REVIEW

Dietary Sodium Intake and Health Indicators: A Systematic Review of Published Literature between January 2015 and December 2019

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ABSTRACT

As the science surrounding population sodium reduction evolves, monitoring and evaluating new studies on intake and health can help increase our understanding of the associated benefits and risks. Here we describe a systematic review of recent studies on sodium intake and health, examine the risk of bias (ROB) of selected studies, and provide direction for future research. Seven online databases were searched monthly from January 2015 to December 2019. We selected human studies that met specified population, intervention, comparison, outcome, time, setting/study design (PICOTS) criteria and abstracted attributes related to the study population, design, intervention, exposure, and outcomes, and evaluated ROB for the subset of studies on sodium intake and cardiovascular disease risks or indicators. Of 41,601 abstracts reviewed, 231 studies were identified that met the PICOTS criteria and ROB was assessed for 54 studies. One hundred and fifty-seven (68%) studies were observational and 161 (70%) focused on the general population. Five types of sodium interventions and a variety of urinary and dietary measurement methods were used to establish and quantify sodium intake. Five observational studies used multiple 24-h urine collections to assess sodium intake. Evidence mainly focused on cardiovascular-related indicators (48%) but encompassed an assortment of outcomes. Studies varied in ROB domains and 87% of studies evaluated were missing information on ≥1 domains. Two or more studies on each of 12 outcomes (e.g., cognition) not previously included in systematic reviews and 9 new studies at low ROB suggest the need for ongoing or updated systematic reviews of evidence on sodium intake and health. Summarizing evidence from assessments on sodium and health outcomes was limited by the various methods used to measure sodium intake and outcomes, as well as lack of details related to study design and conduct. In line with research recommendations identified by the National Academies of Science, future research is needed to identify and standardize methods for measuring sodium intake. *Adv Nutr* 2020;11:1174–1200.

Keywords: dietary sodium, health indicators, reduction, risk of bias, cardiovascular health

Introduction

Based on the large body of evidence demonstrating the adverse health effects of excess sodium intake, numerous public health organizations and authoritative scientific bodies recommend dietary sodium reduction (1–6). In 2013, the Institute of Medicine (IOM) convened an expert panel "to examine the designs, methodologies, and conclusions of emerging" scientific evidence on sodium and health outcomes (2). Although the committee concluded the available evidence indicated a positive relation between higher sodium intake and risk of cardiovascular disease (CVD) outcomes (including stroke, CVD mortality, and all-cause mortality), consistent with efforts to reduce population sodium intake, they found limited evidence that suggested decreasing sodium intake could possibly reduce risk of gastric cancer and no consistent evidence on other health outcomes. Further, they also identified several areas for future research based on a number of methodological and data gaps (2). Research recommendations applicable to this review included standardizing methodological approaches to measuring sodium intake, using sodium levels for analyses (i.e., 1500–2300 mg) corresponding with current guidelines, using appropriate methods to account for potential confounding, and a need for randomized controlled trial (RCT) research (2). As the science on sodium reduction evolves, monitoring and evaluating newly published studies on intake and health can increase our understanding of the reported health benefits and risks and drive directions for future research.

Since the 2013 IOM report, there have been several meta-analyses and reports reviewing evidence related to sodium and health [including the 2019 National Academies of

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Science, Engineering, and Medicine (NASEM) report updating DRIs for sodium and potassium] (3, 7–9); however, reviews focused on specific outcomes and conclusions can become outdated as new evidence emerges. The 2019 DRI for sodium included Adequate Intake (AI) levels at 1500 mg/d and Chronic Disease Risk Reduction (CDRR) levels (i.e., individuals should lower their intake if it is above this level to reduce chronic disease risk) at 2300 mg/d for individuals aged ≥14 y. Lower AI and CDRR levels were set for children aged ≤13 y (3). To our knowledge, there is only 1 ongoing systematic review (i.e., The Science of Salt) (10) of studies related to sodium intake and health outcomes that is published and regularly updated (11). Although the aim of our ongoing systematic review of the literature is similar in relation to health outcomes from The Science of Salt, the scope and methods differ. In brief, the Science of Salt review uses key criteria to select studies that are relevant to clinical and public health (i.e., 24-h urine collections for prospective studies, studies conducted in non-ill populations, intervention periods > 4 wk) (10), whereas our search is broader and includes additional databases and study designs, and is not limited by duration of study or intervention nor the levels of actual sodium intake achieved. The objectives of this ongoing review are to *1*) describe the characteristics of recent studies examining the effects and associations of sodium intake on health risks or indicators; *2*) evaluate the strengths and biases of the study design and methods of prospective cohort studies and intervention trials examining cardiovascular disease (CVD) risks or indicators; and *3*) provide direction for future research. For this report, we evaluated the current literature with respect to the research recommendations outlined in the 2013 IOM report to determine if emerging evidence since that time addressed the aforementioned selected methodological and data gaps, including those not meeting criteria in other systematic reviews (2). In this article, we report the results for the period of January 2015 through December 2019.

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Supplemental Tables 1–10 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
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Abbreviations used: AHRQ, Agency for Healthcare Research and Quality; AI, Adequate Intake; BNP, β-type natriuretic peptide; BP, blood pressure; CDRR, Chronic Disease Risk Reduction; CHF, chronic heart failure; cIMT, carotid intima media thickness; CKD, chronic kidney disease; CVD, cardiovascular disease; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic blood pressure; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; IOM, Institute of Medicine; LS, low sodium; NASEM, National Academies of Science, Engineering, and Medicine; PICOTS, population, intervention, comparison, outcome, time, setting/study design; pre-HTN, prehypertension; PWV, pulse wave velocity; RAAS, renin-angiotensin-aldosterone system; RCT, randomized controlled trial; ROBINS-I, Risk of Bias in Non-Randomised Studies; SBP, systolic blood pressure.

Methodology

This systematic literature review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (12) (**Supplemental Table 1**).

Eligibility criteria

Articles reporting results from studies with an objective to examine the effect or association of dietary sodium intake with ≥1 health indicator were included if they met the population, intervention, comparison, outcome, time, setting/study design (PICOTS) criteria (**Supplemental Table 2**). Briefly, we included studies focused on the general healthy population and populations with specific chronic diseases (Supplemental Table 2). We excluded trials if the independent effect of sodium in the intervention could not be determined and studies that did not quantify sodium intake exposure. We did not exclude any health risks or indicators. We included intervention trials regardless of randomization, observational studies, and systematic reviews/meta-analyses (Supplemental Table 2). Secondary analyses of participants from the same study were treated as independent studies if the authors focused on mutually exclusive health indicators. Systematic reviews/meta-analyses were treated independently as long as the objectives, outcomes, or methods differed.

Search strategy

Relevant abstracts were identified on a monthly basis through an electronic search of 7 online databases (**Supplemental Table 3**). Our search was restricted to humans.

Study selection

Each month, titles and abstracts of potential articles were manually screened by a single reviewer for studies examining ≥1 health indicator in relation to dietary sodium intake. Full-text articles were ordered for selected abstracts. Two researchers independently reviewed the full-text articles against our PICOTS criteria (Supplemental Table 2). Disagreements in assessments were resolved by discussion or a third reviewer. Articles published in a language other than English were reviewed with assistance from a native speaker.

Data extraction

Information from an included article was transcribed by 1 author into tables specific to the study design. For all studies, we abstracted the number of participants, percentage male, mean age, country, study name (if applicable), participant selection criteria, duration of trial/follow-up, health indicators, and methods used to quantify dietary sodium intake. The WHO's regions were reported, if studies were conducted in ≥5 countries (**Supplemental Tables 4–6**) (13). Standard conversions were used to report all sodium intake in milligrams per day (14). Health risks and indicators were categorized similarly to groupings of intermediate markers for health outcomes and clinical health outcomes described previously (2).

We evaluated studies with respect to the following methodological and data gaps adapted from the 2013 IOM report (2). Did studies (or systematic reviews) *1*) focus specifically on African Americans, adults aged 51–70 y, ≥70 y, or other higher-risk subgroups (particularly through RCTs); *2*) include recommended methods to measure sodium intake (e.g., use of multiple 24-h urine collections in observational studies); or *3*) evaluate dietary sodium intake consistent with DRI levels (e.g., 1500–2300 mg/d)? Further, we specifically identified whether published RCTs evaluated the effects of a range of sodium levels *1*) on risk of CVD events, stroke, and mortality (particularly among patients in controlled environments such as chronic care facilities); and *2*) among chronic heart failure (CHF) patients receiving therapeutic treatments typically used in the United States. Lastly, did observational studies examine associations between sodium intake and cancer (particularly, gastric cancer) in the US population (2)?

Sodium intake measures were classified according to collection approach and method: dietary (i.e., FFQs, diet recalls, or food diaries) and urinary [i.e., partial (spot or <24-h urine) or 24-h urine]. Each assessment method (e.g., single 24-h urine) comes with particular strengths, limitations, and applications (3, 15). For example, sodium intake and excretion vary from day to day, thus accurate estimation of long-term dietary sodium intake in observational studies requires >1 nonconsecutive 24-h dietary recall or urine collection to account for random measurement error (3, 16, 17). A 24-h urine collection, when complete, is considered an unbiased indicator of short-term sodium intake and is not subject to systematic error (representing ∼90% of sodium consumed from all sources over the last few days), thus it can be used for characterizing differences in group mean intake in intervention studies (18). Estimation of sodium intake based on dietary methods may be subject to errors in self-report or nutrient databases, whereas spot urine sodium concentration may be subject to errors due to diurnal variation or in other variables used in equations to predict sodium intake (15, 18). Thus, we reported the approach, assessment method, number of collections, time period/duration for the collection, and, if applicable, succession of collections (i.e., on consecutive or nonconsecutive days) (19).

Risk of bias assessment

The totality of evidence from well-designed trials and cohort studies forms the basis for conclusions about causal relations between particular exposures and health indicators (20). Thus, we assessed the risk of bias (ROB) within trials and cohort studies. Owing to the range of health indicators included in the review and the need to develop ROB criteria specific to the outcome of interest, we limited the ROB assessment to all-cause mortality, CVD events (e.g., mortality or hospitalization), subclinical CVD indicators [e.g., pulse wave velocity (PWV)], and blood pressure (BP) (2, 20). ROB criteria used for assessment of trials were adapted from the Cochrane ROB tool (RCTs), Risk of Bias in Non-Randomised Studies (ROBINS-I) tool (nonrandomized trials and cohort studies), and Cobb's criteria (cohort studies) (21, 22). The formation of the ROB assessment tools was guided by study design, focused on studies' internal validity, and required both methodological and subject matter expertise to address challenges inherent in the design, conduct, and analyses of included studies. The ROB abstraction and instruction forms (specific to the study's design and health outcome) went through testing by multiple reviewers and several iterations before the completion of the final tools used for the ROB assessment presented in this review (**Supplemental Tables 7–9**). Adherence to the intervention (defined as a ratio of the measured difference in sodium intake to the expected difference between intervention groups of 90%–110%), a measure that assessed the extent to which participants in each of the intervention groups followed the treatment regimen, diet, or counseling prescribed by the researchers, was also examined in trials to determine the uptake and impact of the intervention. Two researchers independently assessed each study included in the ROB review and any discrepancies were resolved through discussion or by a third reviewer.

Owing to the nature of the review (current, rather than complete, assessment of the literature) and variation in health indicators (e.g., PWV and QT-interval dispersion are both measures of cardiac function) and analyses (e.g., marginal models compared with ANOVA), we did not perform a meta-analysis. However, results of included studies on sodium intake and mortality, CVD, and BP were summarized qualitatively.

Results

Study selection and characteristics

The search identified 41,601 potential articles published between 1 January, 2015 and 31 December, 2019 for inclusion in the current report. Overall, 1369 articles were eligible for full-text review and 230 articles, comprising 231 studies, were included (23–251) (**Figure 1**). One article included both a meta-analysis and a cross-sectional study (182) (Figure 1). Forty-seven intervention trials (34 RCTs and 13 non-RCTs) (23–69), 157 observational studies (52 cohort, 4 case-control, and 101 cross-sectional) (70–226), and 27 systematic reviews/meta-analyses (26 meta-analyses and 1 systematic review) (227–251) were included (Figure 1, Supplemental Tables 4–6).

Most studies were conducted in developed countries and several cohort studies included participants from multiple countries. For example, the Prospective Urban Rural Epidemiological (PURE) cohort recruited participants from 21 countries (136, 152). Trials were conducted in 3 of the 6 WHO regions (Western Pacific, Europe, Americas), whereas observational studies were conducted in all of the WHO regions, with the most studies also coming from the Western Pacific, Americas, and Europe (**Figure 2**A, B). With the exception of 6 meta-analyses that did not specify the locations of their included studies, all meta-analyses included participants from ≥4 countries (Supplemental Table 6).

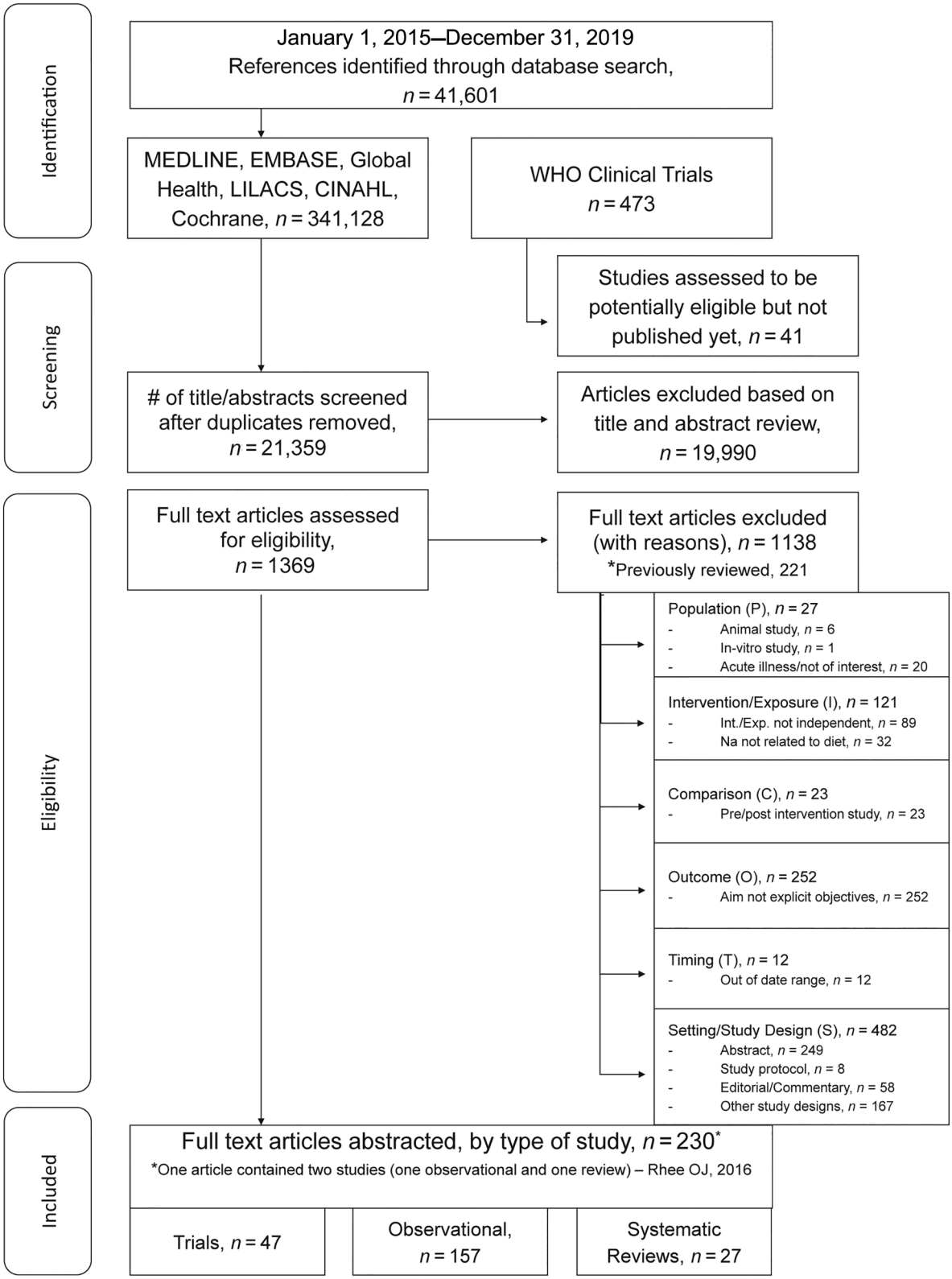

FIGURE 1 Flow diagram depicting the screening and selection of studies.

Population characteristics

Among the studies evaluated, 161 enrolled generally healthy participants and 67 targeted and specifically enrolled participants with ≥1 of the selected chronic conditions [e.g., 15 studies specifically enrolled persons with chronic kidney disease (CKD)]. Eighteen studies recruited participants that fit in ≥2 groupings of interest owing to the analytic design of the study [$n = 6$, 4 case-control (80, 145, 150, 200) and

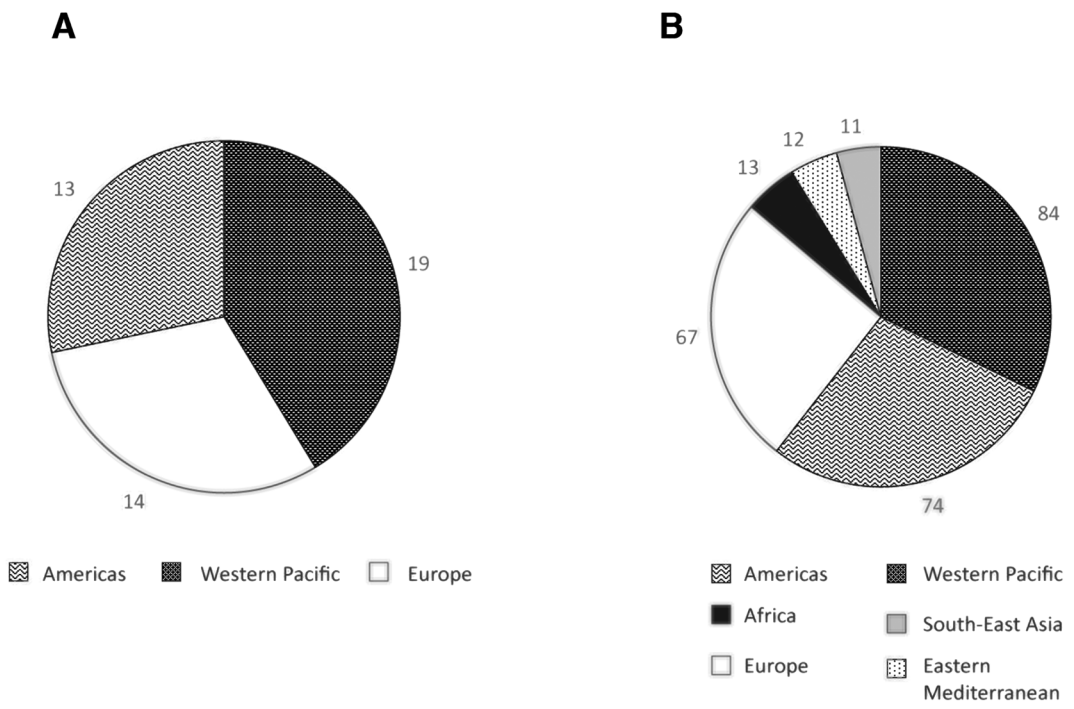

FIGURE 2 Distribution of study location sites by WHO region among trials (A) and observational studies (B), 2015–2019. The number of countries is not equal to the number of studies, because 1 study could enroll participants from multiple countries [e.g., the Prospective Urban Rural Epidemiological (PURE) study was conducted in 21 countries (136, 152)].

2 stratified analyses (34, 232)], health-specific inclusion criteria ($n = 5$) (28, 32, 44, 53, 186), or the inclusion of multiple cohorts/studies ($n = 7$) (152, 154, 233–235, 247) (**Figure 3**A, B, Supplemental Tables 4–6). Three systematic reviews did not report participants' health selection criteria (228, 236, 239). Roughly 49% ($n = 23$) of all RCTs included in this review were conducted among persons with ≥1 specific chronic disease conditions, as opposed to 22% ($n = 34$) of included observational studies (Figure 3A). At least 2 studies (trials and observational studies combined) were conducted among participants with each of the conditions of interest (Figure 3B). Three parallel RCTs (31, 33, 42) and 1 cohort study (186) specifically recruited patients with heart failure (HF) (Figure 3B, Supplemental Table 4). Of these, 2 RCTs evaluated subclinical CVD indicators (31, 42), 1 RCT evaluated serum sodium (33), and 1 cohort evaluated CVD events (186) (Supplemental Table 4) and their results are discussed below in the ROB assessment.

The majority of trials and observational studies were conducted among persons aged 18–79 y of both sexes; however, there were a few exceptions where the study focused on participants of a specific sex, age group, or higher-risk population as defined by the IOM (Supplemental Tables 4–6). Two trials (47, 55) and 1 observational study (191) enrolled only male participants, whereas 1 trial (57) and 9 observational studies (76, 81, 93, 109, 126, 134, 171, 172, 175) enrolled only female participants (Supplemental Tables 4, 5). One trial (37, 38) (Supplemental Table 4) and 19 observational studies (72, 76, 77, 85, 90, 92, 101, 110, 132, 133, 150, 159, 169, 176, 190, 196, 203, 214, 226) enrolled children or adolescents (Supplemental Table 5). Four trials (25, 29, 42, 43) and 9 observational studies (74, 81, 109, 138, 140, 154, 175, 184, 194) specifically enrolled adults aged 50–80 y. While no trials specifically enrolled adults aged ≥70 y, 4 observational studies (117, 123, 131, 165) focused on this population. One RCT recruited only untreated, African-American hypertensives to examine the effects of dietary sodium reduction on changes in metabolomics profiling in this population (30). Further, 7 trials included African-American participants (24, 27, 29, 32, 44, 53, 58), although none had objectives to examine the effects of sodium on health indicators among this group separately, whereas 13 observational studies had objectives specific to examining the association between sodium and health indicators among African Americans (76, 94, 123, 139, 147, 178, 188, 197, 209, 226), American Indians (108), or Mexican Americans (97, 158).

Sodium intake exposure

RCTs.

Among the 47 trials included in this review, researchers administered 5 types of sodium interventions: feeding trials of different levels of sodium in foods ($n = 23$), dietary trials of 1 level of sodium in food plus sodium supplements and/or placebos ($n = 5$), dietary counseling trials ($n = 12$), a trial using warning stickers on high-sodium foods ($n = 1$), and trials using a combination of ≥2 intervention types ($n = 6$) (**Table 1**). Of the 15 parallel trials, 10 (67%) were dietary counseling trials, whereas of the 32 crossover trials, 20 (63%)

TABLE 1 Characteristics of dietary sodium interventions among 46 published trials with health indicators, January 2015–December 2019[1]

Reference	Type[2]	Place	Duration, wk[3]	Intended sodium intakes, mg/d			Sodium measure	Actual sodium intakes, mg/d			Adherence[4]
				LS	HS	Diff		LS	HS	Diff	
Parallel RCT											
Fabricio et al. (33)	Diet + supp	Hospital	1	1200	2800	1600	Multiple, 24-h recalls	998	2467	1469	103%
Hummel et al. (42)[5]	Diet	Home	4	1500	2000	500	Single, 24-h urine	NR	NR	NR	Cannot be calculated
Kang et al. (45)	Diet	Home	8	2000	5000	3000	Single, 24-h urine	2848	3517	669	22%
Serizawa et al. (57)[6]	Diet	Hospital	2.3	2400	4800	2400	Multiple, spot urine samples	NR	NR	NR	NR
Chen L et al. (29)	Edu	Study center	156	<1800	NA	NA	Multiple, non consecutive, 24-h urine collections	2371	3314	943	Cannot be calculated
Colin-Ramirez et al. (31)	Edu	Home	24	1500	2300	800	Multiple, 3-d diet recalls	1398	1461	63	8%
Gant et al. (35)	Edu	Home	6	1200	4800	3600	Single, 24-h urine	2047	4600	2553	71%
He FJ et al. (37)[7]	Edu	School + home	14	—	—	Reduce intake by 20%	Multiple, consecutive, 24-h urine collections	2574 (C); 4056 (A)	3120 (C); 4719 (A)	741 (C); 1131 (A)	Reduced by 27% (C) and 25% (A)
He FJ et al. (38)[7]	Edu	School + home	14	—	—	Reduce intake by 20%	Multiple, consecutive, 24-h urine collections	2574 (C); 4056 (A)	3120 (C); 4719 (A)	741 (C); 1131 (A)	Reduced by 27% (C) and 25% (A)
Keyzer et al. (46)	Edu	Study center + home	8	1150	4600	3450	Multiple, nonconsecutive, 24-h urine collections	2484	4002	1518	44%
Meuleman et al. (49)	Edu	Study center + home	12	NR	NR	NR	Multiple, nonconsecutive, 24-h urine collections	3181	4069	888	Cannot be calculated
Nakano et al. (51)	Edu	Study center	12	<2340	NA	NA	Single, 24-h urine	2652	3354	702	Cannot be calculated
Parvanova et al. (52)	Edu	Study center + home	8	2400	4800	2400	Multiple, nonconsecutive, 24-h urine collections	3831	4523	692	29%
Takada et al. (59)	Edu	Study center + home	4	3432	3822	390	Multiple, consecutive, overnight urine collections	3354	3498	144	37%
Pinjuh Markota et al. (48)	Warning stickers	Home	8	4025	4600	575	Single, 24-h urine	4057	4600	543	94%
Median value of parallel trials			8	1900	4600	2340		2848; 2652 (with C)	4002; 3517 (with C)	888; 741 (with C)	

(*Continued*)

TABLE 1 (*Continued*)

Reference	Type[2]	Place	Duration, wk[3]	Intended sodium intakes, mg/d			Sodium measure	Actual sodium intakes, mg/d			Adherence[4]
				LS	HS	Diff		LS	HS	Diff	
Crossover RCT											
Babcock et al. (23)	Diet	Home	1	460	6900	6440	Single, 24-h urine	483	4545	4062	63%
Babcock et al. (24)	Diet	Home	1.4	1000	2300	1300	Single, 24-h urine	846	1950	1104	85%
Brian et al. (27)	Diet	Home	1	520	7119	6599	Single, 24-h urine	661	5405	4744	72%
Derkach et al. (32)[8]	Diet	Study center + home	4	1150	3450	2300	Single, 24-h urine	NR	NR	NR	Cannot be calculated
Muth et al. (50)[9]	Diet	Home	1	460	6900	6440	Single, 24-h urine	∼900	∼5750	∼4850	75%
Juraschek et al. (44)[8]	Diet	Study center + home	4	1150	3450	2300	Single, 24-h urine	NR	NR	NR	Cannot be calculated
Peng et al. (53)[8]	Diet	Study center + home	4	1150	3450	2300	Single, 24-h urine	NR	NR	NR	Cannot be calculated
Rorije et al. (55)	Diet	Study center + home	2	<1200	>4800	≥3600	Multiple, nonconsecutive, 24-h urine collections	920	6072	5152	143%
Foo et al. (34)	Diet + supp	Study center	0.86	920	4140	3220	Single, 24-h urine	1804	5653	3849	119%
Gijsbers et al. (36)	Diet + supp	Study center + home	4	2000	5000	3000	Single, 24-h urine	2417	4667	2250	75%
Riphagen et al. (54)	Diet + supp	Study center + home	4	2400	5400	3000	Single, 24-h urine	2346	4623	2277	76%
Baqar et al. (25)	Comb (edu + supp)	Study center	3	NR	NR	NR	Single, 24-h dietary recall	3541	4715	1174	Cannot be calculated
Cashman et al. (28)	Comb (edu + bread)	Study center + home	5	NR	NR	NR	Single, 24-h urine	1784	2438	654	Cannot be calculated
Jablonski et al. (43)	Comb (supp + edu)	Study center + home	5	1150	3450	2300	Multiple, nonconsecutive, 24-h urine collections	1610	3519	1909	83%
Suckling et al. (58)	Comb (supp + edu)	Study center + home	6	2070	4140	2070	Multiple, consecutive, 24-h urine collections	2682	3797	1115	54%
Chen L et al. (30)	Comb (supp + edu)	Study center + home	6	<2000	NA	NA	Multiple, consecutive, 24-h urine collections	2650	3751	1101	Cannot be calculated
Todd et al. (60)	Comb (diet—tomato juice + supp)	Home	4	1380	5750	4370	Multiple, nonconsecutive, spot urine samples	NR	NR	NR	Cannot be calculated
Saran et al. (56)	Edu	Study center	4	<2000	NA	NA	Single, 24-h urine	2419	3928	1509	Cannot be calculated
Toering et al. (61)	Edu	Study center + home	1	1150	4600	3450	Single, 24-h urine	920	4842	3922	114%

(*Continued*)

TABLE 1 (*Continued*)

Reference	Type[2]	Place	Duration, wk[3]	Intended sodium intakes, mg/d			Sodium measure	Actual sodium intakes, mg/d			Adherence[4]
				LS	HS	Diff		LS	HS	Diff	
Crossover non-RCT											
Baric et al. (26)	Diet + supp	Study center + home	1	1400	5880	4480	Single, 24-h urine	2461	5750	3289	73%
He M et al. (39)[9]	Diet	Study center	1	1170	7020	5850	Single, 24-h urine	~1150	~6325	~5175	88%
Hu J-W et al. (40)	Diet	Study center	1	1170	7020	5850	Single, 24-h urine	1819	6483	4664	80%
Hu J-W et al. (41)	Diet	Study center	1	1170	7020	5850	Single, 24-h urine	1868	3855	1987	34%
Liu F-Q et al. (47)	Diet	Study center	1	1170	7020	5850	Single, 24-h urine	2291	5624	3333	57%
Wan et al. (62)	Diet	Study center	1	1170	7020	5850	Multiple, consecutive, overnight urine collections	NR	NR	NR	Cannot be calculated
Wang Y et al. (64)	Diet	Study center	1	1170	7020	5850	Single, 24-h urine	2335	5808	3473	59%
Wang Y et al. (65)	Diet	Study center	1	1170	7020	5850	Single, 24-h urine	2332	5824	3491	60%
Wang Y-Y et al. (67)	Diet	Study center	1	1170	7020	5850	Single, 24-h urine	2328	5789	3462	59%
Wang K et al. (63)	Diet	Study center	1	1170	7020	5850	Single, 24-h urine	1819	6484	4665	80%
Wang Y et al. (66)	Diet	Study center	1	1170	7020	5850	Single, 24-h urine	2098	6134	4036	69%
Zhang et al. (69)	Diet	Study center	1	1170	7020	5850	Single, 24-h urine	2272	6164	3892	67%
Zhang et al. (68)[8]	Diet	Study center	1	1170	7020	5850	Single, 24-h urine	~2300	~5750	~3450	59%
Median values of crossover trials			1	1170	6900	5850		1983	5515	3456	
Median values of all trials			4	1170	5000	3450		2310; 2334 (with C)	4645; 4612 (with C)	2119; 1948 (with C)	
Range of all trials			0.86–156	460–4025	2000–7119	390–6599		483–4057	1461–6484	63–5175	8%–143%

[1] A, adults; C, children; Comb, combination; Diff, difference; Edu, education; HS, high sodium; LS, low sodium; NA, not applicable; NR, not reported; RCT, randomized controlled trial; Supp, supplements.
[2] Diet was defined as studies that prepared food on-site and provided all foods and beverages to participants (i.e., feeding trials). Diet + Supp intervention was where participants were prescribed an LS "baseline" diet and then were allocated to receive either placebo tablets or salt supplements. Edu was where participants were either counseled on diet, provided personalized meal plans, or provided dietary materials such as menus. A Comb intervention was defined as the use of ≥1 intervention type (e.g., dietary education/counseling + supplements).
[3] Duration refers to the period of time for each intervention (e.g., participants received tablets or placebo for 6 wk, crossing over to take the opposite tablet for a further 6 wk) (58). Six crossover RCTs used a washout period between intended sodium levels of 4-wk (24, 34), 3-wk (25) and 2-wk (56, 60) duration. A standard dietary run-in period was used in 12 of the 19 crossover RCTs (range: 7–14 d) (23, 27, 30, 32, 36, 43, 44, 50, 53, 54, 58, 60).
[4] Adherence was calculated by taking the ratio of the measured difference in sodium intake to the expected difference between intervention groups. Inadequate adherence was defined as <90% or >110%.
[5] Hummel et al. (42) reported changes in urinary sodium excretion over the duration of the intervention in a supplementary figure; however, they did not provide numbers. The figure indicates that the LS and HS groups were similar in "actual sodium levels."
[6] Secondary analysis of a 2004 metabolic study (253). No data on actual measured sodium levels were reported.
[7] Baseline sodium intake was 3822 mg/d in the control group and 4212 mg/d in the intervention group (mean: 4017 mg/d). Actual difference estimates were adjusted for age, sex, BMI, stratification variables at randomization (school location/class size), and indoor and outdoor temperature.
[8] Secondary analyses of the Dietary Approaches to Stop Hypertension-Sodium trial using subsets of participants from the original trial. Actual low and high sodium intake levels were not reported in these subpopulations.
[9] Data on the actual measured sodium levels were presented graphically in the publication. Reported levels are estimated from the graph.

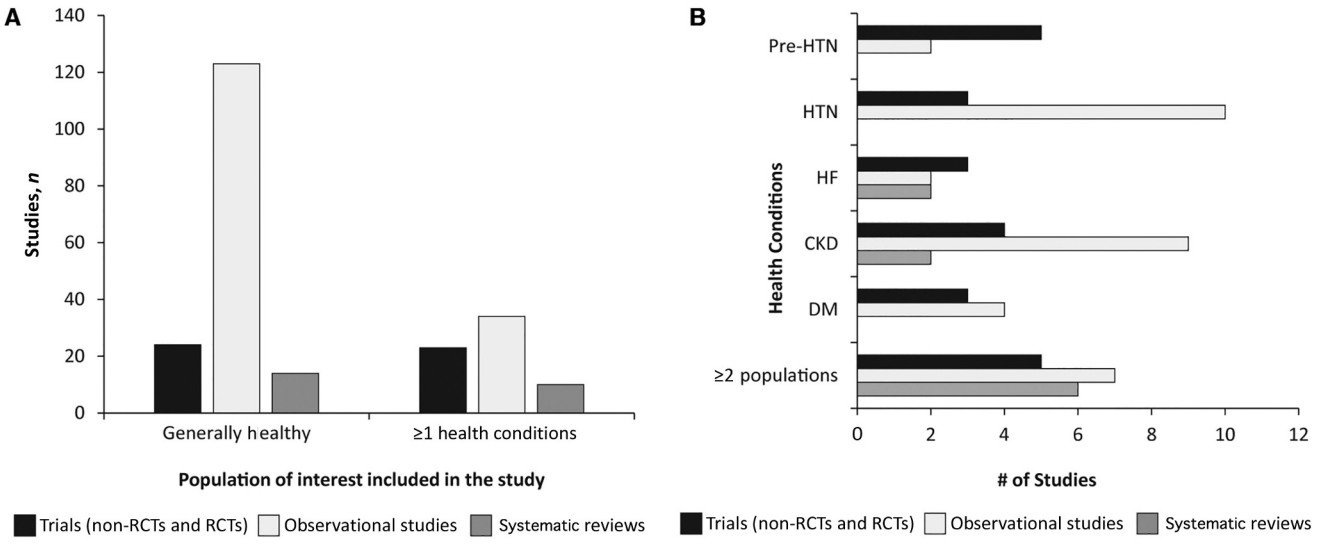

FIGURE 3 Distribution of the population health status (i.e., generally healthy populations compared with populations with health conditions of interest) of included studies by study design (A) and distribution of specific health conditions of interest among studies of populations with ≥1 health conditions ($n = 64$) (B). Healthy population refers to recruiting participants from the general population which can include healthy participants with health conditions (i.e., DM, HTN, HF, and/or pre-HTN). CKD, chronic kidney disease; DM, diabetes mellitus; HF, heart failure; HTN, hypertension; pre-HTN, prehypertension; RCT, randomized controlled trial.

were feeding trials. The assigned dietary interventions took place in a variety of locations: 17 at a study center, 10 in the participant's home, 2 in a hospital, and 18 in >1 location.

The median duration of the dietary interventions included in this review was 4 wk (range: 5 d–6 mo) (Table 1); however, intervention duration varied by trial design. Parallel trials had a median duration of 8 wk (range: 1–156 wk), whereas crossover trials had a median duration of 1 wk (range: 5 d–6 wk). A standard dietary run-in period was used in 12 of the 19 randomized crossover trials (range: 7–14 d) (23, 27, 30, 32, 36, 43, 44, 50, 53, 54, 58, 60). One randomized crossover trial required a 6-wk washout period before trial entry for participants prescribed antihypertensive agents capable of affecting the renin-angiotensin-aldosterone system (RAAS) (25). Of the 32 crossover trials included, 5 had a defined washout period of ≥2 wk (25, 56, 60) or ≥4 wk (24, 34), within the design of the dietary intervention. Participants could resume their usual diets during 5-d breaks in 3 ancillary reports of the Dietary Approaches to Stop Hypertension (DASH)-Sodium trial (32, 44, 53), because the investigators reported that the intervention period at each level of sodium intake was long enough to minimize the potential for carryover effects, i.e., 4 and 8 wk, respectively (252). Two studies reported that intervention periods were not separated by a washout (36, 55) and, of these, only 1 had an intervention period lasting ≥4 wk (36). One randomized crossover trial, that had an intervention period ≥4 wk with no washout, tested for and found no significant carryover or residual effects for each outcome (28).

Among the included trials, the intended level of sodium intake in the low-sodium (LS) group ranged from 460 (23) to 4025 mg/d (48) (median: 1170 mg/d) and in the high-sodium group from 2000 (42) to 7119 mg/d (27) (median: 3450 mg/d). With the exception of 7 trials included in this review that did not report actual sodium values (32, 42, 44, 53, 57, 60, 62) and 4 trials that used a single dietary recall (25), multiple dietary recalls (31, 33), or overnight urine samples (59), investigators quantified the actual difference in sodium between intake groups using the mean (average) of one or more 24-h urine collections per participant ($n = 36$) (Table 1). The range of the mean actual difference in sodium consumed between intake groups was 63 (31) to 5175 mg/d (39) (median: 2310 mg/d) for trials with only adult participants (median: 2334 mg/d including 1 cohort of children). This varied by trial design where the median actual difference in sodium consumed between groups was 888 mg/d in parallel trials (adults only, $n = 15$) compared with 3456 mg/d in crossover trials ($n = 32$). Of the 33 trials that reported intended and actual sodium measures, only 3 trial populations (33, 37, 38, 48) adhered to the intervention. Fewer than half (48%, $n = 40$) of the included trials reporting actual intake examined dietary sodium intake levels in the LS arm ≤2300 mg/d. The actual mean 24-h urinary sodium excretion at the end of the intervention in the LS arm was <1500 mg/d in 9 trials (23, 24, 27, 31, 33, 39, 50, 55, 61), within 1500–2300 mg/d in 10 trials (28, 34, 35, 40, 41, 43, 47, 63, 66, 69), and ≥2300 mg/d in the remaining 21 trials. The actual mean sodium 24-h urinary sodium excretion value at the end of the trial could not be determined from the figure presented in 1 trial (42) and was not reported in 2 trials (60, 62), 3 ancillary studies of the DASH-Sodium trial (32, 44, 53), or 1 ancillary study of a metabolic balance trial (57). Except for 1 trial (57), the target intake levels in the LS arms of these trials were ≤1500 mg/d.

TABLE 2 The distribution of exposure assessment methods used to quantify dietary sodium intake among observational studies by study design[1]

Study design	Prospective cohorts	Cross-sectional studies	Case-control studies	All observational studies
Urinary measures				
Multiple 24-h urine collections[2]	9[3]	7	0	16
Single 24-h urine	7	39	1	47
Multiple spot urine samples[4]	3	3	0	6
Single spot urine	13[5]	28	1	42
Dietary measures				
Multiple FFQs	6[3]	0	0	6
Single FFQ	12	7	2	21
Multiple, multiple-day diet recalls/records/diaries	1	0	0	1
Single, multiple-day diet recalls/records/diaries[6]	1	1	0	2
Multiple 24-h diet recalls/records/diaries	0	5	0	5
Single 24-h recall/record/diary	1	11	0	12
Totals	53	101	4	158[3]

[1] $n = 157$. WLVS, Women's Lifestyle Validation Study.
[2] All multiple 24-h urine collections were collected on nonconsecutive days with the exception of 3 observational studies [1 prospective (127) and 2 cross-sectional (102, 208)].
[3] One prospective cohort study conducted by Cortese et al. (93) used both a dietary and a urinary measurement to estimate dietary sodium intake and is counted in both categories. Sodium excretion was measured using multiple 24-h urine samples from women in the WLVS to correct the sodium intake estimated by FFQ in the study for measurement error. The correction equation was based on a linear regression with energy-adjusted sodium intake assessed by FFQ in the WLVS as exposure and urinary sodium as outcome: [corrected sodium intake = 1455.83 + (0.767∗ uncorrected FFQ sodium intake)] (93). This study was counted under both categories of multiple nonconsecutive 24-h urine collections and multiple FFQs.
[4] Multiple spot urine samples were collected nonconsecutively in 4 studies (93, 143, 174, 185), whereas the sodium intake was averaged from early-morning urine samples collected on 3 consecutive days in 1 study (162, 163).
[5] Takase et al. (201) instructed participants to "collect overnight urine in a paper cup and to bring in a sample of the urine in a plastic tube." It is unclear if the overnight collection was timed or if just a spot sample from the overnight urine was used.
[6] All of the studies assessed sodium using a multiple, consecutive-day diet recall (e.g., one 3-d recall from foods eaten on Monday, Tuesday, and Wednesday).

Observational studies.
Methods to assess sodium intake exposure among observational studies varied. In the majority of studies, researchers estimated sodium intake exposure using a variety of urinary biomarkers ($n = 111$, 70%) (**Table 2**); the remainder were dietary methods, i.e., FFQs ($n = 27$, 17%) or 24-h dietary recall or food diaries ($n = 20$, 13%).

In most observational studies ($n = 122$), researchers estimated sodium intake exposure at a single time point and mostly based on short-term indicators, i.e., urinary biomarkers (spot or 24-h urine) ($n = 89$) or 24-h dietary recall/diary collected on a single day ($n = 12$). For FFQs measured at a single time point ($n = 21$), the duration of exposure for the majority of studies was 1 y, with the exception of 4 studies with a duration < 1 y (72, 109, 150, 166) and 1 study whose duration of exposure could not be determined (196) (**Supplemental Table 10**). Researchers in the remaining studies ($n = 36$) estimated sodium intake exposure at ≥1 time point, the majority of which had a cohort design ($n = 19$). In 5 cohort studies (91, 93, 110, 133, 156), sodium intake exposure was estimated using ≥3 nonconsecutive 24-h urine collections with a duration of exposure ranging from 1 (93) to 3 y (111, 133, 156) (median: 3 y). In 2 cohort studies sodium intake exposure was estimated using >3 spot urine samples collected on ≥3 d over a duration of 2 seasons (143) or 5 y (185). For the remainder of the cohort studies which estimated sodium intake exposure at ≥1 time point ($n = 10$), the duration between exposure measures ranged from 3 mo (174) to 8 y (76). Researchers in most studies ($n = 15$) estimated sodium intake using the mean of multiple measures, except in 4 studies where researchers estimated the temporal change in sodium intake (146, 154, 158, 163).

Researchers categorized sodium intake in the majority of observational studies ($n = 104$, 66%) (Supplemental Table 10). Of these, in 23 studies, mean sodium intake in the LS group was <1500 mg/d (77, 83, 87, 101, 114, 122, 123, 134, 144, 151, 173, 176–179, 189, 192, 194, 197, 206, 207, 222, 224); in 30, 1500–2300 mg/d (86, 91, 92, 95, 98, 109, 111, 124, 128–131, 149, 155, 161, 165, 172, 183, 184, 187, 190, 198, 199, 204, 205, 208, 210, 213, 217, 221); and in 51, ≥2300 mg/d (71, 74, 76, 78, 81, 82, 84, 85, 90, 93, 96, 99, 100, 102, 105, 106, 113, 115, 116, 118, 127, 136–138, 142, 143, 148, 152, 153, 156, 160, 162, 164, 167, 174, 180, 182, 185, 186, 191, 195, 196, 201–203, 211, 212, 214, 218, 223, 226).

Health indicators and outcomes

Health indicators and outcomes varied widely (**Table 3**). More than 1 health indicator or outcome was examined in 53 studies (23%) included in this review (Supplemental Tables 4–6). The most frequently studied health indicators over this time period were BP ($n = 875$), followed by renal function/CKD indicators ($n = 45$), subclinical CVD indicators ($n = 30$), and clinical CVD indicators ($n = 24$) (Table 3). In 2 observational studies, a cross-sectional study in Korea (195) and a cohort study in Japan (206), investigators evaluated the association between sodium intake and gastric cancer (Supplemental Table 5). Other indicators evaluated included

TABLE 3 Categorization and definition of health indicators assessed by study design[1]

Health outcome	Indicators assessed	Trials			Observational				Systematic review/meta-analyses	Total outcomes[2]
		Total	RCT	Non-RCT	Total	Case control	Cross-sectional	Prospective		
All-cause mortality and CVD indicators										
All-cause mortality	Death from causes other than cardiovascular-related problems	0	0	0	12	0	0	12	3	15
Clinical CVD indicators	Fatal or nonfatal cardiovascular events (e.g., stroke, CHD, CVD, MI, TIA, HF, arrhythmia, pulmonary edema, aneurysm, atrial fibrillation, angina pectoris)	0	0	0	19	0	1	18	5	24
Subclinical CVD indicators	Cardiovascular functional measures (e.g., ejection fraction, heart rate, atrial filling fraction, pulse wave velocity, β-type natriuretic peptide, augmentation index); cardiovascular structural measures (e.g., LV mass index, LA diameter)	12	10	2	13	0	10	3	5	30
Blood pressure	SBP; DBP; hypertension; blood pressure variability (ARV index)	17	17	0	59	1	45	13	11	87
Other indicators										
Renal function/CKD	CKD (incidence, prevalence, progression); markers of renal function (e.g., urinary albumin:creatinine ratio, eGFR); fluid measures (e.g., overload, volume); albuminuria	13	10	3	26	0	10	16	6	45
Gastric cancer	Gastric cancer	0	0	0	2	0	1	1	0	2
Indicators of body fatness	BMI; adiposity; total body percentage fat; waist-to-hip ratio; waist circumference; predictive body fatness	5	4	1	16	0	15	1	3	24
Blood lipids	Total cholesterol; HDL cholesterol; LDL cholesterol; triglycerides	1	1	0	4	0	4	0	2	7
Indicators of IR/glucose tolerance	Insulin resistance; fasting glucose; metabolic clearance rate of glucose	2	1	1	8	0	8	0	2	12
Bone measures	Bone mineral density; osteoporosis; bone turnover markers (e.g., CTX-I, OC, ALP)	1	1	0	6	0	5	1	1	8
RAAS	Renin; angiotensin; aldosterone	7	7	0	1	0	1	0	4	12
Metabolic syndrome	Metabolic syndrome	0	0	0	4	0	4	0	0	4
Rheumatoid arthritis	Rheumatoid arthritis	0	0	0	4	3	1	0	0	4
Other	Cognition (e.g., headaches, function, decline, mental distress, lightheadedness); gastric dysfunction (e.g., Crohn disease, ulcerative colitis, *Helicobacter pylori*); cataracts; age-related body composition (sarcopenia, frailty); NAFLD; LTL; metabolite profile; QoL measurement; hormones (e.g., serum dopamine, leptin, adiponectin, gastrin, cortisol, XO, corin, cardiotrophin 1, ghrelin); oxidative stress damage; inflammation (e.g., hsCRP, GlycA, IL-6, TNF-α, pentraxin-3); endothelial dysfunction (e.g., microparticles, plasma PAI-1); plasma OPG; iodine; lower urinary tract symptoms; multiple sclerosis; fibroblast growth factor 23; hyponatremia; minerals; hearing loss	20	13	7	27	2	18	7	1	48

[1] ALP, alkaline phosphatase; ARV, average real variability; CAD, coronary artery disease; CKD, chronic kidney disease; CTX-I, C-telopeptides of type 1 collagen; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GlycA, glycoprotein acetylation; HF, heart failure; hsCRP, high-sensitivity C-reactive protein; IR, insulin resistance; LA, left atrium; LTL, leukocyte telomere length; LV, left ventricular; MI, myocardial infarction; NAFLD, nonalcoholic fatty liver disease; OC, osteocalcin; OPG, osteoprotegerin; PAI-1, plasminogen activator inhibitor-1; QoL, quality of life; RAAS, renin-angiotensin-aldosterone system; RCT, randomized controlled trial; SBP, systolic blood pressure; TIA, transient ischemic attack; XO, xanthine oxidase.

[2] Counts are of the number of health indicator categories by study type. One study may assess multiple health indicator categories, which will be counted separately (e.g., an RCT trial examined subclinical CVD indicators and BP—1 count would be put in both categories under RCT). Therefore, the total outcomes will not equal the number of studies included. One study may have assessed >1 indicator per category (i.e., clinical CVD indicators assessed were stroke and CHD); however, we will only count 1 for assessing the category of clinical CVD indicators.

body fatness or weight (24 studies), insulin resistance/glucose tolerance (12 studies), RAAS (12 studies), bone measures (8 studies), blood lipids (7 studies), and metabolic syndrome or rheumatoid arthritis (4 studies each). In addition, 45 focused on indicators that did not fit in prespecified categories (e.g., indicators related to cognition or gastric function). The health indicators/outcomes varied by study design. Whereas BP, followed by renal function/CKD, were the most frequently reported indicators for trials, observational studies, and meta-analyses, clinical CVD outcomes and mortality were frequently reported as outcomes in observational studies, but not in trials, during this time period (Table 3).

ROB assessment

In total, 54 studies [22 RCT (23–25, 28, 31, 33, 34, 36, 37, 42, 46, 48–52, 54–56, 58, 59), 2 non-RCT (39, 64), and 30 cohort studies (76, 91, 96, 108, 111, 122, 123, 128, 133, 136, 138, 143, 152–154, 156, 158, 163, 164, 174, 175, 185, 186, 189, 190, 192, 201, 205, 216, 224)] evaluated sodium intake in relation to the health indicators/outcomes selected for the ROB assessment in this review (**Table 4**). Although not included in the ROB assessment, results of 18 meta-analyses (228, 231–239, 241–243, 249–251) were summarized for each of the selected outcomes.

All-cause mortality.

Twelve cohort studies and 3 meta-analyses evaluated the association of sodium intake with all-cause mortality during this time period. Not accounting for ROB, in 2 cohort studies (91, 136) higher sodium intake was associated with higher mortality (positive association). In 7 cohort studies (96, 111, 123, 143, 154, 192, 216) and 3 meta-analyses (241, 243, 251), no significant association was observed between sodium intake and mortality (null association). In 2 cohort studies, higher sodium was associated with lower mortality [inverse association (138, 178)]. In 1 cohort study, mortality was associated with both low (<4000 mg/d) and high (>7000 mg/d) estimated sodium intake (i.e., a U-shaped association) (152) (Table 4).

The most common biases were systematic or random measurement error in sodium assessment (8 and 7 studies, respectively), potential for confounding (7 studies), and selection bias (6 studies). One study was judged to be at low ROB, except for an unclear ROB due to potential departure from the intended exposure (91). However, all evaluated cohort studies on sodium intake and mortality were judged to be unclear or high ROB on this criterion and this bias most likely attenuated results, e.g., owing to nonadherence to the intervention. Despite potential attenuation, in this low-ROB study, higher sodium intake (estimated using ≥3 nonconsecutive, high-quality, 24-h urinary excretions) was positively associated with higher mortality in a linear dose–response relation (91).

In 2 meta-analyses of observational studies, a null association was observed between sodium intake and mortality and high levels of heterogeneity were found between

TABLE 4 Risk of bias assessment of prospective studies examining dietary sodium and its association with all-cause mortality[1]

Reference	Association	Control of key confounding	Selection unrelated to sodium/outcome	Coinciding follow-up/baseline exam	Departures from intended exposure	Potential for systematic error	Potential for random error	Adequate follow-up
Cook et al. (91)	+	L	L	L	U	L	L	L
Lamelas et al. (136)	+	H	M	U	U	H	H	U
Doukky et al. (96)	0	H	H	U	U	H	L	U
He J et al. (111)	0	L	H	L	U	L	L	U
Kalogeropoulos et al. (123)	0	H	H	H	U	H	L	U
Liu H et al. (143)	0	L	L	H	U	H	H	L
Merino et al. (154)	0	L	U	L	U	H	H	L
Singer et al. (192)	0	H	H	H	H	H	H	U
Welsh et al. (216)	0	L	L	L	U	H	H	U
Lelli et al. (138)	−	L	M	H	U	L	H	U
Saulnier et al. (189)	−	H	H	U	U	H	H	U
Mente et al. (152)	U-shaped	H	H	U	U	H	H	U
Total high rankings		7	6	3	1	8	7	0

[1] *n* = 12. H, high; L, low; M, moderate; U, unclear.

studies included in both reviews (243, 251). One systematic review of RCTs in adults with HF ($n = 4$ studies) lacked enough information for a meta-analysis to evaluate the effects of reduced dietary sodium intake on mortality (241).

Clinical CVD measures.

Despite the fact that no RCTs evaluated CVD events during this time, 17 cohort studies and 5 meta-analyses evaluated the association of sodium intake with CVD events (**Table 5**). Not accounting for ROB, the reported association with sodium intake was positive for 8 cohort studies (136, 143, 153, 154, 156, 174, 186, 224) and 2 meta-analyses (243, 250); null for 6 cohort studies (96, 123, 138, 175, 192, 216) and 1 meta-analysis (241); inverse for 2 cohort studies (128, 189) and 1 meta-analysis (251); and U-shaped for 1 cohort study (152). For HF events, the reported association with sodium intake was positive for 2 studies (156, 175); null for 2 (123, 216); and inverse for 1 (96). For stroke events, the association with sodium intake was positive for 2 cohort studies (143, 156) and 2 meta-analyses (236, 251); inverse in 1 study (128); and null in 1 study (175).

The most common biases for studies examining clinical CVD events were potential for systematic and random measurement error in sodium assessment (11 and 12 studies, respectively), selection bias due to recruiting sick participants (10 studies), and confounding (10 studies) (Table 5). Most studies were judged to be at high ROB for ≥2 of the 8 criteria. One study was judged to be at low ROB, with the exception of a high risk for potential selection bias (because people with a history of CVD were not excluded from the study or the analyses of clinical CVD events), an unclear ROB related to unknown departures from the intended exposure (after the first 2 y of assessment), and blinding of indicator/outcome assessors (156). If people with a history of CVD were lowering their sodium intake, one might expect a higher percentage of participants with a history of CVD to be in the lowest quartile of intake, but the opposite was observed. In this study (156), higher urinary sodium excretion was associated with increased risk of combined CVD events, HF, and stroke among patients with CKD, and adjustment for history of CVD did not change the direction of the association. One study at mostly high/unclear ROB found that higher sodium intake increased the risk of cardiovascular events [separately and in combination with all-cause hospitalizations ($n = 18$ persons)] among persons with HF and comorbid diabetes mellitus (DM) (186). However, this study lacked control of key confounding, had departures from the intended exposure status, and was at a high risk for random error.

Meta-analyses evaluating the effects/associations of dietary sodium on CVD events varied in their results. One review of RCTs conducted in adults with HF lacked sufficient data to evaluate the effects of reduced dietary sodium intake on CVD-related mortality (241). Another review indicated that sodium intake <3000 mg/d, but not 3000–5000 mg/d or >5000 mg/d, was associated with increased risk of cardiac

TABLE 5 Risk of bias assessment of prospective studies examining dietary sodium and its association with clinical cardiovascular disease indicators[1]

Reference	Association	Control of key confounding	Selection unrelated to sodium/outcome	Coinciding follow-up/ baseline exam	Departures from intended intervention	Potential for systematic error	Potential for random error	Adequate follow-up	Indicator assessors blinded to exposure group
Lamelas et al. (136)	+	H	M	U	U	H	H	U	U
Liu H et al. (143)	+	L	L	H	U	H	H	L	U
Mente et al. (153)	+	H	U	H	U	H	H	U	U
Merino et al. (154)	+	L	U	L	U	H	H	L	U
Mills et al. (156)	+	L	H	L	U	L	L	L	U
Polonia et al. (174)	+	H	H	U	U	L	H	U	U
Saleh et al. (186)	+	H	H	U	H	L	H	U	U
Zhao et al. (224)	+	H	H	U	U	L	H	U	U
Doukky et al. (96)	0	H	H	U	U	H	L	U	L
Kalogeropoulos et al. (123)	0	H	H	H	U	H	L	U	U
Lelli et al. (138)	0	L	M	H	U	L	H	U	U
Prentice et al. (175)	0	U	H	U	U	H	L	U	L
Singer et al. (192)	0	H	H	H	H	H	H	U	U
Welsh et al. (216)	0	L	L	L	U	H	H	U	U
Kieneker et al. (128)	−	L	M	U	U	L	L	U	L
Saulnier et al. (189)	−	H	H	U	U	H	H	U	L
Mente et al. (152)	U-shaped	H	H	U	U	H	H	U	U
Total high rankings		10	10	5	2	11	12	0	0

[1] $n = 17$. H, high; L, low; M, moderate; U, unclear.

death in an analysis of 7 cohort studies (251). The results of this meta-analysis were largely driven and limited by 3 studies at high risk of reverse causality. Participants in the lowest sodium group had higher prevalence of CVD factors in 2 studies (254, 255) and had more severe disease status and/or concurrent illness in 1 study of persons with DM (256). Limitations of 1 study have been discussed previously and include possible confounding, concurrent illness of participants, or under-collection of 24-h urine samples, which may explain the inverse association found (257). Two reviews that examined the association of dietary sodium intake and CVD mortality, among observational studies of generally healthy adults with no chronic or acute illnesses, found direct, positive associations (243, 250). Both reviews had high levels of heterogeneity between included studies and were limited by disagreements in methods to assess sodium intake and control for confounding factors in included studies. Lastly, a review by Jayedi et al. (236) found that higher sodium intake was associated with higher risk of stroke among 16 observational studies conducted in generally healthy adults. Results from this review were mainly driven by 2 large-scale cohort studies of Japanese adults and results may not be generalizable to other populations. Further, high levels of heterogeneity and disagreements in sodium assessments and control of confounding factors were found between studies.

Subclinical CVD measures.

From 2015 to 2019, PWV was the most common subclinical CVD measure examined ($n = 6$ studies and 2 reviews), followed by β-type natriuretic peptide (BNP) concentrations ($n = 4$ studies and 2 reviews), heart rate ($n = 4$ studies and 1 review), cardiac baroflex sensitivity ($n = 2$ studies), and pulse augmentation index ($n = 2$ studies). Other subclinical CVD measures evaluated in single studies included QT-interval, C-reactive protein concentrations, carotid intima media thickness (cIMT), microvascular density, and cardiac function and geometry measures.

Of the 4 trials that evaluated PWV as the outcome, the reported effect of sodium intake among middle-aged adults was null in 3 crossover trials (36, 58, 64) and positive in 1 (50) (**Tables 6**, **7**). In the 1 trial that included adults aged <30 y (50), the effect was null (Table 6). Two trials conducted in adults with prehypertension (pre-HTN) and DM with null results (36, 58) were judged to be at low ROB across all domains assessed, although adherence to the intervention was low (<90%) and the difference in intake between groups was >1000 mg/d in both trials (Tables 1 and 6). For the 2 cohort studies that evaluated PWV, the reported associations with sodium were positive (122, 163) (**Table 8**). However, both studies were judged to be at high ROB for ≥2 criteria, lacked control of key confounding, and had a high potential for systematic error in assessment of sodium intake (Table 8).

Of the trials that evaluated BNP as an outcome, 3 trials among persons with HF found a null association (31, 33, 42), whereas 1 trial among persons with pre-HTN found

TABLE 6 Risk of bias assessment of randomized intervention trials examining dietary sodium and its effect on subclinical cardiovascular disease measures[1]

Reference	Indicator	Effect	Intervention randomly allocated	Concealed allocation process	Participants/ staff blinded to intervention	Adequate follow-up	Indicator assessors blinded to intervention	Prespecified indicator
Parallel RCT								
Colin-Ramirez et al. (31)	BNP concentration	0	L	U	NA	L	L	U
Hummel et al. (42)	BNP concentration; C-reactive protein; troponin	0	U	U	NA	H	L	L
Fabricio et al. (33)	BNP concentration; HR	0	L	L	L	L	L	L
Crossover RCT								
Riphagen et al. (54)	BNP concentration	+	L	L	NA	L	L	L
Babcock et al. (23)	Cardiovagal baroflex sensitivity; HR	+	U	U	NA	U	L	U
Baqar et al. (25)	Cardiac baroflex sensitivity; AIX; HR	+; 0; 0	U	U	L	L	L	U
Gijsbers et al. (36)	PWV; HR; AIX	0	L	L	L	L	L	L
Muth et al. (50)	PWV	+ (A); 0 (C)	U	U	NA	U	U	U
Suckling et al. (58)	PWV	0	L	L	L	L	L	L
Rorije et al. (55)	Microvascular density	0	L	L	NA	H	L	L
Total high rankings		0	0	0	0	2	0	0

[1] $n = 7$. A, adults; AIX, Augmentation Index; BNP, β-type natriuretic peptide; C, children; H, high; HR, heart rate; L, low; NA, not applicable; PWV, pulse wave velocity; RCT, randomized controlled trial; U, unclear.

TABLE 7 Risk of bias assessment of crossover nonrandomized intervention trials examining dietary sodium and its effect on subclinical cardiovascular disease measures[1]

Reference	Indicator	Association	Selection unrelated to sodium/outcome	Coinciding follow-up/ baseline exam	Departures from intended intervention	Adequate follow-up	Indicator assessors blinded to intervention group	Prespecified indicator
He M et al. (39)	QT-interval	+	L	L	L	L	L	U
Wang et al. (64)	PWV	0	U	L	L	L	U	U
Total high rankings			0	0	0	0	0	0

[1] $n = 2$. L, low; PWV, pulse wave velocity; U, unclear.

a positive association (54) (Table 6). In 2 of the trials, ROB was unclear or high for ≥2 criteria and both had significant differences in sodium intake between intervention groups (31, 42), whereas the other 2 trials were at mostly low ROB (33, 54). Results for heart rate variability were mixed: in 3 trials at mostly low ROB the association was null (25, 33, 36), whereas in 1 trial at mostly unclear ROB, the association was positive (23). In 2 trials with unclear ROB for ≥2 criteria, conducted in normotensive adults (23) and adults with DM (25), sodium supplementation increased cardiac baroflex sensitivity, whereas in 2 trials at mostly low ROB the augmentation index was not significantly different by sodium intake (25, 36). In 1 RCT at mostly low ROB, higher sodium intake had no effect on microvascular density (without nitroglycerin) among healthy adult males; however, the authors did not disclose reasons for losses to follow-up and there was no mention of an intent-to-treat (55). In 1 non-RCT with mostly low ROB (39), higher sodium intake increased the QT-interval; however, this outcome was not prespecified (Table 7). For the remaining subclinical CVD indicators [C-reactive protein (42), cIMT (122), and left ventricular cardiac geometry and function measures (108)], the ROB of the published studies was judged to be uncertain or high for ≥2 indicators.

Two meta-analyses of trials evaluated the effect of sodium reduction on PWV. In 1 review of RCTs or non-RCTs in generally healthy adults, PWV was similar across dietary sodium interventions of ≥4 wk duration (237), whereas in another review of RCTs in adults with no specifications on disease status or intervention, a positive association was reported (228). In 2 reviews the effect of sodium on BNP concentrations was evaluated. One review identified only 1 trial that met their criteria with results that suggested a positive association in adults with CKD (242), whereas the other review had 7 trials that met their criteria with results that varied based on HF classification (New York Heart Association Functional Classification I–VI) (238). In 1 review of 72 RCTs among generally healthy or hypertensive adults, sodium reduction, assessed using 8-h or 24-h urine collections, significantly increased heart rate by ∼2% (234).

BP.

Roughly 60% of RCTs indicated that higher sodium intake increased systolic blood pressure (SBP) and diastolic blood pressure (DBP) (**Table 9**). In 3 trials judged to be low ROB on the criteria examined, higher sodium intake increased both SBP and DBP among persons with DM or pre-HTN (36, 58), whereas no effect was found on SBP or DBP among persons with HF (33). In contrast, among the cohort studies that evaluated BP as an outcome, the reported association with sodium intake was more variable and all studies evaluated were judged to be at high or uncertain ROB for at least half of the criteria examined (**Table 10**). The most common biases for the 12 cohort studies examining BP were potential for systematic and random measurement error in sodium assessment (10 and 9 studies, respectively), confounding (10 studies), and selection bias due to recruiting sick participants (4 studies) (Table 10).

Of the 8 meta-analyses of trials examining the effect of sodium on SBP and DBP, 6 indicated a positive effect—4 among persons with normotension, pre-HTN, or hypertension (HTN) (9, 232, 233, 235) and 2 among persons with CKD (231, 242); 1 indicated no significant change among generally healthy adults (237); and in 1 among persons with HF, investigators concluded evidence was insufficient (241). Two reviews indicated a positive relation between sodium intake and SBP in experimental and observational studies among generally healthy children and children with clinical conditions (239, 249). Lastly, in 1 review of observational studies a positive association was reported with risk of HTN in both urban and rural populations of lower- to middle-income countries (250).

Discussion

Since January 2015, the majority of the evidence on the relation between sodium intake and health, among the general population and specific subgroups, was based on results from observational studies or analyses, rather than RCTs, and thus subject to potential bias from error in assessment of sodium intake and confounding. Most of the published evidence from observational studies was based on cross-sectional surveys or analyses, which are subject to reverse causality. In addition, most of the recently published studies on sodium intake and health focused on CVD or renal risk. The number of studies varied by region and some studies, such as observational studies on sodium intake and gastric cancer conducted in Asia, may not apply to other regions, because the sources and distribution of sodium intake differ. For CVD risk indicators, the direction

TABLE 8 Risk of bias assessment of prospective studies examining the association between dietary sodium and subclinical cardiovascular disease measures[1]

Reference	Indicator	Association	Control of key confounding	Selection unrelated to sodium/ outcome	Coinciding follow-up/ baseline exam	Departures from intended intervention	Potential for systematic error	Potential for random error	Adequate follow-up	Indicator assessors blinded to intervention group	Prespecified indicator
Nerbass et al. (163)	PWV	+	H	H	H	H	H	H	U	U	L
Jung et al. (122)	PWV; cIMT	+	H	L	U	L	H	L	U	L	L
Haring et al. (108)	LV cardiac geometry and function	0	H	U	L	U	U	L	U	U	L
Total high rankings			3	1	1	1	2	1	0	0	0

[1] $n = 3$. cIMT, carotid intima-media thickness; H, high; L, low; LV, left ventricular; PWV, pulse wave velocity; U, unclear.

of sodium intake effects and associations varied; however, results of studies with low ROB confirmed higher sodium intake increased risk of mortality, CVD events, and BP, but did not affect PWV.

Most studies published since 2015 did not address the research gaps or meet recommendations for research methods published in the 2013 IOM report (2), suggesting lack of knowledge about the recommendations, resources necessary, or time for implementation and reporting. For instance, only a few studies used recruitment strategies to specifically enroll African Americans ($n = 1$ trial) (30), adults aged 51–70 y ($n = 4$ trials and 9 observational studies), 70 y or older ($n = 4$ observational studies), or other high-risk subgroups such as persons with DM ($n = 3$ trials, 4 observational studies) or CKD ($n = 4$ trials, 9 observational studies, 2 reviews). Most observational studies did not apply the recommended methods for assessment of sodium intake exposure and about one-third of RCTs included interventions with <4 wk duration, with few trials or studies focused on children or people with CHF. A minority of studies evaluated dietary sodium intake levels corresponding to levels in current guidelines (i.e., 1500–2300 mg) (3). During the time frame of this review, no trials evaluated risk of CVD events, stroke, or mortality, and in 1 review of adults with HF investigators concluded data were insufficient to evaluate the effects of reduced dietary sodium intake on cardiovascular-associated mortality (241). Further, few trials were conducted among patients with HF and examined measures related to symptoms of the disease (31, 33, 42). Lastly, gastric cancer was examined in 2 observational studies among Asian adults and results from both studies indicated that higher dietary sodium was associated with higher risk of gastric cancer but may not be generalizable to US adults (195, 206).

The results of this review are difficult to compare with previous reviews because the objectives differed. This review did not encompass the totality of evidence, but rather evidence published since 2015, and the selection criteria for included studies were broad. Unlike in previous reviews (3, 258), cross-sectional surveys, case-control studies, and nonrandomized trials were included. In addition, we did not exclude studies based on outcomes evaluated or inclusion of study methods that might bias results. This allowed us to understand the extent to which the 2013 IOM research recommendations (2) were applied in recent published studies and the extent to which different ROB criteria might affect the assessment of evidence. Two recent RCTs, for example, were judged to be at low ROB based on the criteria in this review but were excluded from the Agency for Healthcare Research and Quality (AHRQ) review (243) and the NASEM DRI (3) because 1 trial did not include a washout period between sodium intervention levels (36) and 1 trial enrolled persons with diabetes (58). Since the 2019 NASEM and AHRQ reviews (3, 243), 2 recent RCTs meeting NASEM inclusion criteria have been published (24, 59). Both examined the effect of sodium reduction on BP and were judged to be at mostly unclear or low ROB (24, 59). Further,

TABLE 9 Risk of bias assessment of RCTs examining dietary sodium and its effect on blood pressure[1]

Reference	Association[2]		Intervention randomly allocated	Concealed allocation process	Participants/ staff blinded to intervention	Adequate follow-up	Indicator assessors blinded to intervention	Prespecified indicator
	SBP	DBP						
Parallel RCT								
Nakano et al. (51)[3]	+	+	L	U	NA	L	H	L
He FJ et al. (37)[2]	+ (A); 0 (C)	0	L	L	NA	L	U	L
Takada et al. (59)	+	0	L	U	NA	L	L	L
Pinjuh Markota et al. (48)	0	0	U	L	NA	L	U	U
Meuleman et al. (49)	0	0	L	L	NA	L	H	L
Fabricio et al. (33)	0	0	L	L	L	L	L	L
Crossover RCT								
Gijsbers et al. (36)[3]	+	+	L	L	L	L	L	L
Muth et al. (50)	+	+	U	U	NA	U	U	U
Saran et al. (56)	+	+	U	L	NA	H	L	L
Juraschek et al. (44)	+	+	U	U	NA	U	L	L
Suckling et al. (58)[3]	+	+	L	L	L	L	L	L
Brian et al. (27)[2,3]	+ (F); 0 (M)	0	U	U	NA	L	U	U
Cashman et al. (28)	+	0	U	U	NA	L	U	L
Babcock et al. (24)	0	0	U	U	NA	U	L	L
Baqar et al. (25)	0	0	U	U	L	L	L	U
Total high rankings			0	0	0	1	2	0

[1] $n = 14$. A, adults; BP, blood pressure; C, children; DBP, diastolic blood pressure; H, high; L, low; NA, not applicable; RCT, randomized controlled trial; SBP, systolic blood pressure; U, unclear.
[2] If the authors stratified results to examine specific subpopulations (e.g., by age group or gender), criteria selections are presented for each with the specific subpopulation noted in parentheses.
[3] Results presented are for overall 24-h SBP/DBP (mm Hg), because the authors also evaluated clinic BP and other measures of 24-h BP measurements (e.g., morning 24 h).

3 cohort studies examining clinical CVD events at moderate to high ROB were published since these reviews (128, 143, 216), although only 1 met the NASEM/AHRQ inclusion criteria (128). Despite these differences, the results of this review support the findings of previous reviews that conclude that lowering population salt intake would be beneficial for health.

Multiple studies in this review examined associations/effects of sodium intake on health indicators other than those discussed in the previous 2013 IOM report or in other systematic reviews (2). Systematic reviews may be warranted to assess outcomes other than CVD or renal risk, especially for endothelial and vascular function, to better characterize mechanisms underlying CVD risk independent of BP (3). Further, for outcomes or indicators with ≥2 recently published studies, further review and evaluation of ROB may be warranted to update previously published systematic reviews. Such indicators include body fatness, insulin/glucose intolerance, RAAS, metabolic syndrome, bone measures, blood lipids, rheumatoid arthritis, nonalcoholic fatty liver disease, cataracts, inflammation, cognition, and muscle function.

Among recent published trials, crossover research designs were most commonly used when examining the effects of sodium intake and health indicators because these designs allow for smaller sample sizes and reduced resources (259). Trials published since 2015 and included in this review were short in duration (<4 wk) with large between-group differences in sodium intake close to or exceeding public health recommendations, particularly among feeding trials. Although the majority of trials used appropriate and standard measures for assessing mean group intake (i.e., using the mean of more than one 24-h urine collection per participant) (15), noncompliance with the intervention was observed in the majority of trials included in this ongoing review, a well-known problem with dietary studies (19).

Cohort studies suffered from methodological limitations inherent to observational studies including selection, information, and confounding biases. For example, reverse causality due to the recruitment of sick participants, inadequate follow-up/data reporting, or lack of adjustment for key sociodemographic characteristics or pre-existing conditions were common methodological issues with potential to alter the direction of the association (21). In addition, most cohort studies evaluated in the ROB assessment had potential for systematic and random error due to methodological errors in measurement of sodium intake. Roughly 30% of cohort studies used spot urine samples, an inaccurate and unreliable method, whereas <1% collected three or more 24-h urine collections on nonconsecutive days, i.e., the gold standard for assessment of long-term individual intake (260). Missing or unclear reporting of evidence made it difficult to determine biases relevant to our assessment, causing uncertainty around the conduct of studies and reported results.

TABLE 10 Risk of bias assessment of prospective studies examining the association between dietary sodium and blood pressure[1]

Reference	Association		Control of key confounding	Selection unrelated to sodium/outcome	Coinciding follow-up/baseline exam	Departures from intended intervention	Potential for systematic error	Potential for random error	Adequate follow-up	Indicator assessors blinded to intervention group
	SBP	DBP								
Prentice et al. (175)	+ (HTN)		H	H	U	U	H	L	U	L
Zhao et al. (224)	+ (HTN)		H	H	U	U	L	H	U	U
Welsh et al. (216)	+ (MABP)		H	L	L	U	H	H	U	U
Lamelas et al. (136)	+	+	H	M	U	U	H	H	U	U
Nerbass et al. (163)	+	+	H	H	H	H	H	H	U	U
Nguyen et al. (164)	+	+	L	M	L	H	H	H	U	U
Takase et al. (201)	+	NA	H	U	L	L	H	H	U	U
Krupp et al. (133)[2]	+ (B); 0 (G)	0	H	L	L	U	L	L	U	U
Umesawa et al. (205)[2]	+ (OV-WT); 0 (N)	0	H	M	L	L	H	H	U	U
Buendia et al. (76)	0	0	L	L	L	U	H	H	U	U
Morgenstern et al. (158)	0	0	H	H	L	U	H	L	U	U
Setayeshgar et al. (190)	0	+	H	U	H	U	H	H	H	U
Total high rankings			10	4	2	2	10	9	1	0

[1] $n = 12$. B, boy; DBP, diastolic blood pressure; G, girl; H, high; HTN, hypertension; L, low; M, moderate; MABP, mean arterial blood pressure; N, normal weight; NA, not applicable; OV-WT, overweight; SBP, systolic blood pressure; U, unclear.
[2] The authors stratified results to examine specific subpopulations (e.g., by gender, weight, or HTN status). Criteria selections are presented for each with the specific subpopulation noted in parentheses.

Our results indicate there remains a paucity of recent RCT research examining the effects of sodium on CVD outcomes (including stroke and mortality) among the general population and for specific populations that are at higher risk, including CHF patients. Long-term sodium reduction trials are required to evaluate the effects of sodium intake on chronic disease and are difficult to conduct owing to logistic, financial, and ethical constraints (19, 261, 262). Specifically, issues related to compliance, blinding, the nature of the food supply (i.e., >70% of sodium is consumed from processed food in the United States), and the interaction and aggregation of effects across other dietary components and health systems, all limit the feasibility of sustaining and achieving sodium modifications over a long duration (19, 262). To overcome these challenges, researchers have proposed conducting such a trial in a fully or partially institutionalized population (e.g., military personnel, nursing home residents/retirement home communities, prison population) (2, 263). Other proposed solutions are to monitor individuals as part of a natural experiment in areas where sodium policies are in effect or to conduct trials in geographic areas or communities where there is greater potential for sustained sodium reduction (e.g., tribal population or countries where the main source of sodium is discretionary) (2, 262).

Our review has several strengths. We describe recent studies related to any health indicator/outcome to understand whether current recommendations for research were applied. We identified domains of bias from existing risk assessment tools specific to study design (21, 264), defined and extended essential criteria to concepts/challenges inherent in nutritional epidemiology, and systematically applied and assessed the quality of evidence across multiple interventions and numerous outcomes. Through review from a native speaker, we were able to review and make decisions based on our eligibility criteria on 3 non-English full-text articles. We also identified 86 new studies published since the recent systematic reviews included here, as well as in the AHRQ review and 2019 NASEM report (3, 258).

This systematic review also has limitations. Given the objective of the review to examine recent evidence and provide directions for future research, evidence published before 2015 was excluded. Whereas terminology and tools for assessing ROB in individual RCTs have been validated and used consistently throughout the literature (264), a similar tool is unavailable for non-RCTs and observational studies (265). Because no such tool has been recommended to assess risk of bias in nonrandomized studies, we identified the ROBINS-I tool developed by the Cochrane Collaboration which assesses domains through which bias may be introduced into a nonrandomized study, and modified it to evaluate potential issues related to outcomes examined, nutritional epidemiology, and methodological challenges related to measuring sodium intake (21, 22, 265). Although the quality review applied systematic, uniform methods and standards, this approach required numerous judgments

which can be subjective (265). Our evaluation to determine if RCT research was conducted among high-risk groups was limited to trials that specifically enrolled these populations; consequently, trials that conducted stratified analyses using these subgroups were not considered. Lastly, a considerable amount of information to assess ROB criteria was missing, limiting our ability to assess validity in some studies.

Conclusions

This systematic review summarizes the literature of dietary sodium and health published between 2015 and 2019. Most of the published evidence on sodium and CVD risk during this time period was observational rather than interventional and although almost all studies assessed for ROB were subject to some bias, cohort studies suffered more bias because of methodological limitations inherent to their design. Our assessment on sodium and health was complicated by differences in the methods used to measure sodium intake. In addition, trial evidence was limited and measured differences in sodium intake were largely not applicable to population sodium reduction recommendations. However, the results of this review support the findings of previous reviews concluding that lowering population salt intake would be beneficial for health. Overall, data and method gaps remain in studies on sodium and health consistent with those identified by the IOM in 2013. The 2013 IOM review addresses the need for studies to standardize methodological approaches to measure sodium intake and report results consistently and thoroughly, points which were re-emphasized in the 2019 NASEM report as well as other reports (2, 3). In light of studies on new health indicators, broader systematic reviews to update the total body of evidence, including that published before 2015, may be warranted to assess the evidence surrounding the effects and associations of sodium intake with outcomes not identified in the previous reviews.

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