Sodium

No. 2021/41Ie, The Hague, November 16, 2021

Background document to:
Dutch dietary guidelines for people with type 2 diabetes
No. 2021/41e, The Hague, November 16, 2021

Health Council of the Netherlands

contents

01 introduction

The current background document belongs to the advisory report *Dutch dietary guidelines for people with type 2 diabetes*.[1] It describes the methodology for the search, selection and evaluation of the literature regarding the relationship of sodium intake with health outcomes in adults with type 2 diabetes. It furthermore describes the scientific evidence on this topic and the conclusions that have been drawn by the Health Council's Committee on Nutrition.

1.1 Definitions of sodium and table salt

Sodium is present in many foods and is added to foods. An important source of sodium in our food is table salt. Table salt (in Dutch: keuken-zout) is the name given to the sodium chloride that is present in our food through use in the kitchen or at the dinner table, or because it is added to processed foods.[2,3] Sodium chloride consists for 40% of sodium (and 60% of chloride); one gram of table salt is equivalent to approximately 400 mg of sodium.[4] Sodium is also added to foods in other forms, such as sodium bicarbonate in baking soda and sodium lactate in cold cuts. A relatively small amount of sodium is naturally present in foods. Of the total sodium content of the diet, approximately 20% is added in the kitchen or at the table and about 80% is in foods as purchased. Foods often high in sodium are bread, cheese, sausages, hearty snacks and ready-to-eat products.

1.2 Salt recommendation and intake in the Netherlands

The Health Council of the Netherlands included a guideline for table salt consumption in the *Dutch dietary guidelines 2015*, which is as follows[3]: Limit salt intake to 6 gram daily.

Six grams of salt is equivalent to 2400 mg sodium. This guideline is applicable to the general Dutch adult population. The Council has not previously made specific dietary recommendations for people with type 2 diabetes.

Based on the sodium excretion in a 24-hour urine sample[ab], median sodium intake in the Netherlands was estimated to be 9.7 g/d (inter-quartile range (IQR): 7.7-12.6 g/d) for men and 7.4 (5.7-9.0) g/d for women.[5] Discretionary salt is used at preparation or at the table by approximately 85% of the Dutch population. Data from the most recent Dutch National Food Consumption Survey (2012-2016) shows that the most important sources of sodium from food for the general Dutch population aged 19 to 79 years are cereal products including bread (26%), meat products (20%), dairy products including cheese (17%) and sauces and seasonings (10%).[6]

[a] Estimating sodium intake by measuring sodium excretion in 24-hour urine collections is considered more valid than via dietary assessment methods such as 24-hour recalls or food frequency questionnaires.

[b] In the Netherlands, nutritional status surveys (i.e. monitoring intake of minerals via 24-hour urine samples) are collected periodically. In 2015, a nutritional status survey was conducted among 289 adults aged 19 to 70 years from Doetinchem, who collected urine once for 24 hours.[5] Because approximately 95% of daily sodium intake is excreted via urine, urinary sodium excretion was multiplied by 100/95.

02 methodology

2.1 Research question

The Committee aimed to answer the following question: what is the relationship (effect or association) of sodium intake with health outcomes in adults with type 2 diabetes?

The Committee aimed to distinguish between short-term and long-term effects or associations where possible.

2.2 Nutritional topics

The Committee searched for studies into sodium intake or salt intake (i.e. sodium chloride). This could be either studies comparing a high sodium diet with a low sodium diet or studies comparing a sodium chloride supplement with a placebo supplement. The decision to include supplement studies is an exception to the Committee's general rule not to consider studies using food supplements. The reason for this exception is that the dietary guideline for sodium concerns sodium from *table salt,* which includes sodium that is naturally present in foods as well as discretionary sodium added during food processing, cooking or at the table. The Committee regards sodium chloride supplements comparable to added salt (from a salt cellar), amongst others because both do not contain other nutrients that may have an effect itself or interact with sodium. It therefore deemed it relevant to include studies that used a sodium chloride supplement.

Various methods can be used to assess sodium intake (in cohort studies), but not all methods provide valid estimates of daily sodium intake. The Committee followed the *Dutch dietary guidelines 2015* with respect to the criteria for the assessment of dietary sodium.[2] Studies in which sodium intake was estimated using a dietary assessment method, such as the food frequency questionnaire (FFQ) or 24-hour dietary recall, were excluded from the Committee's evaluation. Such methods may incorporate substantial measurement error. Random measurement error may result from the difficulty to precisely estimate the consumed amount of cooking salt and the amount of salt added at the table. Because of this, cooking salt is sometimes completely disregarded in studies, which may lead to systematic measurement error (underestimation of sodium intake). There is thus a high risk of invalid estimates of sodium intake based on these dietary assessment methods. Another method for assessing sodium intake is through measuring urinary sodium excretion, since approximately 95% of sodium intake leaves the body via urine. Studies in which sodium intake was estimated from a 24-hour urine sample were included. Due to the high day-to-day variability of sodium intake, multiple samples of 24-hour urinary sodium excretion are preferred. Studies in which 24-hour urinary sodium excretion was calculated from a *single* urine sample (also called a spot urine sample or morning urine sample) were excluded, because a single urine sample cannot be properly used to derive a valid estimate of 24-hour (daily) sodium intake.

2.3 Outcomes

The Committee selected the following health outcomes for this advisory report (for which a motivation is provided in the background document *Methodology for the evaluation of the evidence*[7]:

Surrogate outcomes:

- Glycated haemoglobin (HbA1c);
- Fasting blood glucose;
- Body weight;
- Systolic blood pressure;
- Low-density lipoprotein (LDL) cholesterol;
- Estimated glomerular filtration rate (eGFR).

Long-term health outcomes:

- All-cause mortality;
- Morbidity and/or mortality from total cardiovascular diseases (CVD), coronary heart disease (CHD), stroke, heart failure, chronic obstructive pulmonary disease, total cancer, breast cancer, colorectal cancer, lung cancer, dementia, depression, chronic kidney disease.

Other:

- Diabetes remission: HbA1c <48 mmol/mol and no use of diabetes medication for ≥1 year;
- Diabetes reversion: HbA1c <53 mmol/mol and less medication use for ≥1 year.

For cohort studies, the Committee included only studies with long-term health outcomes.

2.4 Selection and evaluation of literature

A detailed description of the approach used by the Committee for selecting and evaluating the scientific literature is provided in the background document *Methodology for the evaluation of evidence*.[7]
In short, the Committee aimed to base its evaluation of scientific literature on systematic reviews (SRs), including meta-analyses (MAs), of randomised controlled trials (RCTs) and/or prospective cohort studies (i.e. prospective cohort studies, nested case-control studies and case-cohort studies) examining the relationship of salt or sodium intake with the above-mentioned health outcomes in people with type 2 diabetes.
In addition, the Committee searched for more recent individual studies that were not included in the most recent SR or MA. The literature searches were performed in PubMed and Scopus in February (SRs and MAs) and March (recent RCTs) 2021. The search strategies, flow

diagrams of the literature searches and detailed descriptions of the study selection are provided in **Annex A**.

2.4.1 Selection of randomised controlled trials

The Committee included one MA of RCTs into the effect of sodium intake on HbA1c and blood pressure; the MA by Suckling et al.[8] The Committee complemented the evidence from this MA with recent evidence from individual RCTs published after the inclusion date of the MA by Suckling et al. (January 2010). This search was limited to the outcomes of HbA1c and blood pressure, because these are the outcomes already covered in the MA. A total of four individual RCTs were included in the Committee's evaluation of blood pressure (Table 1) and no additional relevant RCTs were found for HbA1c.

2.4.2 Selection of prospective cohort studies

The Committee found no SRs (or MAs) of prospective cohort studies on sodium intake, so deemed it worthwhile to search for individual prospective cohort studies into the relationship between sodium intake and long-term health outcomes in people with type 2 diabetes. The Committee searched for prospective cohort studies in existing external dietary guidelines for diabetes.[9-14] For the individual studies that were retrieved this way, the Committee screened all "similar articles" and "cited by articles" in PubMed. This yielded one prospective cohort study, which examined association of sodium intake with risks of all-cause mortality and mortality from CVD.[15] Via reference lists of other publications, the Committee found one additional prospective cohort study in which subgroup analyses were performed in people with diabetes. This study examined associations of sodium intake with risks of morbidity from total CVD and CVD subtypes.[16] The studies selected for inclusion in the Committee's evaluation are presented in Table 1. The Committee did not find cohort studies within the pre-specified in- and exclusion criteria for any of the other specified chronic diseases and diabetes remission or diabetes reversion.

Table 1 Overview of meta-analyses, individual randomised controlled trials and prospective cohort studies selected by the Committee for the evaluation of the relationship of sodium intake with health outcomes.

Health outcome[a]	Meta-analysis (of RCTs)	Individual RCTs	Prospective cohort studies
HbA1c	Suckling et al., 2010[8]	None	None
Blood pressure	Suckling et al., 2010[8]	Ames, 2001[17] Ekinci et al., 2010[18] Kwakernaak et al., 2014[19] Parvanova et al., 2018[20]	None
All-cause mortality	None	None	Ekinci et al., 2011[15]
Mortality due to CVD	None	None	Ekinci et al., 2011[15]
Morbidity due to CVD	None	None	Mills et al., 2016[16]
Morbidity due to CHD	None	None	Mills et al., 2016[16]
Morbidity due to stroke	None	None	Mills et al., 2016[16]
Heart failure (non-fatal)	None	None	Mills et al., 2016[16]

CHD: coronary heart disease; CVD: cardiovascular disease; 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.

2.4.2 Risk of bias assessment

Four domains of risk of bias were assessed in the MA by Suckling et al.[8]: allocation concealment, blinding (of investigators, participants, outcome assessors and data analysis), intention to treat analysis and funding source. The risk of bias of the individual RCTs was assessed by the Committee using the revised Cochrane Collaboration's tool RoB 2.[21]

2.4.4 Drawing conclusions

A detailed description of the approach used by the Committee for drawing conclusions is provided in the background document *Methodology for the evaluation of evidence*.[7] In short, the Committee drew conclusions on (the certainty of) the evidence regarding the effects of higher salt or sodium intake on HbA1c and blood pressure and regarding associations of sodium intake and risks of all-cause mortality, mortality due to CVD and morbidity due to CVD, CHD, stroke and heart failure in people with type 2 diabetes, based on the number of studies, number of participants and number of cases that contributed to the evaluation. Also, it took into account the risk of bias and the heterogeneity between studies.
The Committee used the decision tree (**Annex B**) as a tool to support consistency in drawing conclusions.

03
effects and associations of sodium intake

3.1 Evidence from randomised controlled trials

3.1.1 HbA1c

The characteristics and results of the MA by Suckling et al.[8] providing evidence regarding effects of sodium restriction on HbA1c in people with type 2 diabetes are summarised in Table 2.

Table 2 Overview of effects of reduced sodium intake on HbA1c in people with type 2 diabetes: meta-analysis of randomised controlled trials.

Study; **Study duration**	**Suckling et al., 2010[8];** **3 months**
Number of studies	3 RCTs
Number of participants in intervention (i) and control (c) group	i: 54, c: 54 (37 unique participants; 17 are counted double since they participated in a cross-over study)
Study design (number of RCTs)	Parallel (1), cross-over (2)
Dietary exposure of intervention (i) and control (c) group (number of RCTs)	i: Moderate sodium restriction (1) Low sodium diet (50-70 mmol/d = 1150-1610 mg/d) (2) c: Usual diabetic diet (1) Regular sodium diet (>100 mmol/d = >2300 mg/d) (2)
Heterogeneity	No: 0%
Strength of the effect: Between-group MD[a] (95%CI)	-0.12% (-0.58-0.34) (absolute value); fixed effect)
Study population	People with type 2 diabetes and hypertension; BMI: NR; diabetes duration: NR; diabetes medication: NR; men and women; Europe, Australia

BMI: body mass index; c: control group; CI: confidence interval; i: intervention group; MD: mean difference; NR: not reported; RCT: randomised controlled trial; y: years.

[a] Calculated as the difference between the two treatment groups in the change in outcomes from baseline.

The Committee concluded the following:

There is too little research to draw conclusions regarding effects of sodium intake on HbA1c 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 is one MA of three RCTs included in the evaluation. The MA included in total fewer than 90 (unique) participants, which is too little evidence to base a conclusion on.

Explanation:

The Committee included one MA of 3 RCTs (by Suckling et al.[8]) in its evaluation of the effect of sodium intake on HbA1c in people with type 2 diabetes.

Study characteristics and main effects

The MA by **Suckling et al.**[8] only included RCTs in which at least a 2-g difference in salt intake (= 800 mg sodium) was achieved between intervention and control groups. Both people with type 1 and type 2 diabetes were included in the MA; the Committee only used the subgroup analyses among adults with type 2 diabetes (n=37) for its evaluation.

This analysis included three RCTs, of which one with a parallel design and two with a cross-over design. One study had four intervention arms (two arms received antihypertensive agents and two arms did not) with

non-overlapping study samples, so this study was counted as two separate RCTs. In all RCTs, it concerned hypertensive people with type 2 diabetes. In the RCTs, a sodium-restricted diet (intervention) was compared with a regular sodium diet or a usual diabetic diet (control) over a follow-up period of three months.

Overall, following a sodium-restricted diet had no statistically significant effect on HbA1c levels in people with type 2 diabetes within three months. No heterogeneity was observed. All RCTs were of relatively short duration, so the Committee could not determine whether there would be a long-term effect of sodium restriction on HbA1c.

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. assessed risk of bias in four domains: allocation concealment, blinding (of investigators, participants, outcome assessors and data analysis), intention to treat analysis and funding source. The authors judged the risk of bias as high for all studies due to the funding source, participants not being blinded and/or because no intention-to-treat analysis was performed. However, no information on compliance is available, so the Committee could not judge whether the latter would have affected the results.

Funding

No notable funding sources or author's conflicts of interests were reported with respect to the MA itself (**Annex C**).

Compliance

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

Summary

The Committee included one MA of three RCTs, with a total of only 37 participants, in the evaluation of the effect of sodium restriction on HbA1c levels in people with type 2 diabetes. The MA showed that a sodium restriction of at least 800 mg/d had no effect on HbA1c levels within three months. No heterogeneity was observed.

3.1.2 Blood pressure

Table 3 summarises the characteristics and results of the MA by Suckling et al. providing evidence regarding effects of sodium restriction on blood pressure in people with type 2 diabetes. Table 4 summarises the characteristics and results of the individual RCTs regarding effects of sodium restriction on blood pressure in people with type 2 diabetes. For the benefit of readability and interpretability, in the description of the

results below, a sodium restriction (e.g. reduced-sodium diet, placebo supplements, low sodium intake) is consistently considered the intervention as the hypothesis is that sodium reduction is beneficial for systolic blood pressure.

Table 3 Summary of the effects of reduced sodium intake on systolic blood pressure in people with type 2 diabetes: meta-analysis of randomised controlled trials.

Study; **Study duration**	**Suckling et al., 2010[8];** **5 days to 3 months**
Number of studies; Number of participants in intervention (i) and control (c) group	7 RCTs i: 62, c: 62 (79 unique participants; 45 are counted double since they participated in a cross-over study)
Study design (number of RCTs)	Parallel (1), cross-over (6)
Dietary exposure of intervention (i) and control (c) group (number of RCTs)	i: Moderate sodium restriction (1); Low sodium diet (50-70 to 80 mmol/d = 1150-1610 to 1840 mg/d) (4); Sodium restriction with placebo (2), c: Usual diabetic diet (1); Regular sodium diet (>100 to 200 mmol/d = >2300 to 4600 mg/d) (4); Sodium restriction with slow release sodium supplement (of 80 or 120 mmol/d = 1840 to 2760 mg/d) (2)
Heterogeneity	Yes: 54%
Strength of the effect (of a sodium restriction): Between-group MD[a] (95%CI)	-6.90 mm Hg (-9.84- -3.95), fixed effect
Study population	People with type 2 diabetes and majority hypertensive; BMI: NR; diabetes duration: NR; diabetes medication: NR; men and women; Europe, Australia, Asia

BMI: body mass index; c: control group; CI: confidence interval; d: day; i: intervention group; MD: mean difference; NR: not reported; RCT: randomised controlled trial; y: years.

[a] Calculated as the difference between the two treatment groups in the change in outcomes from baseline.

Table 4 Summary of the effects of reduced sodium intake on systolic blood pressure in people with type 2 diabetes: individual randomised controlled trials.

Study; study duration	Ames, 2001[17]; 4 weeks	Ekinci et al., 2010[18]; 4 weeks	Kwakernaak et al., 2014[19]; 6 weeks	Parvanova et al., 2018[20]; 3 months
Total number of participants	8 (completers)	29 (completers)	45 (randomised)[b]	115 (58/57)[b]
Study design	Cross-over, no wash-out period	Cross-over, washout-out period of 6 weeks	Multi-centre trial (3 centres); cross-over, no wash-out period	Multi-centre trial (6 centres); parallel
Sodium dose[a]; diet of intervention (i) and control (c) group	3200 mg/d prescribed, 2650 mg/d achieved; i: Placebo (gelatin) supplements four times/d, c: 2-g sodium chloride supplements (= 800 mg sodium) four times/d	2300 mg/d prescribed, 1300 mg/d achieved; i: Placebo (lactose) supplements five times/d, c: 20-mmol sodium chloride supplements (= 460 mg sodium) five times/d	3600 mg/d prescribed, 1550 mg/d achieved; i: Sodium-restricted diet of 1200 mg/d (advised), c: Regular sodium diet of ~4800 mg/d (advised)	2400 mg/d prescribed, 700 mg achieved; i: Low sodium diet of <2400 mg/d (advised), c: High sodium diet of >4800 mg/d (advised)
Result for the effect of a sodium restriction	Mean values after intervention phase and control phase: i: 148 mmHg, c: 154 mmHg; NS	Between-group MD[c]: -5.6 mmHg (95%CI: -9.4- -1.7)	Between-group MD[c]: in those not treated with hydrochlorothiazide: -5.3 mmHg (95%CI: -1.5- -9.1) in those treated with hydrochlorothiazide: P=0.0009	NS (effect size NR)
Study population	Adults with type 2 diabetes and hypertension; BMI: NR; diabetes duration: NR; diabetes medication: oral hypoglycaemic agents (38%), insulin therapy (0%); men and women; North-America	Adults with type 2 diabetes and hypertension; BMI[d]: 33 ± 1 kg/m^2; diabetes duration: NR; diabetes medication: NR; sex: NR; Australia	Adults with type 2 diabetic nephropathy and albuminuria; BMI[d]: 32 ± 5 kg/m^2; diabetes duration[e]: 9 y (5-19); diabetes medication: insulin (56%), metformin (71%), sulfonylurea (38%); men and women; Europe	Adults with type 2 diabetes and macro-albuminuria; BMI[d]: 31 ± 5 kg/m^2; diabetes duration: NR; diabetes medication: NR; men and women; Europe

BMI: body mass index; c: control group; CI: confidence interval; d: day; i: intervention group; MD: mean difference; NR: not reported; NS: not statistically significant; RCT: randomised controlled trial; y: years.

[a] Difference between intervention group/phase and control group/phase.
[b] Intention-to-treat analysis was performed.
[c] Mean difference between intervention phase and control phase in change from baseline.
[d] Mean ± standard deviation.
[e] Median (interquartile range).

The Committee concluded the following:

Intervention studies show that a reduced sodium intake lowers systolic blood pressure within 5 days to 3 months in people with type 2 diabetes. The evidence is limited.

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

1. The Committee included one MA of seven RCTs and four recent individual RCTs, with a total of more than 150 participants (n=276), in its evaluation. This is the first step required to mark the evidence as strong. However, there were other considerations that lead to the conclusion of limited evidence, as described below.
2. The MA as well as two RCTs showed a reducing effect of a lower sodium intake on systolic blood pressure in people with type 2 diabetes. Two recent RCTs did not show a statistically significant effect but one of those RCTs showed a tendency towards a reducing effect of sodium restriction. There was no indication of heterogeneity in direction of the effect.
3. There is moderate heterogeneity in the size of the effect, for which no clear explanation was found based on the data available. The type of salt intervention and the use of antihypertensive medication were likely no sources of heterogeneity. Because of the unexplained heterogeneity in the size of the effect, the Committee judged the evidence as limited.

Explanation:

The Committee included one MA (Suckling et al.[8]) and four individual RCTs (Ames[17], Ekinci et al.[18], Kwakernaak et al.[19] and Parvanova et al.[20]) in its evaluation of the effect of sodium intake on systolic blood pressure in people with type 2 diabetes.

Study characteristics and main effects

The MA by **Suckling et al.[8]** was described in more detail in section 3.1.1 (HbA1c). The subgroup analysis among adults with type 2 diabetes included seven RCTs (n=79), of which one with a parallel design and six with a cross-over design. Two studies each had four intervention arms (two arms received antihypertensive agents and two arms did not, or two arms comprised of people with normoalbuminuria and two arms comprised of people with microalbuminuria) with non-overlapping study samples, so both studies were counted as two separate RCTs. Another study consisted of two phases: it started with a parallel study comparing a sodium-restricted diet with a usual diabetic diet (n=34) and was followed by a cross-over study comparing sodium supplements with placebo (n=9). Those two phases were counted as two separate RCTs. The Committee notes that there may be some degree of dependence between those RCTs within the same study. In five of the seven RCTs it concerned hypertensive people with type 2 diabetes. In five RCTs, a sodium-restricted diet (intervention) was compared with a regular sodium diet or a usual diabetic diet (control). In two RCTs, all participants followed a sodium-restricted

diet and were additionally prescribed either sodium chloride supplements (control) or placebo (intervention). The study duration ranged from five days to three months.

Overall, systolic blood pressure was on average 6.90 mmHg (95%CI: 3.95-9.84) lower after five days to three months of sodium restriction. Heterogeneity was high (I^2=54%). Factors causing the heterogeneity are unknown, because the results presented here were already based on a subgroup analysis of people with type 2 diabetes, and no further subgroup analyses were performed within this subgroup. Also, visual inspection of the forest plot did not reveal any potential source of heterogeneity. The majority of the RCTs included in this MA were of short duration; consequently, it is difficult to determine whether the systolic blood pressure-lowering effect of sodium reduction persists in the long-term.

Ames[17] examined the effect of a sodium chloride supplementation compared to placebo on systolic blood pressure among people with primary hypertension. For the current advisory report, the Committee included only the results for the subgroup of people with type 2 diabetes (n=8). The RCT had a cross-over design with no wash-out period. During the control phase, participants were instructed to take four tables each of 2 grams of sodium chloride (= 800 mg sodium) daily. During the intervention phase, participants received an equal number of placebo tablets (gelatin). Because all participants had hypertension, they were generally used to consume a modest sodium-restricted diet and they were advised to continue their habitual diet throughout the study period. Blood pressure was measured by auscultation and mercury manometry, and the average of two measurements (3 minutes apart) were used for analysis.

At baseline, mean sodium intake (based on sodium excretion in a 24-hour urine sample) was approximately 2800 ± 1250 mg/day and mean systolic blood pressure among the participants with type 2 diabetes was 153 ± 20 mmHg. Mean systolic blood pressure was 154 mmHg after four weeks of sodium chloride supplementation (control phase) and 148 mmHg after four weeks of placebo supplementation (intervention phase). The mean difference between intervention and control was not statistically significant, indicating no effect of sodium restriction on systolic blood pressure.

Ekinci et al.[15] examined the separate and combined effects of sodium chloride supplementation and the diuretic hydrochlorothiazide on systolic blood pressure in hypertensive people with type 2 diabetes treated with telmisartan. Participants with either a low (<2300 mg/d) or high (>4600 mg/d) habitual sodium intake were included. This cross-over RCT had a factorial design comprising of four consecutive phases: (1) placebo supplementation without hydrochlorothiazide, (2) placebo supplementation with hydrochlorothiazide, (3) sodium chloride supplementation without

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:

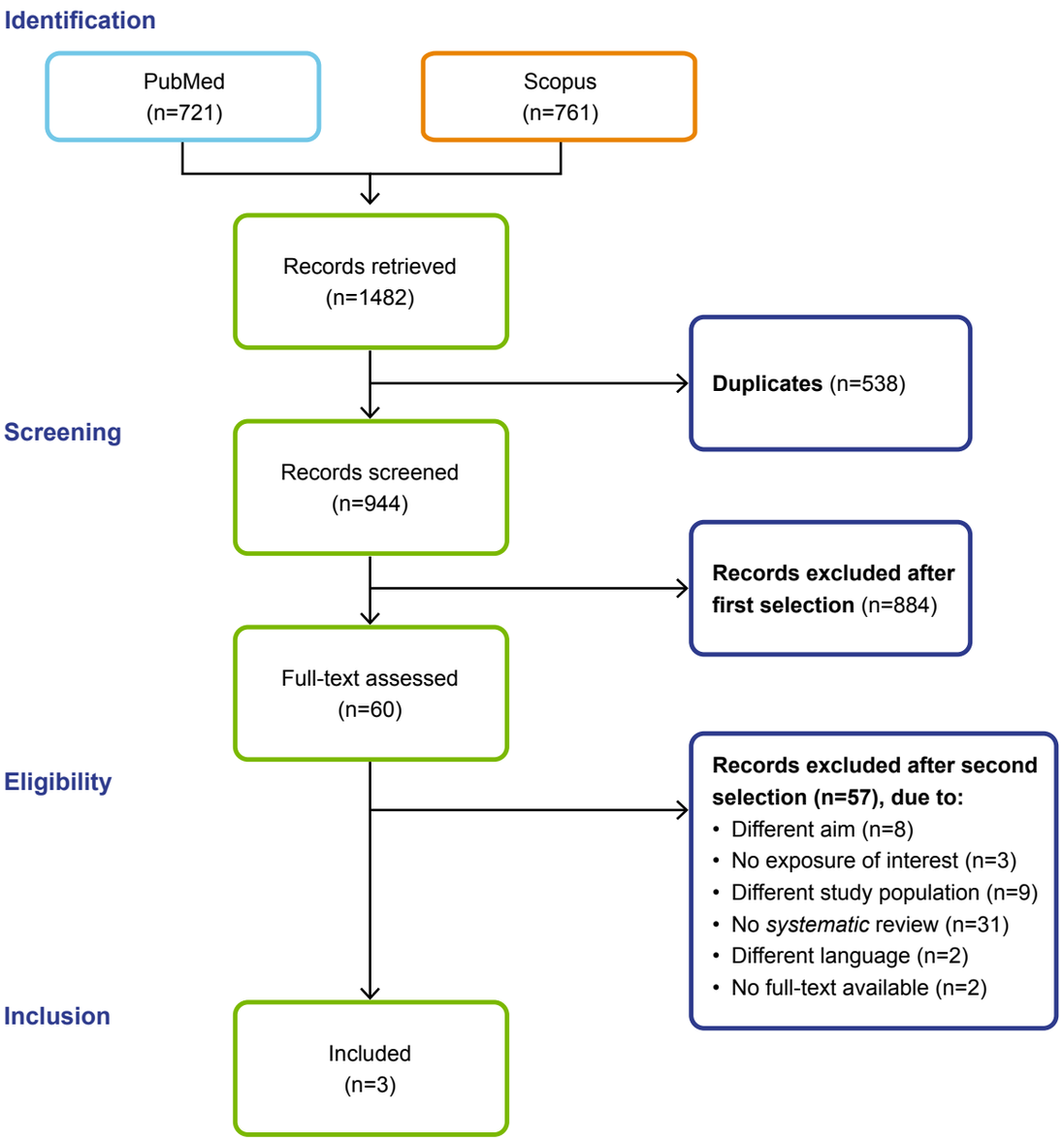
- Dutch Diabetes Federation (Nederlandse Diabetes Federatie (NDF)), 2020[9]
- European Association for the Study of Diabetes (EASD) & European Society of Cardiology (ESC), 2020[10]
- American Diabetes Association (ADA), 2019[11]
- Diabetes UK, 2018[12]
- Diabetes Canada, 2018[13]
- Swedish Council, 2010[14]

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:

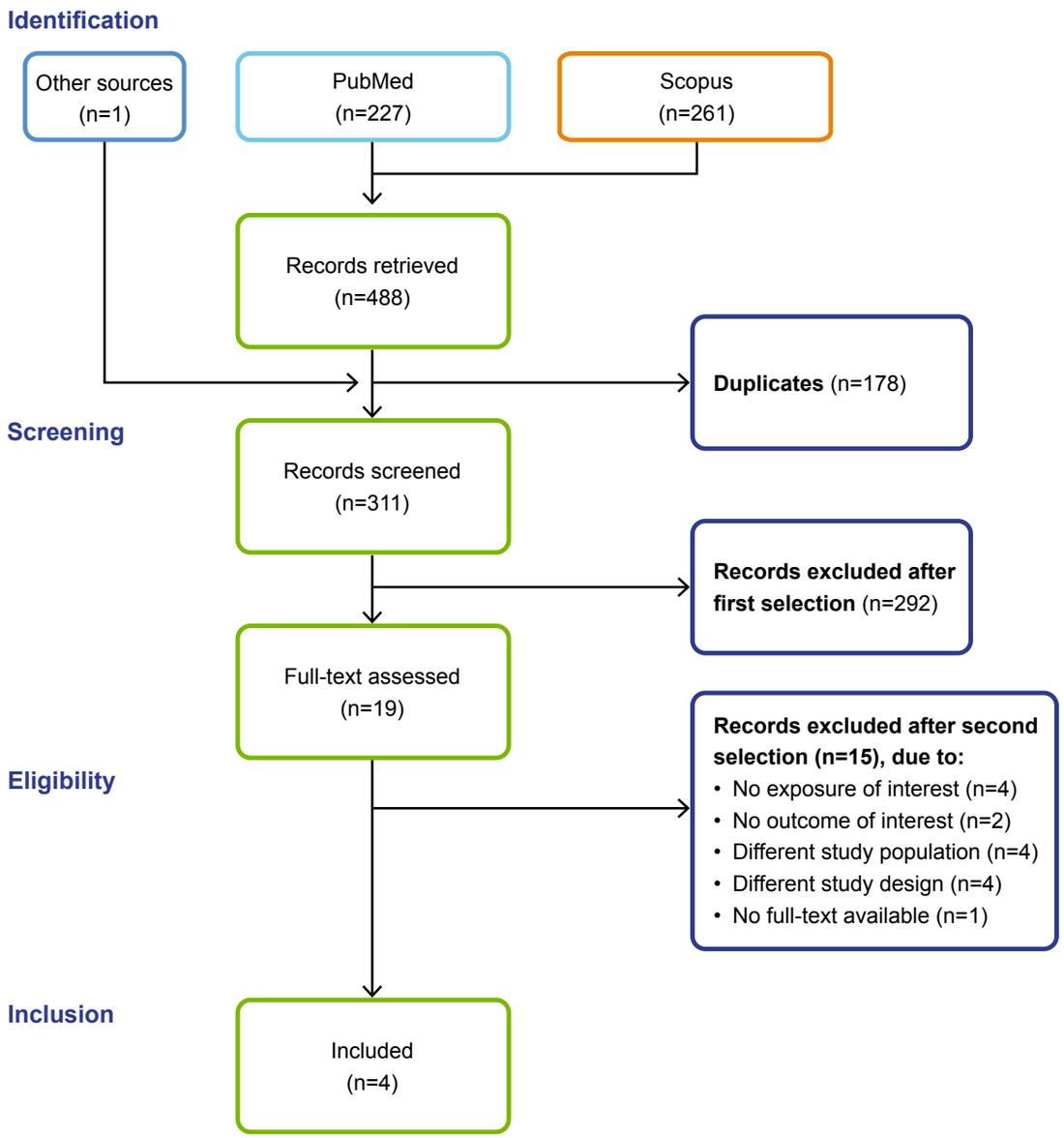
- Ekinci et al., 2011[15]
- Mills et al., 2016[16]

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



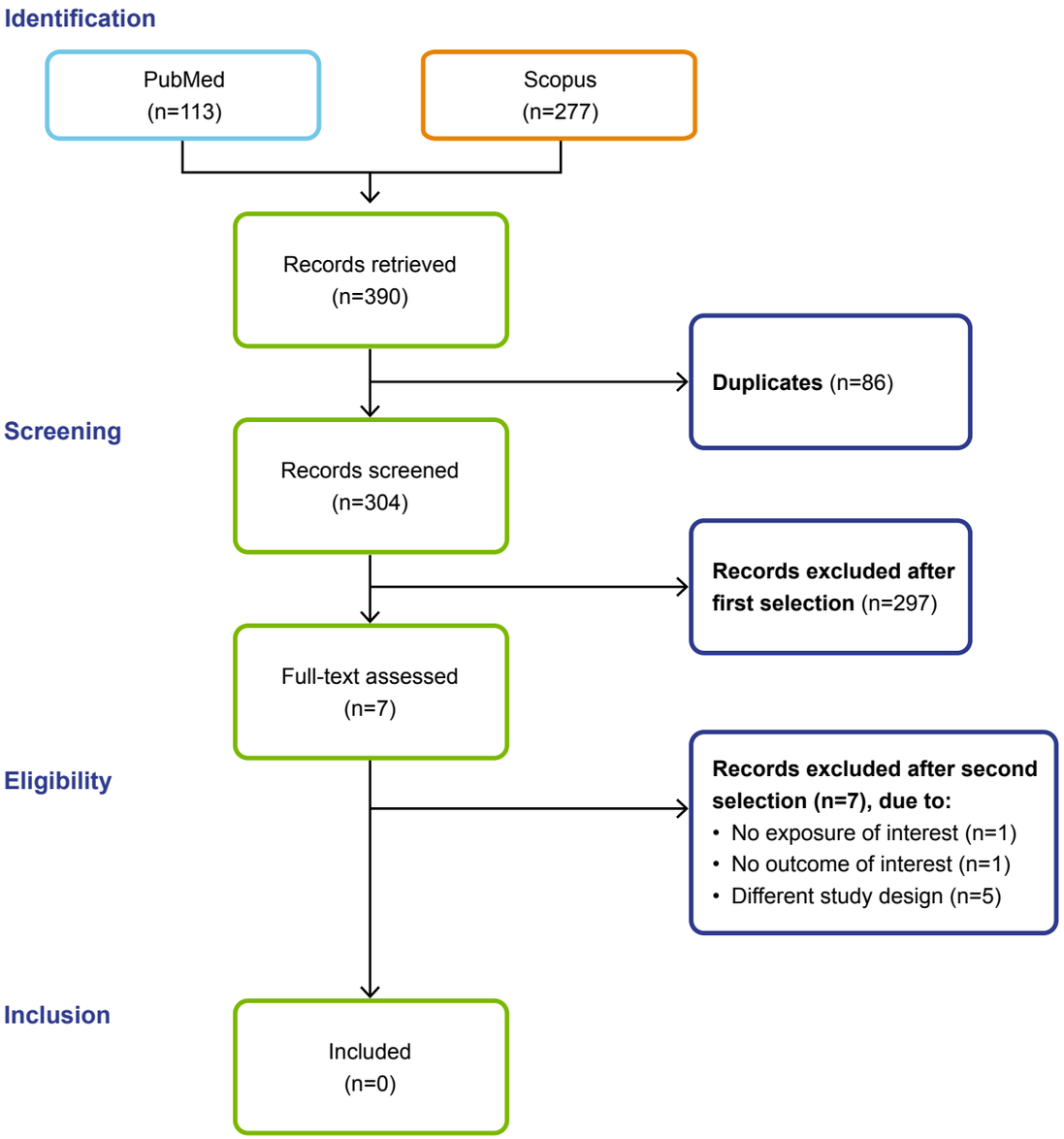
Flow diagram for the selection of recent individual randomised controlled trials

Table salt/sodium and systolic blood pressure

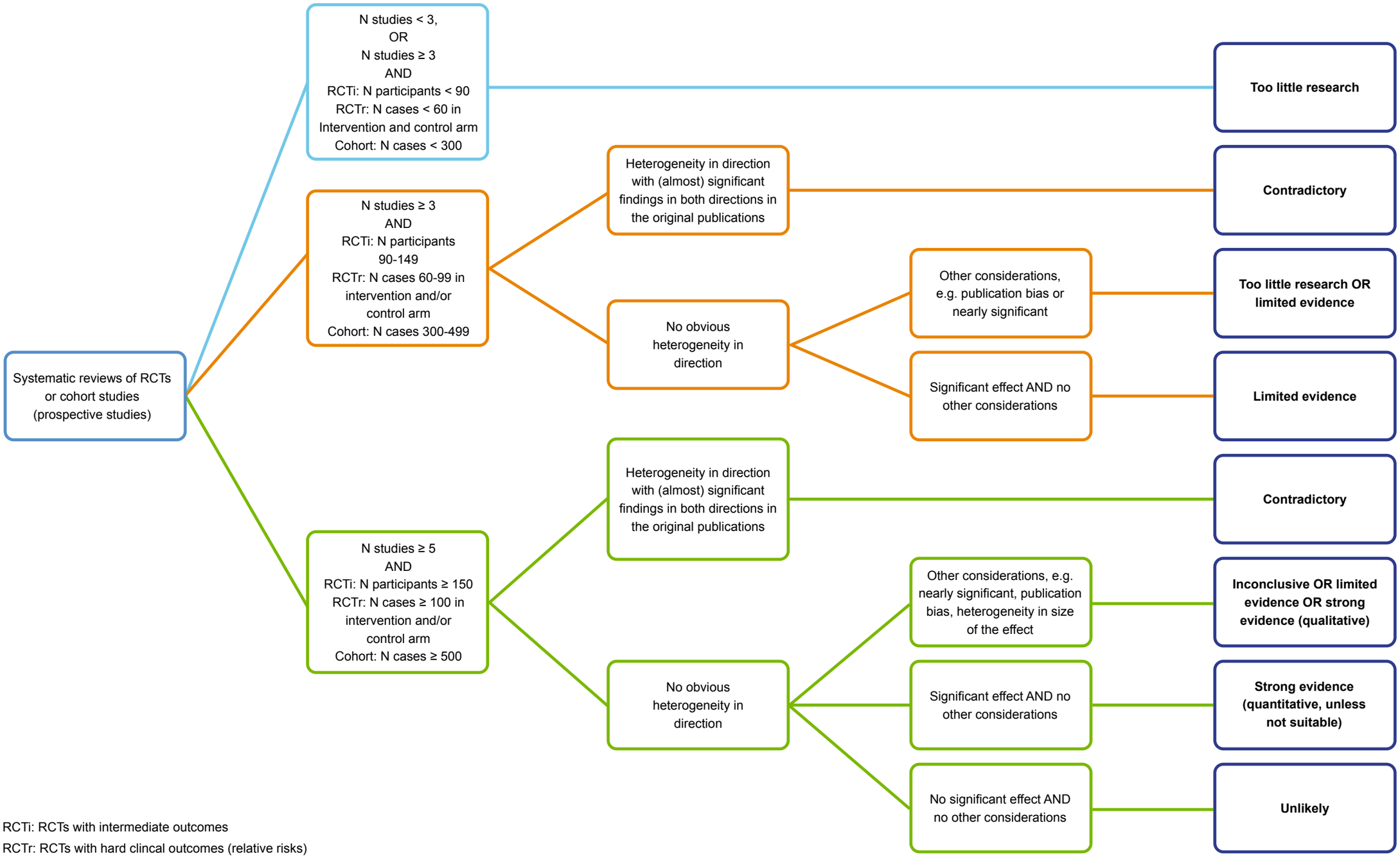


Flow diagram for the selection of recent individual randomised controlled trials

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.

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