley, 1989 [36]	USA	Retrospective, pre-post, self-control	22 hypothyroid	Form NA, dose NA	Lovastatin	No positive results before and during lovastatin therapy	-
Abbasinazari, 2011 [37]	Iran	Prospective, pre-post, self-control	41 hypothyroid with hypercholestloremia	Form NA, 50-150 μg/d	Simvastatin	No positive results on TSH and FT4	-
Kisch, 2005 [38]	Israel	Case report	2 hypothyroid with hypercholestloremia	Form NA, 115μg/d	Simvastatin	TSH rose to 28.63 and 23.9 mU/L respectively	Excess formation of CYP3A4 in the liver by simvastatin, which accelerates catabolism of L-thyroxine
Ananthakrishnan, 2008 [18]	USA	Prospective, pre-post, self-control	10 euthyroid	Tablet, 600μg once	Ezetimibe	No positive results onT4, T3 and TSH	-

John-Kalarickal, 2007 [39]	USA	Prospective, pre-post, self-control	7 euthyroid	Tablet, 1mg once	Ezetimibe	No positive results on the AUC of LT4	Intestinal absorption of levothyroxine is probably NOT mediated by the cholesterol transporter
Harmon, 1991 [40]	USA	Case report	1 hypothyroid with coronary artery disease	Tablet, 125µg/d	Cholestyramine	TSH rose from 0.17 mU/L to 20.65 mU/L	Binding of LT4 to cholestyramine irreversibly
Northcutt, 1969 [41]	USA	Case report	2 hypothyroid with hypercholesterolemia	Tablet, 100 µg/d of LT4 or 60mg/d of thyroid	Cholestyramine	Urine I-131 decreased by >20%, while stool I-131 increased by >35%	Binding of LT4 to cholestyramine
Weitzman, 2009 [42]	USA	Prospective, pre-post, self-control	6 euthyroid	Tablet, 1000µg once	Colesevelam hydrochloride	AUC were 107.5±45.8 (SE) µg-min/dL for levothyroxine plus colesevelam hydrochloride, and 1692±183.5 (SE) µg-min/dL for LT4 alone	Binding of LT4 to colesevelam hydrochloride
Brown, 2010 [43]	USA	Prospective, cohort	110 euthyroid	Tablet, 600µg once	Colesevelam	$AUC_{0\text{-}48h}$ decreased to 78.0% compared to LT4 given alone, C_{max} decreased to 67.1% compared to LT4 given alone	Binding of LT4 to colesevelam
Madhava, 2005 [44]	UK	Case report	1 hypothyroid	Form NA, 250 µg/d	Orlistat	TSH rose to 73.6 mU/L	Binding to Orlistat
Balapatabendi, 2011 [45]	UK	Case report	1 hypothyroid at 13-day-old	Crushed tablet, 13-17µg/kg/day	Simethicone	TSH increased to >100 mU/L with simeticone	Direct complexing
Vigersky, 2006 [46]	USA	Case series	4 hypothyroid with diabetes type 2	Form NA,125-224 µg/d	Metformin	TSH decreased in four patients	Changing the affinity and/or number of thyroid hormone receptors
Isidro, 2007 [47]	Spain	Prospective, pre-post, self-control	8 hypothyroid with diabetes type 2	Form NS, 1.21 ± 0.13µg/kg/d	Metformin	TSH: 3.11 ± 0.50 at baseline vs. 1.18 ± 0.36 mU/L with metformin	Reducing body weight
Cappelli, 2009 [48]	Italy	Retrospective, pre-post, self-control	58 hypothyroid with diabetes mellitus	Form NA, 89.8 ± 11.5 µg/d	Metformin	TSH decreased from 4.52 ± 0.37 to 2.93 ± 0.48 mU/L	Enhancing the inhibitory modulation of thyroid hormones on central TSH secretion, Ameliorating the thyroid function reserve

Al-Alusi, 2015 [49]	USA	Prospective, pre-post, self-control	26 euthyroid	Tablet, 600μg once	Metformin	AUC were 3893 ± 568 and 3765 ± 588 μg/dL-min in pre- and post-metformin groups respectively, p = 0.09	Decreasing both hypothalamic TRH and pituitary TSH secretion
John-Kalarickal, 2007 [39]	USA	Prospective, pre-post, self-control	7 euthyroid	Tablet, 1mg once	Chromium picolinate	T4 absorption dropped to 83%	Binding of LT4 to drug, drug-induced alterations in mucosal transport processes
McLean, 1993 [50]	Australia	Case report	1 hypothyroid with renal failure	Form NA, 150μg/d	Cation-exchange resin (sodium polystyrene sulphonate)	FT4 decreased to 3.5 pmol/L and TSH rose to 139.5 mU/L	Binding to Resin, proved by *in vitro* study
John-Kalarickal, 2007 [39]	USA	Prospective, pre-post, self-control	7 euthyroid	Tablet, 1mg once	Sevelamer hydrochloride	T4 absorption dropped to 50.4%	Binding of LT4 to drug, drug-induced alterations in mucosal transport processes
Diskin, 2007 [7]	USA	Retrospective, pre-post, self-control	13 hypothyroid	Tablet, 173.08 ± 25.94μg/d	Sevelamer hydrochloride	TSH increased to 20.29 ± 30.83 mU/L	Binding of LT4 to phosphate binder
Iovino, 2014 [51]	Italy	Case report	1 hypothyroid with chronic renal failure	Tablet, 150μg/d	Sevelamer carbonate	TSH rose to 650 IU/ml	Binding of LT4 by phosphate binder
Weitzman, 2009 [42]	USA	Prospective, pre-post, self-control	6 euthyroid	Tablet, 1000μg once	Lanthanum carbonate	AUC were 982.5±172.3 (SE) μg-min/dL for LT4 plus Lanthanum carbonate, and 1692±183.5 (SE) μg-min/dL for LT4 alone	Binding of LT4 to lanthanum carbonate
Bone, 2017 [52]	USA	Randomized, open-label, crossover	30 euthyroid	Tablet, 600μg once	Alendronate	No positive results on C_{max} and AUC_{0-48}	-
Siraj, 2003 [53]	USA	Case report	1 hypothyroid with osteopenia	Tablet, 150μg/d	Raloxifene	TSH increased to 14.5μU/mL, serum T4 levels at 1-2 hour after ingestion were lower with coadministration of raloxifene	Inducing malabsorption of LT4
Garwood, 2006 [54]	USA	Case report	1 hypothyroid with osteoporosis	Tablet, 50μg/d	Raloxifene	TSH rose to 5.14 mU/L	-

Arafah, 1994 [55]	USA	Retrospective, pre-post, self-control	4 hypothyroid	Tablet, 62.5-150μg/d	Androgen	FT4 increased while TSH decreased, T4-binding globulin decreased.	Decreasing serum T4-binding globulin
Arafah, 2001 [56]	USA	Prospective, pre-post, self-control	25 hypothyroid	Form NA, mean dose of 114±34μg/d	Estrogen	FT4 decreased from 1.7±0.4 ng/dL to 1.4±0.3 ng/dL, TSH rose from 0.9±1.1 to 3.2±3.1 mU/L	Increasing the serum thyroxine-binding globulin concentration
Irving, 2015 [1]	UK	Retrospective, pre-post, self-control	483 from database	Form NA, dose NA but constant	Estrogen	TSH were 1.22 at baseline and 1.37 mU/L after interferants, p=0.013	-
Guarda, 2019 [57]	USA and Chile	Case series	5 hypothyroid with Cushing disease	Form NA, a median dose of 137μg /d	Mifepristone	The median increase in levothyroxine requirement was 83.3% to maintain a normal range of FT4	Intestinal malabsorption, decreased residual thyroid function or increased inactivation of T4 via deiodinases
Irving, 2015 [1]	UK	Retrospective, pre-post, self-control	471 from database	Form NA, dose NA but constant	Glucocorticoid	No positive results on TSH	-
Isley, 1987 [58]	USA	Case report	1 hypothyroid with Turner syndrome and hypertension	Form NA, dose NA	Rifampin	FT4 decreased by ~70%, TSH increased by ~100%	Increased nondeiodonative and deiodinative hepatic metabolism, accelerated T4 metabolic clearance
Nolan, 1999 [59]	USA	Case report	1 hypothyroid with coronary artery disease and sternal wound infection	Form NS, 50 μg/d	Rifampin	TSH rose to 9.44 mU/L	Increasing the clearance of T4, increasing thyroid-binding globulin
Goldberg, 2013 [60]	Canada	Double-blind, randomized, crossover	8 euthyroid	Tablet, 1000μg once	Rifampin	AUC increased by 25%	Inhibited hepatic T4 uptake mediated by liver-specific transporters relative to intestinal T4 transporters Increased net intestinal absorption of L-T4 through inhibition of an intestinal efflux transporter such as P-glycoprotein

Cooper, 2005 [61]	Norway	Case report	2 hypothyroid	Form NA, 125μg/d for patient A and 150μg/d for patient B	Ciprofloxacin	A: TSH rose to 44 mU/L, FT4 fell to 4 pmol/L, FT3 fell to 1.0 pmol/L. B: TSH rose to 19 mU/L, FT4 fell to 13 pmol/L.	Decreasing the absorption of LT4
Goldberg, 2013 [60]	Canada	Double-blind, randomized, crossover	8 euthyroid	Tablet, 1000μg once	Ciprofloxacin	AUC decreased by 39%	Inhibition of an intestinal T4 uptake transporter
Berger, 2017 [62]	France	Case report	2 hypothyroid with HIV	Form NA, 125-165μg/d	Ritonavir	TSH decreased after the discontinuation of ritonavir, with presentation of hyperthyroid symptoms	Inactivate LT4 via induction of glucuronidation
Sahajpal, 2017 [63]	Canada	Case report	1 hypothyroid with HIV	Form NA, 75μg/d	Ritonavir	TSH rose to 95.11	Inactivate LT4 via induction of CYP2B6
Lanzafame, 2002 [64]	Italy	Case report	1 hypothyroid with HIV	Form NA, 0.75 mg/die	Indinavir	TSH decreased to <0.1 mU/L, FT4 increased to 57pmol/L, FT3 increased to 33pmol/L	Inhibition of glucuronosyl transferase activity
Touzot, 2006 [65]	France	Case report	1 hypothyroid with HIV	Form NA, 225μg/d	Lopinavir, Ritonavir, Nelfinavir	TSH could be suppressed until the discontinuation of proteinase inhibitors	Inactivating LT4 via induction of glucuronidation
Larsen, 1970 [66]	USA	Prospective, pre-post, self-control	5 euthyroid	Injection, dose NA	Phenytoin	T4 decreased to 80% of the pretreatment level after the ingestion of diphenylhydantoin	Competing combination with TBG, increased thyroxine elimination
Blackshear, 1983 [67]	USA	Case report	1 hypothyroid	Form NA, 150μg/d	Phenytoin	T4 decreased to 3.6 μg/dL, TSH increased to 44 mU/L	Decreasing protein-binding T4, accelerating T4 clearance
Faber, 1985 [68]	Denmark	Prospective, pre-post, self-control	6 hypothyroid	Form NA, mean dose: 133μg/d	Phenytoin	TSH increased by 137%, TT4 decreased by 16%	Reducing the intestinal absorption of T4 and increasing the nondeiodinative metabolism of T4, proved by *in vivo* study
Aanderud, 1981 [69]	Norway	Prospective, pre-post, self-control	9 hypothyroid	Form NA, 100-400μg/d	Carbamazepine	T3, T4, FT3 and FT4 decreased after the intake of carbamazepine with significant difference ($p<0.01$). TBG increases after the co-ingestion ($p=0.01$). TSH was not altered.	Elevating the serum TBG levels

Deluca, 1986 [70]	Italy	Retrospective, pre-post, self-control	5 hypothyroid with epilepsy, age between 4.5 and 11.9 years	Form NA, 100-120 $\mu g/m^2/d$	Carbamazepine	TT4 decreased from 12.7 ± 1.1 to 7.5 ± 2.3µg/dL, FT4 from 15.5 ± 1.8 to 10.1 ± 1.7 pg/mL, T3:T4 ratio rose from 10.3±1.8 to 15.4±4.4 ng:µg, TSH rose from 2.8±1.4 to 10.0±8.1 mU/L	Accelerated T4 metabolic clearance, augmented T4 to T3 conversion rate (increased the deiodinative metabolism of T4)
McCowen, 1997 [71]	USA	Case series	11 hypothyroid with depression	Form NA, dose NA	Sertraline	TSH increased by 10-50%	Accelerated T4 metabolic clearance
de Carvalho, 2009 [72]	Brazil	Prospective, pre-post, self-control	28 hypothyroid with major depression	Form NA, dose NA	Fluoxetine, Sertraline	No positive results on T3, T4 and TSH over the 90-day period	Induction of type 1 and type 2 deiodinases, increased conversion of T4 to T3
Figge, 1990 [73]	USA	Case report	2 hypothyroid with myocardial infarction	Tablet, 75-100µg/d	Amiodarone	FT3 dropped below the normal range, T3/T4 ratio decreased by 35%, TSH rose to 20-30 mU/L	Impaired T4-to-T3 conversion, blocked T3 and T4 bind to pituitary receptors
Lumholtz, 1978 [74]	Denmark	Prospective, pre-post, self-control	7 hypothyroid	Form NA, 100-250µg/d	Propranolol	TT3 decreased from 86±14 to 75±14ng/100ml, rT3 increased from 38±10 to 44±14 ng/100ml	Inhibition of the monodeiodination of T4 to T3, inhibition of LT4 intestinal absorption
Chiu, 1998 [75]	USA	Prospective, pre-post, self-control	8 euthyroid	Tablet, 600µg once	Calcium polycarbophil	No positive results on T4 and TSH	-
Chiu, 1998 [75]	USA	Prospective, pre-post, self-control	8 euthyroid	Tablet, 600µg once	Psyllium hydrophilic mucilloid	No positive results on T4 and TSH	-
Narula, 2004 [76]	USA	Case report	1 hypothyroid with metastatic breast cancer	Form NA, 125µg/d	Capecitabine	TSH elevated to 90.1 mU/L with capecitabine	Accelerating the deiodination of T4 to T3.
de Groot, 2005 [77]	Netherland	Retrospective, pre-post, self-control	8 hypothyroid	Form NA, 100-225µg/d	Imatinib	TSH increased to 384±228% of the upper limit	Stimulation of T4 and T3 clearance (nondeiodination clearance)

Abdulrahman, 2010 [78]	Netherlands	Prospective, pre-post, self-control	21 hypothyroid after thyroidectomy	Form NA, 2.48±0.67μg/kg/day	Sorafenib	LT4 dose increased from 2.48±0.67 to 2.71±0.61μg/kg/day, T3 increased from 1.90±0.33 to 1.60±0.34 nmol/L, T3/T4×100 decreased from 1.28±0.00 to 1.05±0.00 ($p<0.001$), T3/rT3 decreased from 2.74±0.50 to 2.16±0.53, ($p<0.001$), T4/rT3 decreased from 220±27 to 205±32 ($p=0.036$)	Increasing deiodinase type 3 activity.
Schlumberger, 2009 [79]	International	Prospective, pre-post, self-control	91 hypothyroid with medullary thyroid cancer	Form NA, dose NA	Motesanib	Hypothyroidism and/or elevated TSH was observed in 37 patients (41%)	Inhibition of thyroid peroxidase
Irving, 2015 [1]	UK	Retrospective, pre-post, self-control	96 from database	Form NA, dose NA but constant	Disease modifying antirheumatic drugs	No positive results on TSH	-
Antúnez, 2011 [80]	Argentina	Prospective, pre-post, self-control	28 hypothyroid	Tablet, >1.70 μg/kg/d	Vitamin C	TSH decreased by 69.79±22.19%	VtC → gastric pH↓ → LT4 absorption↑
Jubiz, 2014 [81]	Colombia	Prospective, pre-post, self-control	31 hypothyroid with gastrointestinal diseases	Form NA, median dose of 100μg/d	Vitamin C	TSH decreased from 10.5 to 4.2 mU/L, FT4 rose from 1.1 to 1.3 ng/dL	Increased solubility of L-T4 in the stomach
Food and beverages							
Lamson, 2004 [82]	USA	Randomized, open-label, crossover	48 euthyroid	Tablet, 600μg once	Food	C_{max} decreased by 40-49%, T4 AUC_{0-48h} decreased by 38-40%	-
Wenzel, 1977 [83]	Germany	Prospective, pre-post, self-control	13 euthyroid	Tablet, 100μg once	Food (lactose and corn starch)	Lactose: LT4 absorption was 79.9±6.4% without food and 59.0±9.0% with food Corn starch: LT4 absorption was 78.6±8.6% without food and 68.2±10.4% with food	-
Dickerson, 2010 [84]	USA	Retrospective, cohort	13 hypothyroid	Form NA, 1.36 ± 0.77μg/kg/d	Food (continuous enteral feeding)	TSH increased significantly after 8 days of continuous enteral feeding	Binding of LT4 to enteral nutrition formula

Pirola, 2014 [85]	Italy	Prospective, cohort	20 euthyroid	Tablet and solution, 1.6μg/kg/d	Food (via enteral feeding tube)	No positive results on FT3, FT4 and TSH	-
Bach-Huynh, 2009 [86]	USA	Randomized, open-label, crossover	65 hypothyroid	Form NA, mean dose of 128μg/d	Breakfast	TSH was higher when taking with breakfast (2.93 ± 0.45 vs 1.06 ± 0.46 mU/L), LT4 was lower when taking with breakfast (1.24 ± 0.04 vs. 1.35 ± 0.04 ng/dL)	-
Silva Perez, 2013 [87]	Brazil	Randomized, open-label, crossover	42 hypothyroid	Tablet, 1.35 ± 0.48μg/kg/d	Breakfast	TSH were 2.89 ± 2.82 with breakfast and 1.9 ± 1.76 when fasting, p = 0.028	-
Cappelli, 2014 [88]	Italy	Retrospective, cohort	54 hypothyroid	Liquid solution, dose NA	Breakfast	No positive results	-
Cappelli, 2016 [89]	Italy	Prospective, pre-post, self-control	60 hypothyroid	Tablet, capsule and solution, dose NA	Breakfast	FT3: capsule 2.5 (2.4-3.1), solution 2.7 (2.4-3.3) pg/mL, p < 0.05 FT4: capsule 9.9 (8.0-13), solution 10.6 (8.6-13.8) pg/mL, p < 0.0001	The absorption of softgel capsule and solution is not impaired by concomitant food.
Cappelli, 2016 [90]	Italy	Randomized, double-blind, placebo-controlled, crossover	77 hypothyroid	Solution, dose NA	Breakfast	No positive results on TSH, FT3 and FT4	-
Marina, 2016 [91]	Italy	Retrospective, cohort	14 hypothyroid	Solution and tablet, 200μg/d	Breakfast	No positive results observed when liquid LT4 is ingested with food	-
Morelli, 2016 [92]	Italy	Prospective, crossover	61 hypothyroid	Solution, dose NA	Breakfast	No positive results on TSH and quality of life	The absorption of the liquid formulation not affected by food and are refractory to the altered pH of the gastric environment
Pirola, 2018 [93]	Italy	Retrospective, cohort	761 hypothyroid	Solution, dose NA	Breakfast	No positive results	-
Cappelli, 2020 [94]	Italy	Case report	1 hypothyroid	Liquid solution, 75μg/d	Lunch	No positive results	-

Pinchera, 1965 [95]	Italy	Case report	1 hypothyroid infant	T3 preparation, desiccated thyroid and T4 solution, 30-60mg/d for desiccated thyroid	Soy formula	Fecal excretion of I-131 on milk diet is 31.6%, while 51% on soy feeding.	Inhibition on intestinal absorption, intestinal hurry and changes in intestinal flora
Conrad, 2004 [96]	USA	Retrospective, cohort	8 hypothyroid infants	Form NA, median dose of 3.3μg/kg/d	Soy formula	TSH were 42.6 and 6.6 mU/L in soy diet group and non-soy diet group respectively.	Malabsorption and increased fecal loss of levothyroxine
Fruzza, 2012 [97]	USA	Case report	2 hypothyroid infants	Form NA, 15μg/kg/d for patient A, 6μg/kg/d for patient B	Soy formula	Patient A: T4 decreased to 2.6 μg/dL, TSH rose to 248 mU/L Patient B: FT4 decrease to <0.4μg/dL, TSH rose to 248 mU/L	Malabsorption and increased fecal loss of levothyroxine
Bell, 2001 [98]	USA	Case report	1 hypothyroid	Form NA, dose NA	Soy protein supplement	TSH rose beyond the upper limit of the normal range	NA
Persiani, 2016 [99]	Italy	Randomized, crossover, open-labeled	12 hypothyroid postmenopausal	Form NA, 25–125 μg/d	Soy isoflavones	No positive results on C_{max}, AUC, T_{max}	-
Liel, 1996 [100]	Israel	Case series	13 hypothyroid	Form NA, 50-470μg/d	Fiber	TSH increased in every case	Adsorption, proved by *in vitro* study
Benvenga, 2008 [101]	Italy	Case report	8 hypothyroid	Form NA, 1.4-3.2μg/kg/d	Coffee	LT4 uptake decreased by 36%, T_{max} was delayed by 50 mins	Binding to LT4 to certain substances in coffee
Benvenga, 2008 [101]	Italy	Prospective, pre-post, self-control	8 hypothyroid and 10 euthyroid	Tablet, 200μg once	Coffee	Average T4 increments dropped by 19-36%, total LT4 uptake dropped by 27-36%, T_{max} delayed by 43 mins	Binding to LT4 to certain substances in coffee
Vita, 2013 [102]	Italy	Prospective, pre-post, self-control	8 hypothyroid	Tablet and capsule, 1.5-2.8μg/kg/d	Coffee	TSH decreased from 5.8-22.4 to 0.06-0.16 mU/L after switching to capsules	-
Wegrzyn, 2016 [103]	USA	Case report	1 hypothyroid	Tablet, 175μg/d	Coffee	TSH rose to 8.270 mU/L	Lipid sequestration of L-T4 by coffee

Chon, 2018 [104]	USA	Prospective, pre-post, self-control	10 euthyroid	Tablet, 1000μg once	Milk	T4 absorption were 67.3 ± 12.1% in LT4+milk group and 73.5 ± 17.0% in LT4 group	Nonspecific adsorption (complexing)
Lilja, 2005 [105]	Finland	Randomized, open-label, crossover	10 euthyroid	Tablet, 600μg once	Grapefruit juice	C_{max} of T4 decreased from 66.4 nmol/L to 59.4 nmol/L, AUC_{0-4} decreased by 13% ($p < 0.05$), from 195 nmol/L/h to 169 nmol/L/h, LT4 absoption decreased from 511 ± 87.7 to 457 ± 59.9μg	Inhibition of uptake transporters in the intestinal wall
Deiana, 2012 [106]	Italy	Case report	1 hypothyroid	Form NA, 1.6 μg/kg/d	Papaya fruit	TSH rose to 25 mU/L	Reduction of gastric acid secretion by papain, binding of LT4 to fibers in papaya
Mahapatro, 2019 [107]	India	Case report	1 hypothyroid at two-year-old	Form NA, 50 μg/d	Dentifrice	TSH rose to 42 mU/L	Binding of LT4 to some substances in toothpaste

[a] The initial doses before co-administration are documented here. Some patients had dose adjustment after the therapy of interfering drugs. Although the LT4 formulations in many articles are not reported, we could assume with reason that tablets are the predominant formulations, since liquid solution and capsules were firstly introduced to Italian market in 2011.

[b] Only the results of significant difference or exceeding the normal ranges are reported here. The normal range of TSH in most studies is defined as 0.5-4.5 mU/L. Values are present as mean ± standard deviation.

Abbreviation: NA, not available, C_{max}, maximum serum concentration, T_{max}, amount of time at peak serum concentration, AUC, area under the curve (of pharmacokinetic chart), PPI, proton pump inhibitor, SE, standard error, HIV, human immunodeficiency virus

Supplement 4. Quality assessment of included studies

Supplementary Table 1. Quality assessment of included interventional studies.

Reference	Study type	Interferants	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Rating
Singh, 2001 [6]	Randomized, single-blind, crossover	Calcium carbonate	Y	Y	N	Y	N	Y	Y	NA	Y	Y	Y	NR	Y	Y	Good
Yue, 2015 [19]	Prospective, pre-post, self-control, randomized, crossover	Esomeprazole (PPI)	Y	NR	N	N	N	Y	Y	Y	Y	Y	Y	NR	Y	Y	Fair
Dietrich, 2006 [20]	Randomized, crossover, two-arm	Pantoprazole	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	NR	Y	Y	Fair
Campbell, 1994 [32]	Randomized, single-blinded, two-arm	Sucralfate	Y	NR	Y	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	Y	Good
Jonderko, 1992 [34]	Randomized, double-blind, crossover	Cimetidine	Y	NR	Y	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	Y	Good
Jonderko, 1992 [34]	Randomized, double-blind, crossover	Ranitidine	Y	NR	Y	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	Y	Good

Bone, 2017 [52]	Randomized, open-label, crossover	Alendronate	Y	NR	N	N	N	Y	Y	Y	Y	Y	Y	NR	Y	Y	Fair
Goldberg, 2013 [60]	Double-blind, randomized, crossover	Rifampin	Y	NR	Y	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	Y	Good
Goldberg, 2013 [60]	Double-blind, randomized, crossover	Ciprofloxacin	Y	NR	Y	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	Y	Good
Lamson, 2004 [82]	Randomized, open-label, crossover	Food	Y	NR	N	N	N	Y	Y	Y	Y	Y	Y	NR	Y	Y	Fair
Bach-Huynh, 2009 [86]	Randomized, open-label, crossover	Breakfast	Y	NR	N	N	N	Y	Y	Y	Y	Y	Y	NR	Y	Y	Fair
Silva Perez, 2013 [87]	Randomized, open-label, crossover	Breakfast	Y	NR	N	N	N	Y	Y	Y	Y	Y	Y	NR	Y	Y	Fair
Cappelli, 2016 [90]	Randomized, double-blind, placebo-controlled, crossover	Breakfast	Y	NR	Y	Y	Y	Y	Y	Y	Y	Y	Y	NR	Y	Y	Good
Persiani, 2016 [99]	Randomized, crossover, open-labeled	Soy isoflavones	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	NR	Y	Y	Fair

Lilja, 2005 [105]	Randomized, open-label, crossover	Grapefruit juice	Y	N R	N	N	N	Y	Y	Y	Y	Y	Y	NR	Y	Y	Fair

Abbreviations: Y, yes; N, no; NA, not applicable; NR, not reported

Questions of NHLBI Quality Assessment of Controlled Intervention Studies:
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?
3. Was the treatment allocation concealed (so that assignments could not be predicted)?
4. Were study participants and providers blinded to treatment group assignment?
5. Were the people assessing the outcomes blinded to the participants' group assignments?
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?
9. Was there high adherence to the intervention protocols for each treatment group?
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?

Supplementary Table 2. Quality assessment of included interventional randomized studies.

Reference	Study type	Interferants	D1/1a	DS	D2	D3	D4	D5
Singh, 2001 [6]	Randomized, single-blind, crossover	Calcium carbonate	Low risk	Low risk	Low risk	Low risk	Low risk	Some concerns
Yue, 2015 [19]	Prospective, pre-post, self-control, randomized, crossover	Esomeprazole (PPI)	Some concerns	Some concerns	Low risk	Low risk	Low risk	Some concerns
Dietrich, 2006 [20]	Randomized, crossover, two-arm	Pantoprazole	Low risk	Low risk	High risk	Low risk	Low risk	Some concerns
Campbell, 1994 [32]	Randomized, single-blinded, two-arm	Sucralfate	Low risk	Not applicable	Low risk	Low risk	Low risk	Some concerns
Jonderko, 1992 [34]	Randomized, double-blind, crossover	Cimetidine	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Jonderko, 1992 [34]	Randomized, double-blind, crossover	Ranitidine	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Bone, 2017 [52]	Randomized, open-label, crossover	Alendronate	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns

Goldberg, 2013 [60]	Double-blind, randomized, crossover	Rifampin	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
Goldberg, 2013 [60]	Double-blind, randomized, crossover	Ciprofloxacin	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
Lamson, 2004 [82]	Randomized, open-label, crossover	Food	Low risk	Some concerns	High risk	Low risk	Low risk	Some concerns
Bach-Huynh, 2009 [86]	Randomized, open-label, crossover	Breakfast	Low risk	Low risk	Low risk	Low risk	Low risk	Some concerns
Silva Perez, 2013 [87]	Randomized, open-label, crossover	Breakfast	Low risk	Low risk	Some concerns	Low risk	Low risk	Some concerns
Cappelli, 2016 [90]	Randomized, double-blind, placebo-controlled, crossover	Breakfast	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Persiani, 2016 [99]	Randomized, crossover, open-labeled	Soy isoflavones	Low risk	High risk	Some concerns	Low risk	Low risk	Some concerns
Lilja, 2005 [105]	Randomized, open-label, crossover	Grapefruit juice	Low risk	Low risk	High risk	Low risk	Low risk	Some concerns

These 15 randomized clinical trials were assessed with the Revised Cochrane risk-of-bias tool for randomized crossover trials (RoB 2) [108].

Domains:
1/1a: Risk of bias arising from the randomization process
S: Risk of bias arising from period and carryover effects
2: Risk of bias due to deviations from the intended interventions
3: Risk of bias due to missing outcome data
4: Risk of bias in measurement of the outcome
5: Risk of bias in selection of the reported result

Supplementary Table 3. Quality assessment of included pre-post studies.

Reference	Study type	Interferants	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Rating
Singh, 2000 [4]	Prospective, pre-post, self-control	Calcium carbonate	Y	Y	Y	N	NR	Y	Y	N	Y	Y	Y	NA	Good
Zamfirescu, 2011 [9]	Prospective, pre-post, self-control	Calcium carbonate	Y	Y	N	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Zamfirescu, 2011 [9]	Prospective, pre-post, self-control	Calcium acetate	Y	Y	N	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Zamfirescu, 2011 [9]	Prospective, pre-post, self-control	Calcium citrate	Y	Y	N	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Benvenga, 2017 [12]	Prospective, pre-post, self-control	Calcium, iron	Y	Y	Y	N	NR	Y	Y	N	Y	Y	Y	NA	Good
Campbell, 1992 [13]	Prospective, pre-post, self-control	Ferrous sulfate	Y	Y	Y	N	NR	Y	Y	N	Y	Y	Y	NA	Good
Vita, 2014 [16]	Prospective, pre-post, self-control	PPIs	Y	Y	Y	N	NR	N	Y	N	Y	Y	Y	NA	Fair
Ananthakrishnan, 2008 [18]	Prospective, pre-post, self-control	Esomeprazole	Y	Y	N	N	NR	Y	Y	N	Y	Y	N	NA	Fair

Abi-Abib, 2014 [23]	Prospective, pre-post, self-control	Omeprazole	Y	Y	Y	N	NR	Y	Y	N	Y	Y	Y	NA	Good
Vita, 2017 [25]	Prospective, pre-post, self-control	PPIs, calcium, iron, sevelamer, aluminum/magnesium hydroxide and sodium alginate	Y	Y	Y	N	NR	N	Y	N	Y	Y	Y	NA	Fair
Benvenga, 2019 [26]	Prospective, open-labeled, pre-post	PPIs, calcium and iron supplements	Y	Y	Y	N	NR	N	Y	N	Y	Y	Y	NA	Fair
Liel, 1994 [28]	Prospective, pre-post, self-control	Aluminum hydroxide	Y	Y	Y	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Sherman, 1994 [33]	Prospective, pre-post, self-control	Sucralfate	Y	Y	N	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Ananthakrishnan, 2008 [18]	Prospective, pre-post, self-control	Famotidine	Y	Y	N	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Abbasinazari, 2011 [37]	Prospective, pre-post, self-control	Simvastatin	Y	Y	Y	Y	NR	Y	Y	N	Y	Y	N	NA	Good
Ananthakrishnan, 2008 [18]	Prospective, pre-post, self-control	Ezetimibe	Y	Y	N	N	NR	Y	Y	N	Y	Y	N	NA	Fair

John-Kalarickal, 2007 [39]	Prospective, pre-post, self-control	Ezetimibe	Y	Y	N	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Weitzman, 2009 [42]	Prospective, pre-post, self-control	Colesevelam hydrochloride	Y	Y	N	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Isidro, 2007 [47]	Prospective, pre-post, self-control	Metformin	Y	N	Y	N	NR	N	Y	N	NR	Y	N	NA	Poor
Al-Alusi, 2015 [49]	Prospective, pre-post, self-control	Metformin	Y	Y	N	N	NR	Y	Y	N	Y	Y	N	NA	Fair
John-Kalarickal, 2007 [39]	Prospective, pre-post, self-control	Chromium picolinate	Y	Y	N	N	NR	Y	Y	N	Y	Y	N	NA	Fair
John-Kalarickal, 2007 [39]	Prospective, pre-post, self-control	Sevelamer hydrochloride	Y	Y	N	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Weitzman, 2009 [42]	Prospective, pre-post, self-control	Lanthanum carbonate	Y	Y	N	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Arafah, 2001 [56]	Prospective, pre-post, self-control	Estrogen	Y	Y	Y	N	NR	Y	Y	N	Y	Y	Y	NA	Good
Larsen, 1970 [66]	Prospective, pre-post, self-control	Phenytoin	Y	Y	N	N	NR	Y	Y	N	Y	Y	Y	NA	Fair

Faber, 1985 [68]	Prospective, pre-post, self-control	Phenytoin	Y	Y	Y	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Aanderud, 1981 [69]	Prospective, pre-post, self-control	Carbamazepine	Y	Y	Y	N	NR	Y	Y	N	Y	Y	N	NA	Fair
de Carvalho, 2009 [72]	Prospective, pre-post, self-control	Fluoxetine, Sertraline	Y	Y	Y	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Lumholtz, 1978 [74]	Prospective, pre-post, self-control	Propranolol	Y	Y	Y	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Chiu, 1998 [75]	Prospective, pre-post, self-control	Calcium polycarbophil	Y	Y	N	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Chiu, 1998 [75]	Prospective, pre-post, self-control	Psyllium hydrophilic mucilloid	Y	Y	N	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Abdulrahman, 2010 [78]	Prospective, pre-post, self-control	Sorafenib	Y	Y	Y	N	NR	Y	Y	Y	N	Y	Y	NA	Fair
Schlumberger, 2009 [79]	Prospective, pre-post, self-control	Motesanib	N	Y	Y	N	NR	Y	N	Y	Y	Y	NR	NA	Poor
Antúnez, 2011 [80]	Prospective, pre-post, self-control	Vitamin C	Y	Y	Y	N	NR	Y	Y	N	Y	Y	N	NA	Fair

Jubiz, 2014 [81]	Prospective, pre-post, self-control	Vitamin C	Y	Y	Y	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Wenzel, 1977 [83]	Prospective, pre-post, self-control	Food (lactose and corn starch)	Y	Y	N	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Cappelli, 2016 [89]	Prospective, pre-post, self-control	Breakfast	Y	Y	Y	Y	NR	Y	Y	N	Y	Y	Y	NA	Good
Benvenga, 2008 [101]	Prospective, pre-post, self-control	Coffee	Y	Y	N	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Vita, 2013 [102]	Prospective, pre-post, self-control	Coffee	Y	Y	Y	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Chon, 2018 [104]	Prospective, pre-post, self-control	Milk	Y	Y	N	N	NR	Y	Y	N	Y	Y	N	NA	Fair
Irving, 2015 [1]	Retrospective, pre-post, self-control	Calcium	Y	Y	Y	Y	NR	N	N	N	NA	Y	NR	NA	Fair
Diskin, 2007 [7]	Retrospective, pre-post, self-control	Calcium carbonate	Y	Y	Y	Y	NR	N	N	N	NA	Y	NR	NA	Fair
Morini, 2019 [10]	Retrospective, pre-post, self-control	Calcium carbonate	Y	Y	Y	Y	NR	N	N	N	NA	Y	N	NA	Fair

Diskin, 2007 [7]	Retrospective, pre-post, self-control	Calcium acetate	Y	Y	Y	Y	NR	N	N	N	NA	Y	NR	NA	Fair
Irving, 2015 [1]	Retrospective, pre-post, self-control	Iron	Y	Y	Y	Y	NR	N	N	N	NA	Y	NR	NA	Fair
Irving, 2015 [1]	Retrospective, pre-post, self-control	PPIs	Y	Y	Y	Y	NR	N	N	N	NA	Y	NR	NA	Fair
Trifiro, 2015 [17]	Retrospective, pre-post, self-control	PPIs	Y	Y	Y	Y	NR	N	N	N	NA	Y	NR	NA	Fair
Sachmechi, 2007 [24]	Retrospective cohort, pre-post, self-control	Lansoprazole	Y	Y	Y	Y	NR	N	N	N	NA	Y	NR	NA	Fair
Khan, 1993 [31]	Retrospective, pre-post, self-control	Sucralfate	Y	N	Y	N	NR	N	N	N	NA	Y	N	NA	Poor
Irving, 2015 [1]	Retrospective, pre-post, self-control	H2 antagonist	Y	Y	Y	Y	NR	N	N	N	NA	Y	NR	NA	Fair
Irving, 2015 [1]	Retrospective, pre-post, self-control	Statins	Y	Y	Y	Y	NR	N	N	N	NA	Y	NR	NA	Fair
Gormley, 1989 [36]	Retrospective, pre-post, self-control	Lovastatin	Y	N	Y	N	NR	N	N	N	NA	Y	N	NA	Poor

Cappelli, 2009 [48]	Retrospective, pre-post, self-control	Metformin	Y	Y	Y	N	NR	N	N	N	NA	Y	N	NA	Fair
Diskin, 2007 [7]	Retrospective, pre-post, self-control	Sevelamer hydrochloride	Y	Y	Y	Y	NR	N	N	N	NA	Y	NR	NA	Fair
Arafah, 1994 [55]	Retrospective, pre-post, self-control	Androgen	Y	Y	Y	N	NR	N	N	N	NA	Y	N	NA	Poor
Irving, 2015 [1]	Retrospective, pre-post, self-control	Estrogen	Y	Y	Y	Y	NR	N	N	N	NA	Y	NR	NA	Fair
Irving, 2015 [1]	Retrospective, pre-post, self-control	Glucocorticoid	Y	Y	Y	Y	NR	N	N	N	NA	Y	NR	NA	Fair
Deluca, 1986 [70]	Retrospective, pre-post, self-control	Carbamazepine	Y	Y	Y	Y	NR	N	N	N	NA	Y	N	NA	Fair
de Groot, 2005 [77]	Retrospective, pre-post, self-control	Imatinib	Y	Y	Y	Y	NR	N	N	N	NA	Y	N	NA	Fair
Irving, 2015 [1]	Retrospective, pre-post, self-control	Disease modifying antirheumatic drugs	Y	Y	Y	Y	NR	N	N	N	NA	Y	NR	NA	Fair

Abbreviations: Y, yes; N, no; NA, not applicable; NR, not reported

Questions of NHLBI Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group:

1. Was the study question or objective clearly stated?
2. Were eligibility/selection criteria for the study population prespecified and clearly described?
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?
4. Were all eligible participants that met the prespecified entry criteria enrolled?
5. Was the sample size sufficiently large to provide confidence in the findings?
6. Was the test/service/intervention clearly described and delivered consistently across the study population?
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?

Supplementary Table 4. Quality assessment of included observational cohort studies.

Reference	Study type	Interferants	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q9	Q10	Q11	Q12	Q13	Q14	Rating
Brown, 2010 [43]	Prospective, cohort	Colesevelam	Y	N	N	NR	N	Y	Y	Y	Y	NA	Y	Y	N	NR	Fair
Pirola, 2014 [85]	Prospective, cohort	Food (via enteral feeding tube)	Y	Y	N	Y	N	Y	Y	N	Y	NA	Y	Y	Y	Y	Good
Morelli, 2016 [92]	Prospective, cohort, crossover	Breakfast	Y	Y	N	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Good
Morini, 2019 [11]	Retrospective, cohort	Calcium carbonate	Y	Y	Y	Y	N	N	Y	N	Y	N	Y	N	Y	NR	Fair
Centanni, 2006 [22]	Retrospective, cohort	Omeprazole	Y	Y	Y	Y	N	N	Y	N	Y	N	Y	N	Y	Y	Fair
Dickerson, 2010 [84]	Retrospective, cohort	Food (continuous enteral feeding)	Y	Y	Y	Y	N	N	Y	N	Y	N	Y	N	Y	Y	Fair
Cappelli, 2014 [88]	Retrospective, cohort	Breakfast	Y	Y	Y	Y	N	N	Y	N	Y	N	Y	Y	Y	Y	Good
Marina, 2016 [91]	Retrospective, cohort	Breakfast	Y	N	N	Y	N	N	Y	N	Y	N	Y	Y	Y	Y	Fair
Pirola, 2018 [93]	Retrospective, cohort	Breakfast	Y	Y	Y	Y	N	N	Y	N	Y	N	Y	N	Y	N	Fair
Conrad, 2004 [96]	Retrospective, cohort	Soy formula	Y	Y	Y	Y	N	N	Y	N	Y	N	Y	Y	Y	N	Fair

Abbreviations: Y, yes; N, no; NA, not applicable; NR, not reported

Questions of NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies:

1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Supplementary Table 5. Quality assessment of included case series.

Reference	Study type	Interferants	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Vigersky, 2006 [46]	Case series	Metformin	Y	N	Y	N	Y	Y	Y	N	Y
Guarda, 2019 [57]	Case series	Mifepristone	Y	Y	Y	Y	Y	Y	Y	N	Y
McCowen, 1997 [71]	Case series	Sertraline	Y	N	Y	Y	Y	Y	Y	N	Y
Liel, 1996 [100]	Case series	Fiber	Y	Y	Y	N	Y	Y	Y	Y	Y

Abbreviations: Y, yes; N, no

Questions of NHLBI Quality Assessment Tool for Case Series Studies:
1. Was the study question or objective clearly stated?
2. Was the study population clearly and fully described, including a case definition?
3. Were the cases consecutive?
4. Were the subjects comparable?
5. Was the intervention clearly described?
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?
7. Was the length of follow-up adequate?
8. Were the statistical methods well-described?
9. Were the results well-described?

Supplementary Table 6. Quality assessment of included case reports.

Reference	Study type	Interferants	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Schneyer, 1998 [2]	Case report	Calcium carbonate	N	N	Y	Y	Y	Y	N	Y
Butner, 2000 [3]	Case report	Calcium carbonate	Y	Y	Y	Y	Y	Y	N	Y
Csako, 2001 [5]	Case report	Calcium carbonate	Y	Y	Y	Y	Y	Y	N	Y
Mazokopakis, 2008 [8]	Case report	Calcium carbonate	Y	Y	Y	Y	Y	Y	N	Y
Shakir, 1997 [14]	Case report	Ferrous sulfate	Y	Y	Y	Y	Y	Y	N	Y
Leger, 1999 [15]	Case report	Ferrous sulfate	Y	Y	Y	Y	Y	Y	N	Y
Vita, 2014 [21]	Case report	Pantoprazole (PPI)	Y	Y	Y	Y	Y	Y	N	Y
Sperber, 1992 [27]	Case report	Aluminum hydroxide	Y	N	Y	Y	Y	Y	N	Y
Mersebach, 1999 [29]	Case report	Aluminum hydroxide, magnesium oxide	Y	Y	Y	Y	Y	Y	N	Y
Havrankova, 1992 [30]	Case report	Sucralfate	Y	N	Y	Y	Y	Y	N	Y
Sherman, 1994 [33]	Case report	Sucralfate	Y	Y	Y	Y	Y	Y	N	Y

Demke, 1989 [35]	Case report	Lovastatin	Y	Y	Y	Y	Y	Y	N	Y
Kisch, 2005 [38]	Case report	Simvastatin	Y	N	Y	Y	Y	Y	N	Y
Harmon, 1991 [40]	Case report	Cholestyramine	Y	N	Y	Y	Y	Y	N	Y
Northcutt, 1969 [41]	Case report	Cholestyramine	Y	N	Y	Y	Y	Y	N	Y
Madhava, 2005 [44]	Case report	Orlistat	Y	Y	Y	Y	Y	Y	N	Y
Balapatabendi, 2011 [45]	Case report	Simethicone	Y	Y	Y	Y	Y	Y	N	Y
McLean, 1993 [50]	Case report	Cation-exchange resin (sodium polystyrene sulphonate)	N	Y	Y	Y	Y	Y	N	Y
Iovino, 2014 [51]	Case report	Sevelamer carbonate	Y	Y	Y	Y	Y	Y	N	Y
Siraj, 2003 [53]	Case report	Raloxifene	Y	Y	Y	Y	Y	Y	N	Y
Garwood, 2006 [54]	Case report	Raloxifene	Y	Y	Y	Y	Y	Y	N	Y
Isley, 1987 [58]	Case report	Rifampin	Y	Y	Y	Y	Y	Y	N	Y
Nolan, 1999 [59]	Case report	Rifampin	Y	Y	Y	Y	Y	Y	N	Y

Cooper, 2005 [61]	Case report	Ciprofloxacin	Y	N	Y	Y	Y	Y	N	Y
Berger, 2017 [62]	Case report	Ritonavir	Y	Y	Y	Y	Y	N	N	Y
Sahajpal, 2017 [63]	Case report	Ritonavir	Y	Y	Y	Y	Y	Y	N	Y
Lanzafame, 2002 [64]	Case report	Indinavir	Y	Y	Y	Y	Y	Y	N	Y
Touzot, 2006 [65]	Case report	Lopinavir, Ritonavir, Nelfinavir	Y	Y	Y	Y	Y	Y	N	Y
Blackshear, 1983 [67]	Case report	Phenytoin	Y	Y	Y	Y	Y	Y	N	Y
Figge, 1990 [73]	Case report	Amiodarone	Y	Y	Y	Y	Y	Y	N	Y
Narula, 2004 [76]	Case report	Capecitabine	Y	Y	Y	Y	Y	Y	N	Y
Cappelli, 2020 [94]	Case report	Lunch	Y	Y	Y	Y	Y	Y	N	Y
Pinchera, 1965 [95]	Case report	Soy formula	Y	Y	Y	Y	Y	Y	N	Y
Fruzza, 2012 [97]	Case report	Soy formula	Y	Y	Y	Y	Y	Y	N	Y
Bell, 2001 [98]	Case report	Soy protein supplement	Y	Y	Y	Y	Y	Y	N	Y
Benvenga, 2008 [101]	Case report	Coffee	N	N	Y	Y	Y	Y	N	Y

Wegrzyn, 2016 [103]	Case report	Coffee	Y	N	Y	Y	Y	Y	N	Y
Deiana, 2012 [106]	Case report	Papaya fruit	Y	Y	Y	Y	Y	Y	N	Y
Mahapatro, 2019 [107]	Case report	Dentifrice	Y	Y	Y	Y	Y	Y	N	Y

Abbreviations: Y, yes; N, no

Questions of JBI Critical Appraisal Checklist for Case Rerports.

1. Were patient's demographic characteristics clearly described?
2. Was the patient's history clearly described and presented as a timeline?
3. Was the current clinical condition of the patient on presentation clearly described?
4. Were diagnostic tests or assessment methods and the results clearly described?
5. Was the intervention(s) or treatment procedure(s) clearly described?
6. Was the post-intervention clinical condition clearly described?
7. Were adverse events (harms) or unanticipated events identified and described?
8. Does the case report provide takeaway lessons?

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