hydrochlorothiazide and (4) sodium chloride supplementation with hydrochlorothiazide. Participants underwent all four phases, but in two different sequences (randomly created): group A (n=16) followed the sequence as described above and group B (n=14) followed the phases in the following sequence: 3-4-1-2. A wash-out period of six weeks was set between the two phases of sodium chloride supplementation (control) and the two phases of placebo supplementation (intervention). For the current advisory report, the Committee considered the results of the effect of sodium chloride restriction within the group treated with hydrochlorothiazide (phase 2 versus 4) and within the group without hydrochlorothiazide treatment (phase 1 versus 3). One phase lasted four weeks. Participants were instructed to take five tables each of 20 mmol of sodium chloride (=460 mg sodium) daily during the last two weeks of the control phase (phase 3 and 4) or an equal number of placebo tablets (lactose) daily during the last two weeks of the intervention phase (phase 1 and 2). 24-hour Ambulatory (systolic) blood pressure was measured at the beginning and the end of each phase.

At baseline, mean sodium intake (based on 24-hour urinary sodium excretion, presumably collected once) was approximately 2700 ± 300 mg and 6250 ± 550 mg in those with a low and a high habitual sodium intake, respectively. Overall, a 2-week sodium chloride restriction of circa 6 grams per day (advised) reduced systolic blood pressure on average with 5.6 mmHg (95%CI: 1.7-9.4) within four weeks. There were no interaction-effects observed with hydrochlorothiazide treatment (yes/no) or habitual sodium intake (low/high).

Kwakernaak et al.[19] examined the separate and combined effects of sodium restriction and the diuretic hydrochlorothiazide on systolic blood pressure in people with type 2 diabetes nephropathy and micro- or macro-albuminuria who were maximally treated with the angiotensin-converting enzyme (ACE) inhibitor lisinopril. This multicenter cross-over RCT comprised of four consecutive phases: (1) regular sodium diet with hydro-chlorothiazide, (2) regular sodium diet without hydrochlorothiazide (placebo, (3) sodium-restricted diet without hydrochlorothiazide (placebo) and (4) sodium-restricted diet with hydrochlorothiazide. Participants underwent all four phases, but in four different sequences. No wash-out period was set. For the current advisory report, the Committee considered the results of the effect of sodium restriction within the group treated with hydrochlorothiazide (phase 4 versus 1) and within the group without hydrochlorothiazide treatment (phase 3 versus 2). One phase lasted six weeks. All participants received dietary counselling by dietitians. In the intervention phases, participants were advised to follow a sodium-re-stricted diet of 1200 mg sodium through not using any added salt and replacing sodium-rich foods with sodium-poor foods (a list with sodium contents of foods was provided). In the control phases, participants were advised to follow a regular sodium diet of approximately 4800 mg sodium, which practically meant that they were advised to maintain habitual salt

consumption. Systolic blood pressure was measured at the beginning and the end of each phase.

When participants were not treated with hydrochlorothiazide, 6-week sodium supplementation reduced systolic blood pressure on average with 5.3 mmHg (95%CI: 1.5-9.1) compared to placebo within six weeks (P=0.008). Similar findings were observed when participants received concomitant hydrochlorothiazide treatment (effect size NR; P=0.0009). Based on sodium excretion in two 24-hour urine samples, it was estimated that sodium excretion was approximately 5150 mg during the control phase and 3600 mg during the intervention phase. This difference in sodium intake between intervention and control was less than anticipated (~1550 mg achieved versus 3600 mg advised).

Parvanova et al.[20] examined the separate and combined effects of sodium restriction and the antiparathyroid agent paricalcitol on systolic blood pressure in people with type 2 diabetes, losartan-resistant macroalbuminuria and a blood pressure below 140/90 mmHg. In this multicentre parallel RCT, participants were randomised to either the intervention group, who was advised to follow a low sodium diet of less than 2300 mg sodium, or the control group, who was advised to follow a high sodium diet of at least 4600 mg sodium. Participants followed this diet for three months. Within these groups, participants were additionally randomised, in a cross-over manner, to 1-month paricalcitol treatment or placebo, with a wash-out period of one month. 24-hour Ambulatory (systolic) blood pressure was measured at baseline, month 1, month 2 and month 3 (after each phase).

At baseline, mean sodium intake (based on three collections of 24-hour urinary sodium excretion) was approximately 4400 mg/d. At each time point, systolic blood pressure was not statistically different between the intervention group and control group (after adjustment for baseline values of blood pressure). The achieved difference in sodium intake between the intervention group and the control group was less than anticipated (~700 mg achieved versus 2400 mg advised). This difference was also smaller than in the other RCTs included in this evaluation, which might explain the lack of an effect in this RCT.

Subgroup and sensitivity analyses

Suckling et al. did not perform subgroup or sensitivity analyses within the subgroup of people with type 2 diabetes.

Risk of bias

Suckling et al. judged the risk of bias as high for all studies. In five studies, the risk of bias was judged as high due to the funding source (e.g. manufacturer of sodium and placebo supplement or financial support by the Diabetic Association or Merck and Apex Diabetes Australia Research Grant). In four studies the risk of bias was judged as high, because no

intention-to-treat analysis was performed. However, no information on compliance is available, so the Committee could not judge whether this would have affected the results. In two studies the risk of bias was high because participants were not blinded to the intervention.

The risk of bias was judged as ‘some concerns’ in the RCTs by Ames and by Ekinci et al., because information was lacking on whether allocation sequence was random and concealed. Also, no trial protocol was available, so selective reporting of results could not be ruled out. The risk of bias was judged as ‘some concerns’ in the RCT by Parvanova et al., because it is unclear if allocation sequence was concealed until participants were enrolled (risk of bias arising from the randomisation process) and there may be deviations from the intended intervention (although the impact on the results is expected to be small). The risk of bias was judged as low in the RCT by Kwakernaak et al.

Funding

No notable funding sources or author’s conflicts of interests were reported (**Annex C**), except for the funding sources in five of the RCTs included in the MA by Suckling et al. (as described above).

Compliance

Information on compliance was not reported in the MA of Suckling et al.

In the RCT by Ames, adherence to the intervention was monitored by measuring 24-hour urine excretion of sodium (containers were collected every two weeks). Mean sodium intake was 3150 mg/d and 5800 mg/d after the control phase and the intervention phase, respectively, resulting in an achieved mean difference in sodium intake between intervention and control of 2650 mg/d. Compared to the target difference in sodium intake of 3200 mg/d, this suggest that compliance was moderate to good.

In the RCT by Ekinci et al., compliance was monitored by counting capsules and measuring 24-hour urinary sodium excretion. Based on the number of capsules dispensed, the compliance was rated as high. However, the increase in 24-hour urinary sodium excretion (on average 56 mmol = 1288 mg) was about half the amount expected based on the prescribed sodium chloride supplementation (100 mmol sodium chloride = 2300 mg sodium). The authors reported that this difference may be caused by the gastrointestinal side effects of the sodium chloride capsules (e.g. nausea and vomiting) reported by some participants. Net salt retention was suggested as another reason, although this was considered less likely because body weight did not change significantly during sodium chloride supplementation.

In the RCT by Kwakernaak et al., compliance to the sodium-restricted diet was monitored by measuring 24-hour urinary sodium excretion in the middle and at the end of each 6-week treatment phase. Sodium excretion was 224 ± 73 mmol/d (= 5150 mg sodium) during the regular sodium diet, and 164 ± 73 and 148 ± 65 mmol/d (= 3770 and 3400 mg) during the sodium-restricted diet with and without with hydrochlorothiazide, respectively. These results suggest that compliance with the sodium-restricted diet was limited since the target sodium intake for this diet was 1200 mg/d. However, there was still a large and statistically significant difference in sodium intake between control and intervention (approximately 1380-1750 mg/d; P<0.0001).

In the RCT by Parvanova et al., compliance to the diets was monitored by measuring urinary sodium excretion in three 24-hour urine samples. Mean sodium intake at baseline was 4370 mg/d and had slightly increased to 4600 mg/d in the control group and had decreased to 3900 mg/d in the intervention group after the 3-month study period, resulting in a mean difference between groups of approximately 700 mg. At each time point, the difference in sodium intake between groups was statistically significant (P<0.01). Compared to the target sodium intake of 1200 mg in the intervention group (and the resulting target mean difference between groups of 3400 mg), the compliance can be rated as poor.

Summary

The Committee included one MA of seven RCTs and four recent individual RCTs in the evaluation of the effect of sodium restriction on systolic blood pressure in people with type 2 diabetes. The MA showed that a reduced sodium intake lowered systolic blood pressure after 5 days to 3 months. The reducing effect of sodium restriction was also observed in two recent individual RCTs. Of the two other recent individual RCTs, one showed a tendency towards a reducing effect and one showed no effect. Moderate heterogeneity was observed. This was likely not the result of the type of sodium intervention or the simultaneous use of antihypertensive medication. Potential sources of heterogeneity might be the achieved difference in sodium intake between intervention and control, the presence of secondary conditions (e.g. hypertension, nephropathy) or the use of medication (other than the antihypertensive drugs), but this could not be properly investigated based on the data available.

3.2 Evidence from prospective cohort studies

The characteristics and results of the prospective cohort studies regarding associations of higher sodium intake with risks of all-cause mortality, mortality due to CVD and morbidity due to CVD, CHD, stroke and heart failure in adults with type 2 diabetes are summarised in Table 5.

Table 5 Overview of associations of sodium intake with risk of health outcomes in people with type 2 diabetes: prospective cohort studies.

Study; Study duration	Ekinci et al., 2011[15]; 10 years[a]	Mills et al., 2016[16]; 7 years[a]
Study design	Individual cohort study	Individual cohort study
Cohort name	NA	Chronic Renal Insufficiency Cohort (CRIC) Study
Exposure(s)	Sodium intake	Sodium intake
Dietary assessment method	Sodium intake was assessed based on 24-hour urinary sodium excretion from a median of two collections (range: 1-5; mean of all collections in 2001 used for analyses).	Sodium intake was estimated using the cumulative mean of 24-hour urinary sodium excretion obtained from the baseline visit and the first 2 annual follow-up visits prior to a study event, and calibrated according to the sex-specific mean.[b]
Number of participants; number of cases	638 participants; All-cause mortality: 175 CVD mortality: 75	1674-1684 participants; number of cases NR
Strength of the association: HR (95%CI)	per 100 mmol/d higher urinary sodium excretion[c]: ALL-CAUSE MORTALITY: 0.72 (0.55-0.94)[d]	per 1000 mg/24 h higher calibrated urinary sodium excretion[e]: CVD (NON-FATAL): 1.11 (1.05-1.17)[f] MI (NON-FATAL): 1.08 (0.98-1.19)[f] STROKE (NON-FATAL): 1.17 (1.05-1.32)[f] HEART FAILURE (NON-FATAL): 1.09 (1.02-1.16)[f]
Strength of the association: HR (95%CI) - continued	CVD MORTALITY: 0.65 (0.44-0.95)[d]	
Study population	People diagnosed with type 2 diabetes; BMI: NR; diabetes duration[g]: 12 ± 8 y; diabetes medication: metformin (55%), sulfonylurea (43%), insulin (41%); men and women; Australia	People with CKD and diabetes; BMI: NR; diabetes duration: NR; diabetes medication: NR; men and women; USA

BMI: body mass index; CI: confidence interval; CKD: chronic kidney disease; CVD: cardiovascular disease; d: days; eGFR: estimated glomerular filtration rate; HR: hazard ratio; NA: not applicable; NR: not reported; USA: United States of America; y: years.

[a] Median.
[b] In the total study population (people with and without diabetes), 58% had 3 measurements of urinary sodium, 26% had 2 measurements and 16% had 1 measurement. Mean urinary sodium excretion did not statistically significantly differ between those with 3 measurements and those with fewer measurements.
[c] 100 mmol of urinary sodium is equivalent to approximately 2400 mg of dietary sodium.
[d] Associations were adjusted for age, sex, diabetes duration, atrial fibrillation, presence and severity of CKD (eGFR and log (urinary) albumin excretion rate).
[e] 1000 mg of urinary sodium is equivalent to approximately 1050 mg of dietary sodium.
[f] Associations were adjusted for age, sex, race, clinic site, education, waist circumference, lean BMI, BMI, cigarette smoking, alcohol drinking, physical activity, low-density lipoprotein cholesterol, glucose, history of CVD, antidiabetic medications, lipid-lowering medications, renin-angiotensin system blocking agents, diuretics, other antihypertensive medications, urinary creatinine excretion and baseline eGFR.
[g] Mean (± standard deviation).

The Committee concluded the following:

There is too little research to draw conclusions regarding associations of sodium intake with the risks of all-cause mortality, mortality due to CVD, and morbidity due to CVD, CHD, stroke or heart failure in people with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

There are no MAs of prospective cohort studies that address associations of sodium intake with risks of chronic disease or mortality. There is only one individual prospective cohort study that addresses the association with all-cause mortality and CVD mortality. Similarly, there is only one individual prospective cohort study that addresses the association with morbidity due to CVD and subtypes of CVD. One individual study is too little evidence to base conclusions on.

Explanation:

For the outcomes of all-cause mortality and mortality due to CVD, the Committee could include only one prospective cohort study, by **Ekinci et al.**[15], in its evaluation of associations with sodium intake in people with type 2 diabetes. This study, including 638 participants and reporting 175 cases of mortality, of which 75 due to CVD, showed that higher sodium intake was statistically significantly associated with a lower risk of all-cause mortality and CVD mortality. No interaction by BMI, age, sex, type of antihypertensive therapy or achieved level of blood pressure control was observed. A strength of this study is the use of (mostly) multiple 24-hour urine collections to estimate sodium intake. A limitation is that the study was performed in a high-risk population, i.e. patients with longstanding type 2 diabetes who were poorly controlled and who had multiple comorbidities at baseline, including renal impairment and pre-existing CVD (34% CHD, 18% atrial fibrillation, 45% macrovascular disease, 14% congestive heart failure), limiting the generalisability of this study's findings to the general type 2 diabetes population.

For the outcomes of morbidity due to CVD and the CVD subtypes CHD (specifically: MI), stroke and heart failure, the Committee could include only one prospective cohort study, by **Mills et al.**[16], in its evaluation of associations with sodium intake in people with type 2 diabetes. This study among people with chronic kidney disease performed subgroup analyses among participants with diabetes (n=1674). Mean calibrated sodium excretion ranged from 2345 ± 436 mg/24h (approximately 2450 mg of dietary sodium) in quartile 1 to 5776 ± 1361 mg/24h (approximately 6050 mg of dietary sodium) in quartile 4 of calibrated urinary sodium excretion. The study showed that higher sodium intake was statistically significantly associated with a higher risk of non-fatal CVD (i.e. non-fatal events of MI, stroke and congestive heart failure), non-fatal stroke and non-fatal heart failure. For example, each 1 g/d higher sodium intake was associated with a 17% (95%CI: 5-32) higher risk of non-fatal stroke. No association was

observed with non-fatal MI. A strength of this study is the use of (mostly) multiple 24-hour urine collections to estimate sodium intake and the calibration procedure applied. A limitation is that this study did not examine sodium intakes below 2300 mg/d (the recommended level for the general population), and thus it is unknown to what extent sodium intakes below the current recommendation are related to CVD risk.

Funding or author's conflicts of interest likely did not affect the study findings of the study included in this evaluation (**Annex C**).

04
summary of conclusions

The Committee's conclusions regarding relationships (effects or associations) of sodium intake with health outcomes in people with type 2 diabetes are summarised in Table 6.

Table 6 Overview of conclusions regarding the relationship (effects/associations) of sodium intake with health outcomes in people with type 2 diabetes, based on randomised controlled trials or prospective cohort studies.

Health outcome[a]	Type of studies	Conclusion
HbA1c	RCTs	Too little research
Blood pressure	RCTs	Limited evidence for a reducing effect of lower sodium intake
All-cause mortality	Prospective cohort studies	Too little research
Mortality due to CVD	Prospective cohort studies	Too little research
Morbidity due to CVD	Prospective cohort studies	Too little research
Morbidity due to CHD	Prospective cohort studies	Too little research
Morbidity due to stroke	Prospective cohort studies	Too little research
Heart failure (non-fatal)	Prospective cohort studies	Too little research

CHD: coronary heart disease; CVD: cardiovascular disease; HbA1c: glycated haemoglobin; RCT: randomised controlled trial.

[a] The table contains the health outcomes for which (relevant) studies were found. For the health outcomes that are not listed in the table, no (relevant) studies were found.

references

1 Health Council of the Netherlands. *Dutch dietary guidelines for people with type 2 diabetes.* The Hague: Health Council of the Netherlands, 2021; publication no. 2021/41e.

2 Gezondheidsraad. *Natrium - Achtergronddocument bij Richtlijnen goede voeding 2015*. Den Haag: Gezondheidsraad, 2015; publicatienummer A15/15.

3 Health Council of the Netherlands. *Dutch dietary guidelines 2015*. The Hague: Health Council of the Netherlands, 2015; publication no. 2015/26E.

4 Kromhout D, Spaaij CJ, de Goede J, Weggemans RM. *The 2015 Dutch food-based dietary guidelines*. Eur J Clin Nutr 2016; 70(8): 869-878.

5 Hendriksen M, Etemad Z, Van den Bogaard CHM, Van der A DL. *Zout-, jodium- en kaliuminname 2015. Voedingsstatusonderzoek bij volwassenen uit Doetinchem*. Bilthoven: RIVM Briefrapport 2016-0081, 2015.

6 van Rossum CTM, Buurma-Rethans EJM, Dinnissen CS, Beukers MH, Brants HAM, Dekkers ALM, et al. *The diet of the Dutch. Results of the Dutch National Food Consumption Survey 2012-2016*. Bilthoven: National Institute for Public Health and the Environment (RIVM), 2020; report no. 2020-0083.

7 Health Council of the Netherlands. *Methodology for the evaluation of evidence. Background document to Dutch dietary guidelines for people with type 2 diabetes.* The Hague: Health Council of the Netherlands, 2021; publication no. 2021/41Ae.

8 Suckling RJ, He FJ, Macgregor GA. *Altered dietary salt intake for preventing and treating diabetic kidney disease*. Cochrane Database Syst Rev 2010; (12): CD006763.

9 Nederlandse Diabetes Federatie. *NDF Voedingsrichtlijn Diabetes*. Amersfoort, November 2020.

10 Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. *2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD*. Eur Heart J 2020; 41(2): 255-323.

11 Evert AB, Dennison M, Gardner CD, Garvey WT, Lau KHK, MacLeod J, et al. *Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report*. Diabetes Care 2019; 42(5): 731-754.

12 Diabetes UK 2018 Nutrition Working Group. *Evidence-based nutrition guidelines for the prevention and management of diabetes*. United Kingdom, 2018.

13 Diabetes Canada Clinical Practice Guidelines Expert Committee, Sievenpiper JL, Chan CB, Dworatzek PD, Freeze C, Williams SL. *Nutrition Therapy*. Can J Diabetes 2018; 42 Suppl 1: S64-S79.

14 Swedish Council on Health Technology Assessment. *Summary and Conclusions of the SBU Report: Dietary Treatment of Diabetes. A Systematic Review.* Stockholm, 2010.

15 Ekinci EI, Clarke S, Thomas MC, Moran JL, Cheong K, MacIsaac RJ, et al. *Dietary salt intake and mortality in patients with type 2 diabetes*. Diabetes Care 2011; 34(3): 703-709.

[16] Mills KT, Chen J, Yang W, Appel LJ, Kusek JW, Alper A, et al. *Sodium Excretion and the Risk of Cardiovascular Disease in Patients With Chronic Kidney Disease*. JAMA 2016; 315(20): 2200-2210.

[17] Ames RP. *The effect of sodium supplementation on glucose tolerance and insulin concentrations in patients with hypertension and diabetes mellitus*. Am J Hypertens 2001; 14(7 Pt 1): 653-659.

[18] Ekinci EI, Thomas G, MacIsaac RJ, Johnson C, Houlihan C, Panagiotopoulos S, et al. *Salt supplementation blunts the blood pressure response to telmisartan with or without hydrochlorothiazide in hypertensive patients with type 2 diabetes*. Diabetologia 2010; 53(7): 1295-1303.

[19] Kwakernaak AJ, Krikken JA, Binnenmars SH, Visser FW, Hemmelder MH, Woittiez AJ, et al. *Effects of sodium restriction and hydrochlorothiazide on RAAS blockade efficacy in diabetic nephropathy: a randomised clinical trial*. Lancet Diabetes Endocrinol 2014; 2(5): 385-395.

[20] Parvanova A, Trillini M, Podestà MA, Iliev IP, Ruggiero B, Abbate M, et al. *Moderate salt restriction with or without paricalcitol in type 2 diabetes and losartan-resistant macroalbuminuria (PROCEED): a randomised, double-blind, placebo-controlled, crossover trial*. Lancet Diabetes Endocrinol 2018; 6(1): 27-40.

[21] Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. *RoB 2: a revised tool for assessing risk of bias in randomised trials*. BMJ 2019; 366: l4898.

[22] Abbasnezhad A, Falahi E, Gonzalez MJ, Kavehi P, Fouladvand F, Choghakhori R. *Effect of different dietary approaches compared with a regular diet on systolic and diastolic blood pressure in patients with type 2 diabetes: A systematic review and meta-analysis*. Diabetes Res Clin Pract 2020; 163: 108108.

[23] de Paula TP, Kramer CK, Viana LV, Azevedo MJ. *Effects of individual micronutrients on blood pressure in patients with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials*. Sci Rep 2017; 7: 40751.

[24] Dodson PM, Beevers M, Hallworth R, Webberley MJ, Fletcher RF, Taylor KG. *Sodium restriction and blood pressure in hypertensive type II diabetics: randomised blind controlled and crossover studies of moderate sodium restriction and sodium supplementation*. BMJ 1989; 298(6668): 227-230.

[25] Kong YW, Baqar S, Jerums G, Ekinci EI. *Sodium and Its Role in Cardiovascular Disease - The Debate Continues*. Front Endocrinol (Lausanne) 2016; 7: 164.

[26] Dunkler D, Dehghan M, Teo KK, Heinze G, Gao P, Kohl M, et al. *Diet and kidney disease in high-risk individuals with type 2 diabetes mellitus*. JAMA Intern Med 2013; 173(18): 1682-1692.

[27] Sievenpiper JL, Chan CB, Dworatzek PD, Freeze C, Williams SL, Diabetes Canada Clinical Practice Guidelines Expert Committee. *Nutrition Therapy*. Can J Diabetes 2018; 42 Suppl 1: S64-S79.

[28] Dunkler D, Kohl M, Teo KK, Heinze G, Dehghan M, Clase CM, et al. *Dietary risk factors for incidence or progression of chronic kidney disease in individuals with type 2 diabetes in the European Union*. Nephrol Dial Transplant 2015; 30 Suppl 4: iv76-85.

[29] Saulnier PJ, Gand E, Ragot S, Bankir L, Piguel X, Fumeron F, et al. *Urinary Sodium Concentration Is an Independent Predictor of All-Cause and Cardiovascular Mortality in a Type 2 Diabetes Cohort Population*. J Diabetes Res 2017; 2017: 5327352.

[30] Horikawa C, Yoshimura Y, Kamada C, Tanaka S, Tanaka S, Hanyu O, et al. *Dietary sodium intake and incidence of diabetes complications in Japanese patients with type 2 diabetes: analysis of the Japan Diabetes Complications Study (JDCS)*. J Clin Endocrinol Metab 2014; 99(10): 3635-3643.

[31] Liu D, Baqar S, Lincz LL, Ekinci EI. *Sodium Intake, Circulating Microvesicles and Cardiovascular Outcomes in Type 2 Diabetes*. Curr Diabetes Rev 2019; 15(6): 435-445.

annexes

A search strategies, study selection and flow diagrams

Systematic reviews including meta-analyses

The Committee performed a literature search to identify relevant SRs including MAs on the relationship of salt or sodium intake with health outcomes in people with type 2 diabetes. Literature searches were performed in PubMed and Scopus on 3rd February 2021 using the following search strategies:

PubMed

(“diabetes mellitus, type 2”[MeSH] OR Diabet*[tiab] OR T2DM[tiab] OR NIDDM[tiab]) AND (“sodium chloride”[MeSH] OR “sodium chloride”[tiab] OR salt*[tiab] or sodium[tiab]) AND (Systematic review[publication type] OR Meta-analysis[publication type] OR review[tiab] OR “meta-analysis” [tiab] OR meta analysis [tiab] OR metaanalysis[tiab] OR quantitative review[tiab] OR quantitative overview[tiab] OR systematic review[tiab] OR systematic overview[tiab] OR methodologic review[tiab] OR methodologic overview[tiab]) NOT (“Sodium-Glucose Transporter 2 Inhibitors”[Mesh] OR SGLT2[tiab] OR SGLT[tiab] OR SGLT2i[tiab] OR “Sodium-Glucose Cotransporter 2 Inhibitor”[tiab] OR Sodium-Glucose Transporter 2 Inhibitors[tiab] OR “sodium-glucose co-transporter-2 inhibitor”[tiab] OR “sodium-glucose co-transporter-2 inhibitors”[tiab] OR “SGLT inhibitor”[tiab] OR “SGLT inhibitors”[tiab] OR “sodium-glucose co-transporter”[tiab] OR “sodium-glucose cotransporter”[tiab] OR “Sodium Bicarbonate”[Mesh])

Limit: from 2000

Scopus

(KEY (“diabetes mellitus, type 2”) OR TITLE-ABS-KEY (t2dm) OR TITLE-ABS-KEY (niddm) OR TITLE-ABS (“diabetes mellitus, type 2”) OR TITLE-ABS (diabet*) OR TITLE-ABS (t2dm) OR TITLE-ABS (niddm)) AND (TITLE-ABS (“sodium chloride”) OR TITLE-ABS (salt) OR TITLE-ABS (sodium)) AND (TITLE-ABS-KEY (“Systematic review”) OR TITLE-ABS-KEY (“Meta-analysis”) OR TITLE-ABS (review) OR TITLE-ABS (meta-analysis) OR TITLE-ABS (metaanalysis) OR TITLE-ABS (“quantitative review”) OR TITLE-ABS (“quantitative overview”) OR TITLE-ABS (“systematic overview”) OR TITLE-ABS (“methodologic review”) OR TITLE-ABS (“methodologic overview”)) AND NOT (TITLE-ABS-KEY (Sodium-Glucose Transporter 2 Inhibitors) OR TITLE-ABS-KEY (SGLT2) OR TITLE-ABS (SGLT) OR TITLE-ABS-KEY (SGLT2i) OR TITLE-ABS-KEY (Sodium-Glucose Cotransporter 2 Inhibitor) OR TITLE-ABS-KEY (sodium-glucose co-transporter-2 inhibitor) OR TITLE-ABS-KEY (sodium-glucose co-transporter-2 inhibitors) OR TITLE-ABS-KEY (SGLT inhibitor) OR TITLE-ABS-KEY (SGLT inhibitors) OR TITLE-ABS-KEY (sodium-glucose co-transporter) OR

TITLE-ABS-KEY (sodium-glucose cotransporter) OR TITLE-ABS-KEY (Sodium Bicarbonate))

Limit: from 2000

In total, 721 publications were found in PubMed and 761 publications in Scopus. After removal of duplicates, 944 publications remained and were screened for title and abstract. A total of 60 publications remained for full-text assessment, of which three publications were included: Abbasnezhad et al.[22], de Paula et al.[23] and Suckling et al.[8] The SRs by Abbasnezhad et al. and de Paula et al. reported on only one RCT: the RCT by Dodgson et al.[24] The SR by Suckling et al. included more RCTs, including the RCT by Dodson et al. Therefore, the Committee included only the SR by Suckling et al. in its evaluation of sodium intake.

Recent individual randomised controlled trials

The Committee performed two literature searches to identify relevant individual RCTs that were published after the inclusion date of the MA by Suckling et al. Specifically, the Committee searched for RCTs into sodium intake and blood pressure or HbA1c in people with type 2 diabetes (published since 2010). Only blood pressure and HbA1c were considered since the Committee focuses only on the health outcomes that were already covered in the selected MA. Literature searches for RCTs into blood pressure (1st March 2021) and HbA1c (16th March 2021) were performed in PubMed and Scopus using the following search strategies:

Sodium intake and blood pressure

PubMed

(“diabetes mellitus, type 2”[MeSH] OR Diabet*[tiab] OR T2DM[tiab] OR NIDDM[tiab]) AND (“sodium chloride”[MeSH Terms] OR “sodium chloride”[tiab] OR salt*[tiab] or sodium[tiab]) AND (“Blood Pressure”[Mesh] OR blood pressure[tiab] OR Diastolic Pressure[tiab] OR Systolic Pressure[tiab] OR pulse pressure[tiab]) AND (“Clinical Trials as Topic”[Mesh] OR “Clinical Trial” [Publication Type] OR “Cross-Over Studies”[Mesh] OR “Double-Blind Method”[Mesh] OR “Single-Blind Method”[Mesh] OR “Controlled Before-After Studies”[Mesh] OR “Historically Controlled Study”[Mesh] OR randomized[tiab] OR randomised[tiab] OR RCT[tiab] OR controlled*[tiab] OR placebo[tiab] OR clinical trial[tiab] OR trial[tiab] OR intervention[tiab]) NOT (“Sodium-Glucose Transporter 2 Inhibitors”[Mesh] OR SGLT2[tiab] OR SGLT[tiab] OR SGLT2i[tiab] OR “Sodium-Glucose Cotransporter 2 Inhibitor”[tiab] OR Sodium-Glucose Transporter 2 Inhibitors[tiab] OR “sodium-glucose co-transporter-2 inhibitor”[tiab] OR “sodium-glucose co-transporter-2 inhibitors”[tiab] OR “SGLT inhibitor”[tiab] OR “SGLT inhibitors”[tiab] OR “sodium-glucose co-transporter”[tiab] OR “sodium-glucose cotransporter”[tiab] OR “Sodium Bicarbonate”[Mesh])

Limit: from 2010

Scopus

(KEY (“diabetes mellitus, type 2”) OR TITLE-ABS-KEY (t2dm) OR TITLE-ABS-KEY (niddm) OR TITLE-ABS (“diabetes mellitus, type 2”) OR TITLE-ABS (diabet*) OR TITLE-ABS (t2dm) OR TITLE-ABS (niddm)) AND (TITLE-ABS (“sodium chloride”) OR TITLE-ABS (salt) OR TITLE-ABS (sodium)) AND (TITLE-ABS (“blood Pressure”) OR TITLE-ABS (“diastolic Pressure”) OR TITLE-ABS (“systolic Pressure”) OR TITLE-ABS (“pulse pressure”)) AND (TITLE-ABS-KEY (“clinical trial”) OR TITLE-ABS-KEY (“cross-over studies”) OR TITLE-ABS-KEY (“double-blind method”) OR TITLE-ABS-KEY (“single-blind method”) OR TITLE-ABS-KEY (“controlled before-after studies”) OR TITLE-ABS-KEY (“historically controlled study”) OR TITLE-ABS (randomized) OR TITLE-ABS (randomised) OR TITLE-ABS (rct) OR TITLE-ABS (controlled*) OR TITLE-ABS (placebo) OR TITLE-ABS (“clinical trial”) OR TITLE-ABS (trial) OR TITLE-ABS (intervention)) AND NOT (TITLE-ABS-KEY (Sodium-Glucose Transporter 2 Inhibitors) OR TITLE-ABS-KEY (SGLT2) OR TITLE-ABS (SGLT) OR TITLE-ABS-KEY (SGLT2i) OR TITLE-ABS-KEY (Sodium-Glucose Cotransporter 2 Inhibitor) OR TITLE-ABS-KEY (sodium-glucose co-transporter-2 inhibitor) OR TITLE-ABS-KEY (sodium-glucose co-transporter-2 inhibitors) OR TITLE-ABS-KEY (SGLT inhibitor) OR TITLE-ABS-KEY (SGLT inhibitors) OR TITLE-ABS-KEY (sodium-glucose co-transporter) OR TITLE-ABS-KEY (sodium-glucose cotransporter) OR TITLE-ABS-KEY (Sodium Bicarbonate))

Limit: from 2010

In total, 227 publications were found in PubMed and 261 publications in Scopus. After removal of duplicates, 310 publications remained and were screened for title and abstract. A total of 18 publications remained for full-text assessment, of which three RCTs[18-20] were included.
One additional RCT[17] was obtained via a review.[25]

The Committee selected the following four recent RCTs for its evaluation of sodium intake and blood pressure:

- Ames, 2001[17]
- Ekinci et al., 2010[18]
- Kwakernaak et al., 2014[19]
- Parvanova et al., 2018[20]

Sodium intake and HbA1c

PubMed

(“diabetes mellitus, type 2”[MeSH] OR Diabet*[tiab] OR T2DM[tiab] OR NIDDM[tiab]) AND (“sodium chloride”[MeSH Terms] OR “sodium chloride”[tiab] OR salt*[tiab] or sodium[tiab]) AND (glycemic control[tiab] OR glycaemic control[tiab] OR glycemia[tiab] OR glycaemia[tiab] OR

“Glycated Hemoglobin A”[Mesh] OR HbA1c[tiab] OR Glycated Hemoglobin[tiab] OR Glycosylated Hemoglobin[tiab]) AND (“Clinical Trials as Topic”[Mesh] OR “Clinical Trial” [Publication Type] OR “Cross-Over Studies”[Mesh] OR “Double-Blind Method”[Mesh] OR “Single-Blind Method”[Mesh] OR “Controlled Before-After Studies”[Mesh] OR “Historically Controlled Study”[Mesh] OR randomized[tiab] OR randomised[tiab] OR RCT[tiab] OR controlled*[tiab] OR placebo[tiab] OR clinical trial[tiab] OR trial[tiab] OR intervention[tiab]) NOT (“Sodium-Glucose Transporter 2 Inhibitors”[Mesh] OR SGLT2[tiab] OR SGLT[tiab] OR SGLT2i[tiab] OR “Sodium-Glucose Cotransporter 2 Inhibitor”[tiab] OR Sodium-Glucose Transporter 2 Inhibitors[tiab] OR “sodium-glucose co-transporter-2 inhibitor”[tiab] OR “sodium-glucose co-transporter-2 inhibitors”[tiab] OR “SGLT inhibitor”[tiab] OR “SGLT inhibitors”[tiab] OR “sodium-glucose co-transporter”[tiab] OR “sodium-glucose cotransporter”[tiab] OR “Sodium Bicarbonate”[Mesh])

Limit: from 2010

Scopus

(KEY (“diabetes mellitus, type 2”) OR TITLE-ABS-KEY (t2dm) OR TITLE-ABS-KEY (niddm) OR TITLE-ABS (“diabetes mellitus, type 2”) OR TITLE-ABS (diabet*) OR TITLE-ABS (t2dm) OR TITLE-ABS (niddm)) AND (TITLE-ABS (“sodium chloride”) OR TITLE-ABS (salt) OR TITLE-ABS (sodium)) AND (TITLE-ABS (glucose) OR TITLE-ABS (“glycemic control”) OR TITLE-ABS (“glycaemic control”) OR TITLE-ABS (glycemia) OR TITLE-ABS (glycaemia) OR TITLE-ABS-KEY (“glycated hemoglobin a”) OR TITLE-ABS (hba1c) OR TITLE-ABS (“glycated hemoglobin”) OR TITLE-ABS (“glycosylated hemoglobin”)) AND (TITLE-ABS-KEY (“clinical trial”) OR TITLE-ABS-KEY (“cross-over studies”) OR TITLE-ABS-KEY (“double-blind method”) OR TITLE-ABS-KEY (“single-blind method”) OR TITLE-ABS-KEY (“controlled before-after studies”) OR TITLE-ABS-KEY (“historically controlled study”) OR TITLE-ABS (randomized) OR TITLE-ABS (randomised) OR TITLE-ABS (rct) OR TITLE-ABS (controlled*) OR TITLE-ABS (placebo) OR TITLE-ABS (“clinical trial”) OR TITLE-ABS (trial) OR TITLE-ABS (intervention)) AND NOT (TITLE-ABS-KEY (Sodium-Glucose Transporter 2 Inhibitors) OR TITLE-ABS-KEY (SGLT2) OR TITLE-ABS (SGLT) OR TITLE-ABS-KEY (SGLT2i) OR TITLE-ABS-KEY (Sodium-Glucose Cotransporter 2 Inhibitor) OR TITLE-ABS-KEY (sodium-glucose co-transporter-2 inhibitor) OR TITLE-ABS-KEY (sodium-glucose co-transporter-2 inhibitors) OR TITLE-ABS-KEY (SGLT inhibitor) OR TITLE-ABS-KEY (SGLT inhibitors) OR TITLE-ABS-KEY (sodium-glucose co-transporter) OR TITLE-ABS-KEY (sodium-glucose cotransporter) OR TITLE-ABS-KEY (Sodium Bicarbonate))

Limit: from 2010

In total, 113 publications were found in PubMed and 277 publications in Scopus. After removal of duplicates, 304 publications remained and were screened for title and abstract. A total of 7 publications remained for full-text assessment, none of which fit within the Committee's inclusion criteria.

Prospective cohort studies

Since no SRs or MAs of (multiple) cohort studies were found, the Committee searched for individual prospective cohort studies on associations of sodium intake with health outcomes in people with type 2 diabetes in the retrieved SRs and in external dietary guidelines for diabetes of the following organisations:

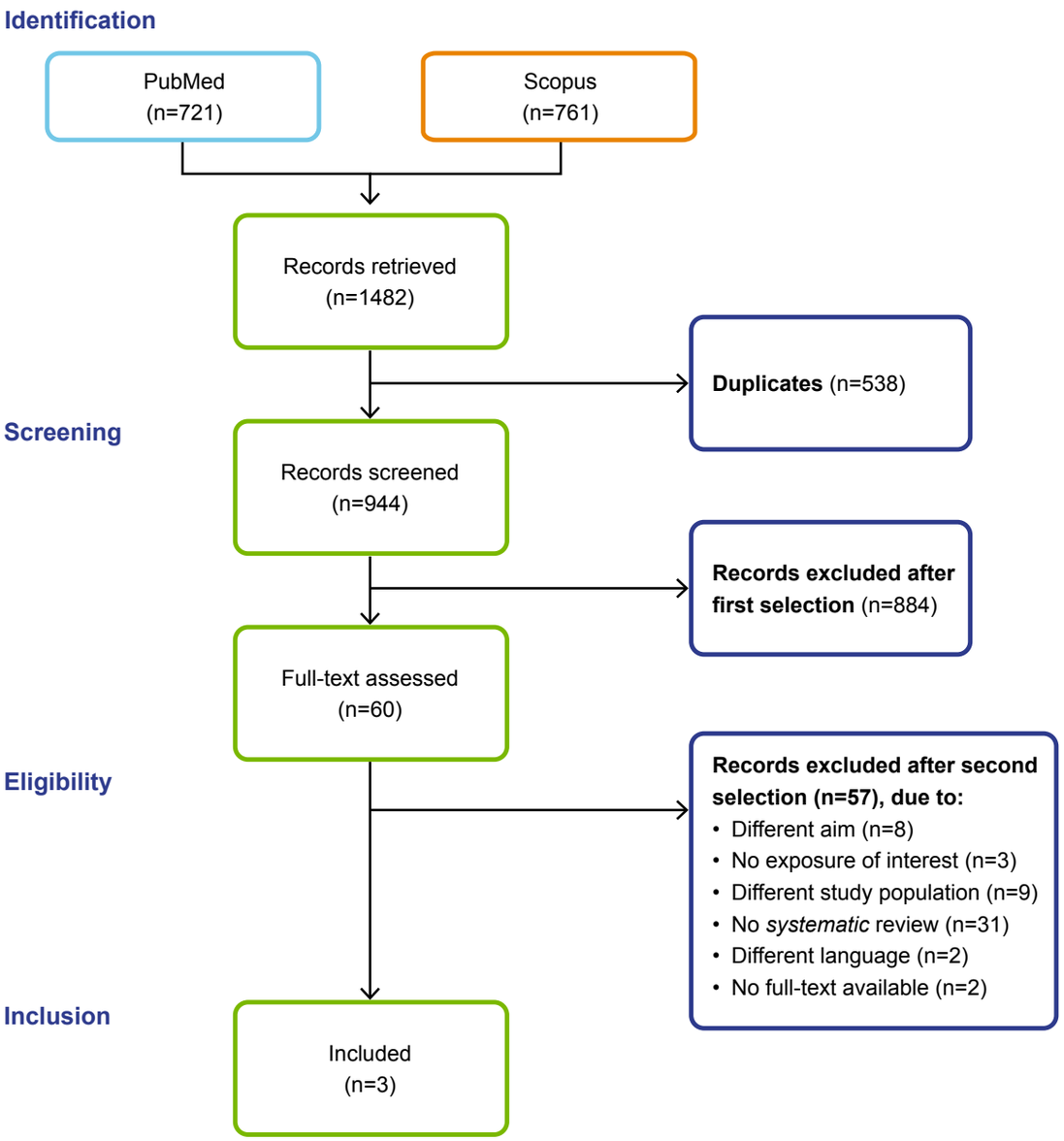
- Dutch Diabetes Federation (Nederlandse Diabetes Federatie (NDF)), 2020[9]
- European Association for the Study of Diabetes (EASD) & European Society of Cardiology (ESC), 2020[10]
- American Diabetes Association (ADA), 2019[11]
- Diabetes UK, 2018[12]
- Diabetes Canada, 2018[13]
- Swedish Council, 2010[14]

Two cohort studies[15,26] were retrieved through screening of the dietary guidelines for diabetes of the NDF,[9] the ADA[11] and Diabetes Canada.[27] Subsequently, articles citing these studies were searched in PubMed. This yielded two additional cohort studies.[28,29] One additional cohort study[30] was obtained via a review.[31] Of those five cohort studies, four studies estimated sodium intake using an FFQ[30] or a spot urine sample[26,28,29], which measurements were considered inappropriate to obtain a valid estimate of sodium intake (see also section 2.2). Those studies were therefore excluded. Screening of reference lists of publications yielded one additional relevant prospective cohort study.[16]

The Committee selected the following two prospective cohort studies for its evaluation of sodium intake:

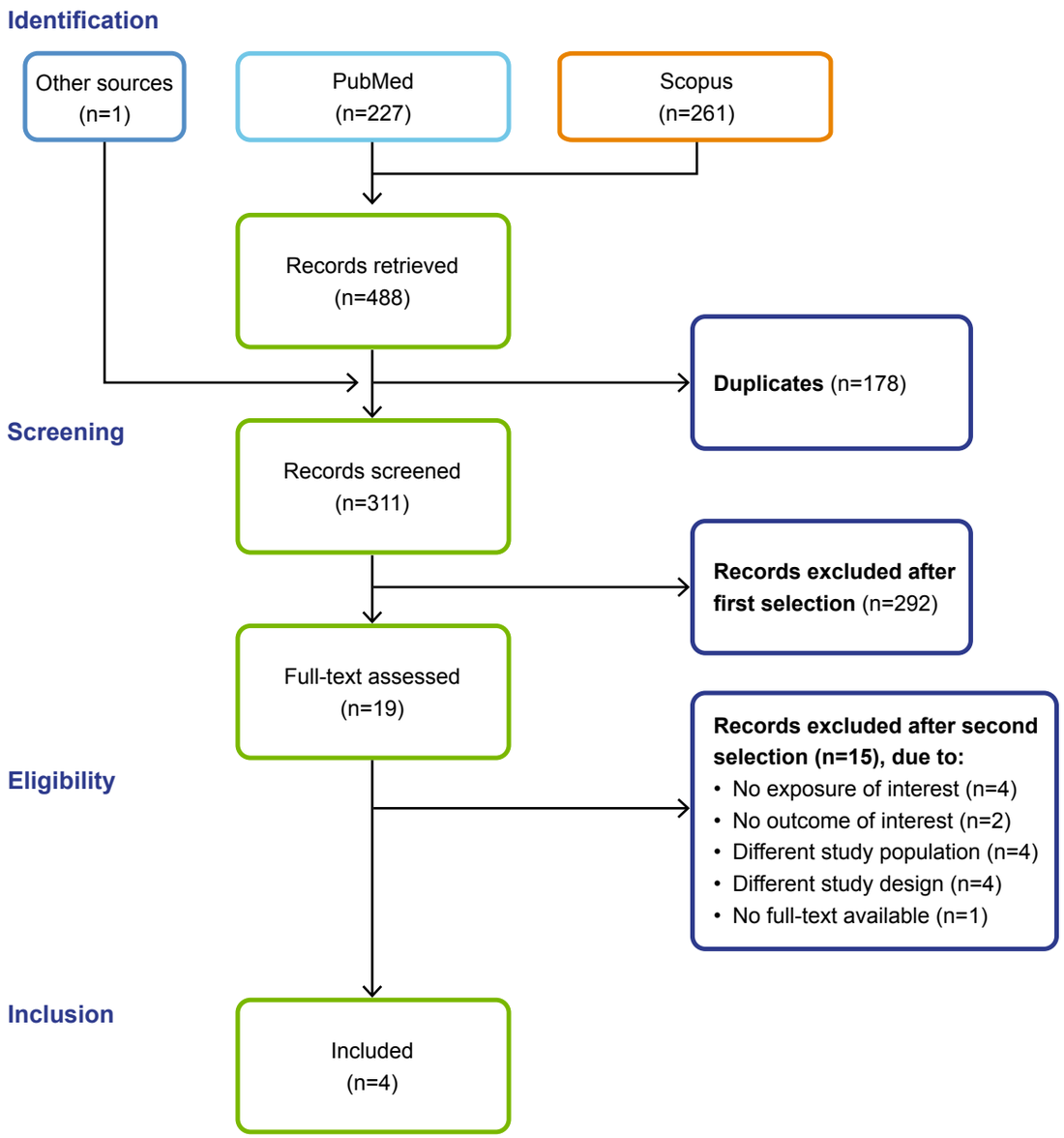
- Ekinci et al., 2011[15]
- Mills et al., 2016[16]

Flow diagram for the selection of systematic reviews including meta-analyses



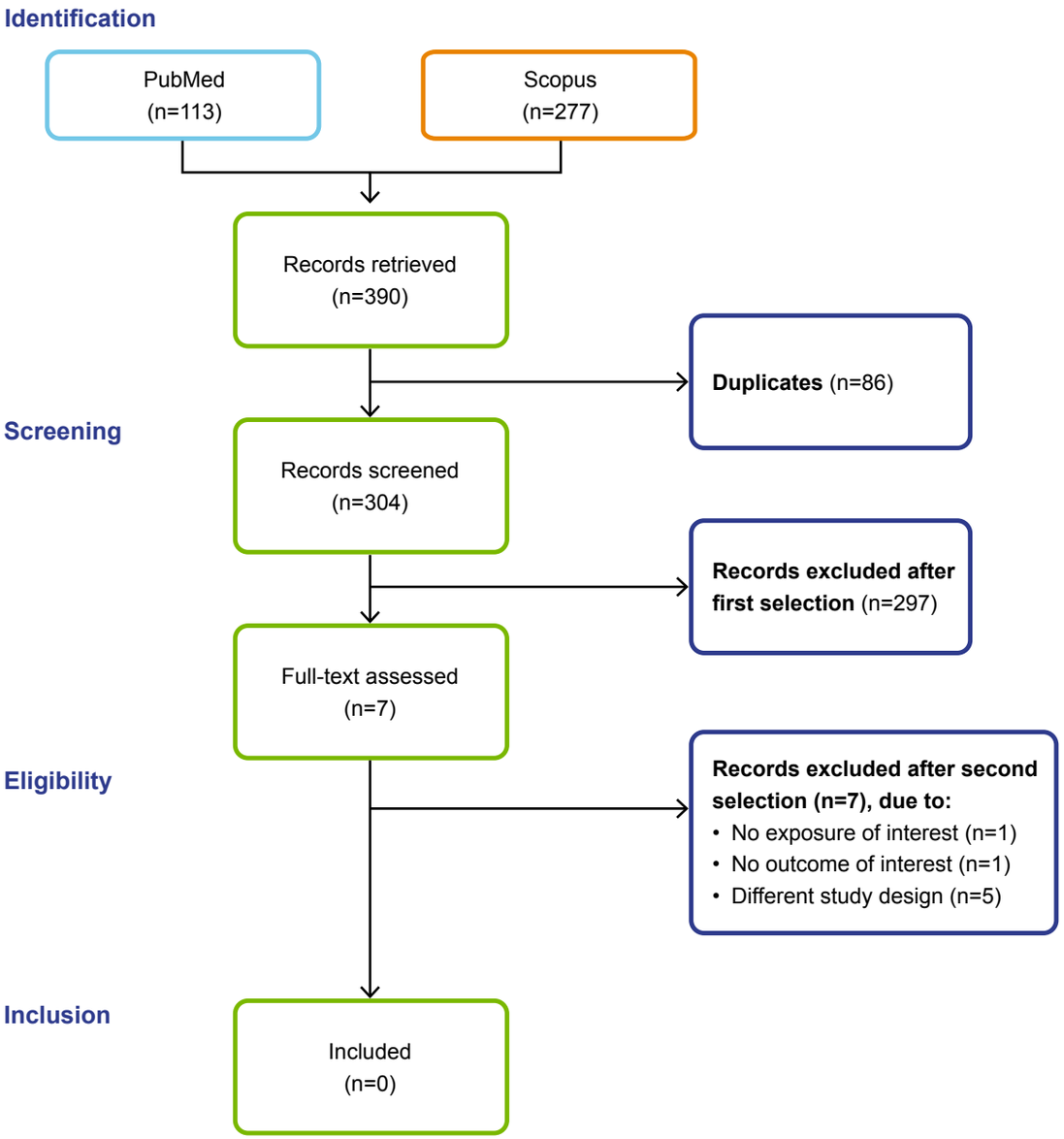
Flow diagram for the selection of recent individual randomised controlled trials

Table salt/sodium and systolic blood pressure

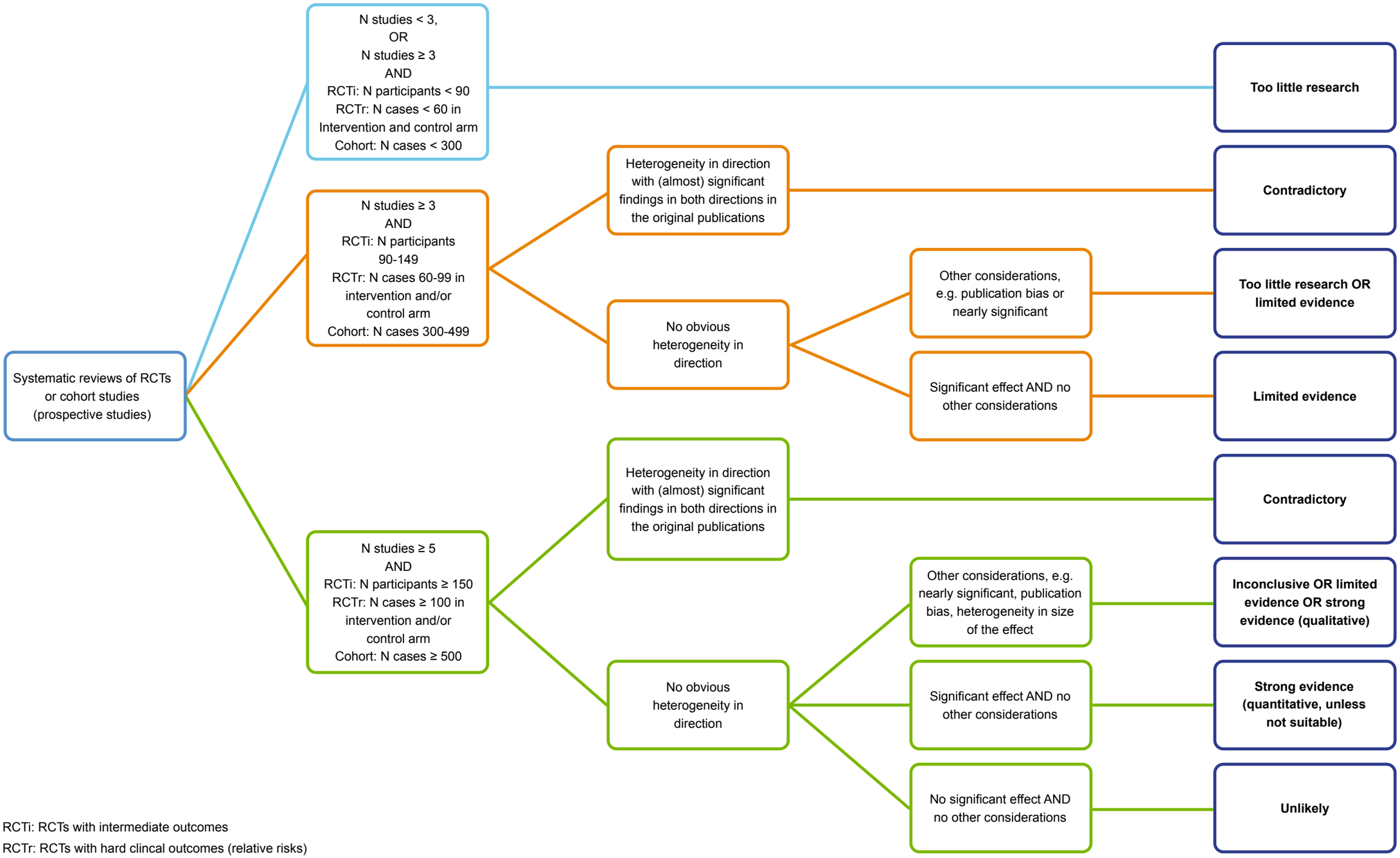


Flow diagram for the selection of recent individual randomised controlled trials

Table salt/sodium and HbA1c



B decision tree



RCTi: RCTs with intermediate outcomes

RCTr: RCTs with hard clincal outcomes (relative risks)

C funding sources and conflicts of interest regarding the articles used in this background document

In the table below, the funding sources of the studies listed in this background document and conflicts of interests of authors contributing to those studies are reported.

Study's first author, year	Funding of the work	Conflicts of interest of authors
Ames, 2001	No information provided.	No information provided.
Ekinci, 2010[18]	The study was supported by the pharmaceutical company Boehringer Ingelheim.[a]	The first author was financially supported by the Austin Hospital Medical Research Foundation and the National Health and Medical Research Council.
Ekinci, 2011[15]	No information provided.	Three authors were supported by the National Health and Medical Research Council, two authors by the Austin Hospital Medical Research Foundation, one author by the pharmaceutical company Pfizer and one author by the KHA Bootle bequest. The other authors declared to have no conflicts of interest.
Kwakernaak, 2014[19]	It was reported that the paper was written without any funding. The study was funded by the University Medical Center Groningen (the Netherlands).	The authors declared to have no conflicts of interest.
Mills, 2016[16]	The study was funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the University of Pennsylvania, Johns Hopkins University, University of Maryland, Clinical and Translational Science Collaborative of Cleveland, Michigan Institute for Clinical and Health Research, University of Illinois at Chicago, Tulane University and Kaiser. The program director at NIDDK contributed to the design and conduct of the study; analysis and interpretation of the data; and review and approval of the manuscript.	The first author is supported by the National Heart, Lung and Blood Institute. One author received support from Medtronic and ATCOR (both medical device companies) and one author from Medtronic, Janssen (pharmaceutical company), Relypsa (pharmaceutical company) and UpToDate (electronic clinical resource tool). The other authors declared to have no conflicts of interest.
Parvanova, 2018[20]	The study was funded by the pharmaceutical company Abbvie. It was reported that the funder freely supplied paricalcitol or placebo capsules and covered the costs of the study, but had no role in data collection, data analysis, data interpretation or writing of the report.[b]	The authors declared to have no conflicts of interest.
Suckling, 2010[8]	No information provided.	No information provided.

[a] The Committee judged that funding by this pharmaceutical company is unlikely to have affected the results regarding the salt intervention (given the hypothesis that higher salt intake increases cardiovascular risk).

[b] The Committee judged that funding is likely no potential source of bias since the results described in the current background document refer to the salt intervention and not to the paricalcitol intervention.

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).
The Health Council receives most requests for advice from the Ministers of Health, Welfare and Sport, Infrastructure and Water Management, Social Affairs and Employment, and Agriculture, Nature and Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.
Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity.
The reports are available to the public.

This publication can be downloaded from www.healthcouncil.nl.

Preferred citation:
Health Council of the Netherlands. Sodium. Background document to Dutch dietary guidelines for people with type 2 diabetes.
The Hague: Health Council of the Netherlands, 2021; publication no. 2021/41Ie.