Title

Evidence-Based Policy Making for Public Health Interventions in Cardiovascular Diseases: Formally Assessing the Feasibility of Clinical Trials

Journal

Circulation Cardiovascular Quality and Outcomes, 13(11)

ISSN

1941-7713

Authors

Foti, Kathryn
Foraker, Randi E
Martyn-Nemeth, Pamela
et al.

Publication Date

2020-11-01

DOI

10.1161/circoutcomes.119.006378

Peer reviewed

HHS Public Access

Author manuscript

Circ Cardiovasc Qual Outcomes. Author manuscript; available in PMC 2021 November 01.

Published in final edited form as:

Circ Cardiovasc Qual Outcomes. 2020 November ; 13(11): e006378. doi:10.1161/CIRCOUTCOMES.119.006378.

Evidence-based policy making for public health interventions in cardiovascular diseases: Formally assessing the feasibility of clinical trials

Kathryn Foti, PhD, MPH[1,2], **Randi E. Foraker, PhD, MA**[3], **Pamela Martyn-Nemeth, RN, PhD**[4], **Cheryl A. M. Anderson, PhD, MPH, MS**[2,5], **Nancy R. Cook, ScD**[6], **Alice H. Lichtenstein, ScD**[7], **Sarah D. de Ferranti, MD, MPH**[8,9], **Deborah Rohm Young, PhD**[10], **Marie-France Hivert, MD, MMSc**[11,12], **Robert Ross, PhD**[13], **Prakash Deedwania, MD**[14], **Laurie P. Whitsel, PhD**[15], **Lawrence J. Appel, MD, MPH**[1,2,16]

[1]-Welch Center for Prevention, Epidemiology, and Clinical Research, Baltimore, MD

[2]-Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

[3]-Department of Internal Medicine, Washington University in St. Louis School of Medicine, St. Louis, MO

[4]-Biobehavioral Health Science, University of Illinois at Chicago, Chicago, IL

[5]-Department of Family Medicine and Public Health, UC San Diego School of Medicine, La Jolla, CA

[6]-Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

[7]-Cardiovascular Nutrition Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging, Tufts University, Boston, MA

[8]-Department of Cardiology, Boston Children's Hospital, Boston MA

[9]-Harvard Medical School, Boston, MA

[10]-Director, Division of Behavioral Research; Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena CA

[11]-Department of Population Medicine, Harvard Medical School, Harvard Pilgrim Health Care Institute, Boston, MA

[12]-Diabetes Unit, Massachusetts General Hospital, Boston, MA

[13]-School of Kinesiology and Health Studies, Queen's University, Kingston, Ontario, Canada

[14]-School of Medicine, University of California at San Francisco, Fresno CA1

[15]-Department of Policy Research and Translation, American Heart Association, Washington, DC

Corresponding Author: Lawrence J. Appel, MD, MPH, Welch Center for Prevention, Epidemiology, and Clinical Research, 2024 E. Monument St, Baltimore, MD 21205, USA (lappel@jhmi.edu, 410-955-4156 (phone), 410-955-0476 (fax)).

Disclosures

Dr. Nancy Cook reports being a one-time consultant to Jazz Pharmaceuticals in 2019. The other authors have no disclosures.

[16]Division of General Internal Medicine, Johns Hopkins University, Baltimore, MD

Abstract

Implementation of prevention policies has often been impeded or delayed due to the lack of randomized controlled trials (RCTs) with 'hard' clinical outcomes (e.g., incident disease, mortality). Despite the prominent role of RCTs in health care, it may not always be feasible to conduct RCTs of public health interventions with hard outcomes due to logistical and ethical considerations. RCTs may also lack external validity and have limited generalizability. Currently, there is insufficient guidance for policymakers charged with establishing evidence-based policy to determine whether an RCT with hard outcomes is needed prior to policy recommendations. In this context, the purpose of this paper is to assess, in a case study, the feasibility of conducting an RCT of the oft-cited issue of sodium reduction on cardiovascular outcomes, and then propose a framework for decision-making, which includes an assessment of the feasibility of conducting an RCT with hard clinical outcomes when such trials are unavailable. We designed and assessed the feasibility of potential individual- and cluster-randomized trials of sodium reduction on cardiovascular outcomes. Based on our assumptions, a trial using any of the designs considered would require tens of thousands of participants and cost hundreds of millions of dollars, which is prohibitively expensive. Our estimates may be conservative given several key challenges, such as the unknown costs of sustaining a long-term difference in sodium intake, the effect of differential co-treatment with anti-hypertensive medications, and long lag-time to clinical outcomes. Thus, it would be extraordinarily difficult to conduct such a trial, and despite the high costs, substantial risk for a spuriously null result. A robust framework, such as the one we developed, should be used to guide policymakers when establishing evidence-based public health interventions in the absence of trials with hard clinical outcomes.

Introduction

Decision-makers charged with protecting and promoting public health and equity often have to rely on imperfect evidence. While much has been written about the need to base policy decisions on the best-available evidence,[1,2] it is not always clear whether better evidence, especially from randomized controlled trials (RCTs), will ever be forthcoming. Thus, there is a tradeoff between waiting for additional evidence regarding risks, benefits, and costs, and failing to take action that may protect the public from avoidable health harms.

Despite the gold-standard level of evidence that RCTs provide, it may not be feasible to conduct RCTs of population-level public health interventions on hard clinical outcomes (e.g., incident disease, mortality) due to practical (e.g., cost, number of participants, trial duration) and ethical considerations (e.g., long-term non-treatment of control participants). Further, RCTs of complex exposures such as diet, physical activity, or other lifestyle factors related to chronic disease risk may be misleading due to interactions and synergies among these factors.[3] RCTs may also lack external validity and might not translate into effective policy. Policies to reduce tobacco use, require seat belts, and establish blood alcohol concentration limits for operating a vehicle were implemented without RCTs and have resulted in substantial public health benefits.[4] For these examples, high-quality observational

studies and continued evidence accumulation, including policy evaluation, have played an important role in implementing and refining prevention policy.

Prevention policy proposals often stir debate. Debates may center on issues of individual liberty versus societal benefits, personal responsibility versus structural or social determinants of health, industry interests versus public good, or the value proposition for investment in prevention.[5,6] These issues are difficult to resolve, and therefore, the focus of deliberations may be shifted to the strength of evidence to support action, which in turn may be debated.[5] Because of their place in the evidence hierarchy, a lack of RCTs with hard clinical outcomes has been cited as a reason to avoid or delay implementation of some prevention policies.[7-9] In cases where RCTs are not feasible, such calls may confuse or delay the debate and subsequent decision-making.

Population-wide sodium reduction is a widely-cited example of a cardiovascular prevention policy issue for which there is disagreement about the evidence for action and the feasibility of conducting an RCT with hard clinical outcomes (i.e., cardiovascular events and deaths). A 2005 Dietary References Intakes report recommended explicit assessment of the feasibility of a large-scale clinical trial on this topic; to our knowledge, a rigorous assessment has yet to be conducted and published.[10] Additionally, while there are several existing frameworks for considering evidence for policymaking,[2] to our knowledge, there is no framework that can be applied to move beyond an impasse when there are calls for RCTs to resolve debates about the evidence to support action. Therefore, the purpose of this paper is to assess, in a case study, the feasibility of conducting an RCT of sodium reduction on cardiovascular outcomes, and propose a framework for decision-making which includes an assessment of the feasibility of conducting an RCT with hard clinical outcomes. Our findings can add to the approaches currently used for evidence-based policy making by stakeholders such as the science advisory committees for the Dietary Guidelines for Americans and Physical Activity Guidelines for Americans, the US Preventive Services Task Force (USPSTF), the Community Preventive Services Task Force, non-governmental organizations, government officials, and research sponsors, including private foundations and the National Institutes of Health (NIH).

Case Study – Randomized controlled trials of sodium reduction on cardiovascular outcomes

Reducing sodium intake lowers blood pressure,[11] a generally accepted surrogate endpoint for clinical cardiovascular outcomes.[12] However, controversy exists within the scientific community. Whereas intervention studies consistently demonstrate reducing sodium intake reduces blood pressure, some observational studies report null or paradoxical findings regarding the association between sodium intake (or excretion) and cardiovascular outcomes.[13,14] Some scientists recommend RCTs with hard outcomes be completed to inform policymakers,[8,9] though others have posited such trials are neither necessary nor feasible.[15,16] To inform decision-making and advance the discussion about the feasibility of an RCT of sodium reduction on clinical outcomes, we designed several types of trials and

estimated the resources required, based on our collective experience in designing, conducting, and overseeing similar human clinical trials.[17-22]

Design considerations in individually-randomized trials

We first considered individually-randomized, multi-center trials of sodium reduction conducted among either a high-risk population or among a general, primary prevention population of adults. In each scenario, design considerations such as intervention duration, primary outcome, event rates, and effect sizes are based on experiences of major cardiovascular disease prevention trials such as PREDIMED, SPRINT, and VITAL.[22-24] The rationale for the parameters used to estimate the required sample size is provided in Table 1. We planned for individual participants to receive the intervention (low-sodium or control diet) for an average of 5 years, similar to the intervention duration in the PREDIMED trial.[23] The primary outcome, a composite of myocardial infarction, other acute coronary syndromes, stroke, heart failure, and death from cardiovascular causes, was the same outcome used in the SPRINT trial.[22] We assumed controls from the high-risk population would have an event rate of 2.25% per year, similar to SPRINT,[22] which included adults aged ≥50 with a systolic blood pressure of 130-180 mmHg with increased cardiovascular disease risk. We assumed controls from the primary prevention population would have an event rate of 1.0% per year, similar to that anticipated in the VITAL study but adjusted upwards due to the broader endpoint we selected.[24] We estimated the sample size required to detect a hazard ratio of 0.85, which is somewhat smaller than the effect size used in SPRINT and other major treatment trials.[22] We expect greater non-adherence to a lifestyle intervention than pill-based interventions and co-treatment of hypertension among controls which could reduce the contrast between groups. We assumed 1% annual loss to follow up based on the experience of another long-term dietary intervention study.[25] To detect a 15% effect size with 90% power, and a type I error rate of 0.05, we estimated a sample size of 16,996 adults in a high-risk population and 37,124 adults in a lower-risk (general) population would be needed. In sensitivity analyses (Appendix 1), we varied the trial duration, expected event rate among controls, effect size, power, and loss to follow-up.

Design considerations in cluster-randomized trials

We also examined cluster-randomized designs among high- and lower-risk adult populations. We assumed clusters would be live-in facilities that receive an environmental intervention; in other words, facilities randomized to the intervention would provide lower-sodium meals than facilities randomized to the control status. Because dietary sodium would be better controlled than in an individually-randomized design, we assumed an effect size of 20% with a cluster size of 100 participants. While we did not have examples of similar facility-based studies to draw on, we assumed an intra-cluster correlation coefficient (ICC) of 0.05. The Salt Substitute and Stroke Study, a community-based, cluster-randomized trial of sodium substitution, estimated its sample size using an ICC of 0.04[26] and we anticipate increased clustering in a facility-based trial (i.e., with greater control over dietary intake) as compared with clustering among villages. Based on the assumptions in Table 1, we estimated a cluster-randomized trial in a high-risk population would require 49,517 adult participants in 472 clusters, and a trial in a lower-risk adult population would require 107,962 participants in 1,028 clusters. Sensitivity analyses are presented in Appendix 1.

Costs

To estimate study costs for an individually-randomized trial, we anticipated 1 year of study planning, followed by 2 years of recruitment, 4 years of intervention (for an average intervention duration of 5 years), and 1 year of closeout. We estimated costs of $3,000 per participant per year based on multiple approaches. A 1993 Institute of Medicine (IOM) report found the average cost per participant per year for NIH-funded lifestyle intervention studies initiated in the 1990s exceeded $3000 per participant per year.[27] While this figure may be lower than current annual costs per participant due to inflation and other factors, there may have been improvements in trial efficiency, which may reduce costs. We also developed a build-up budget including staffing and intervention costs based on one author's (LA) experience implementing lifestyle intervention trials. Our calculations resulted in a similar estimated annual cost per participant (additional information available upon request from the authors). Based on this assumption, we estimated the total cost for an individually-randomized trial conducted among a high-risk population would be approximately $407,904,000 and a trial conducted among a low-risk population would be approximately $890,976,000 (see Appendix 1). Even if costs are reduced by half, such a trial would be likely prohibitively expensive.

Estimating the cost of a cluster-randomized trial is challenging because a cluster-randomized trial approaching this magnitude has never been conducted. However, given the sample size for a cluster-randomized trial is approximately 3 times larger than that for an individually-randomized trial, the average cost per participant per year would have to be reduced 3-fold to $1000 per year to maintain even the same total cost as an individually-randomized trial..

Threats to validity of individually- and cluster-randomized trials

There are several threats to internal validity which could reduce the power to detect a true difference in outcomes and increase sample size and study costs. First, the net reduction in sodium intake could be smaller than anticipated, as a result of cross-over, i.e. drop-in from the control group and/or drop-out from the intervention arm. For example, there could be low adherence to the study diet among those in the intervention arm, particularly given the long duration of intervention, and some participants in the control arm might reduce their sodium intake. A second, related challenge is hypertension co-treatment, particularly among a higher-risk trial population. Those in the control arm, because they are not reducing their sodium intake, might be more likely to be treated for hypertension, thereby lowering their blood pressure and obscuring any true effect of a lower sodium diet on cardiovascular events. Concurrently, those in the intervention arm should experience reduced blood pressure in which case anti-hypertensive medications might be tapered, discontinued, or not further adjusted. Greater pharmacologic treatment of cardiovascular risk factors in the control group may explain, for example, the results in the Look AHEAD trial, in which an intensive lifestyle intervention to promote weight loss through reduced caloric intake and increased physical activity among overweight or obese adults with type 2 diabetes had no significant effect on cardiovascular events and was stopped early for futility.[28] Relatedly, in the Women's Health Initiative Dietary Modification Trial, which tested the effects of a low-fat dietary pattern on cardiovascular health in post-menopausal women, and extended follow-up, there were post-randomization differences in statin use which affected the

interpretation of the study findings.[29,30] Specifically, women in the intervention group with cardiovascular disease or hypertension at baseline were more likely to discontinue statin use than those in the control group; given the expected reduction in LDL cholesterol with statin use is greater than the reduction expected with the dietary intervention, this would explain the apparent risk of cardiovascular disease in the intervention arm for those with prior cardiovascular disease and lack of beneficial effects among women with hypertension. [29,30]

A third risk is the possibility of a lower-than-expected event rate, which could arise from secular decreases in cardiovascular disease, and would necessitate an increased sample size, a change in the primary outcome to include more event types, and/or a longer follow-up to retain power to detect a 15% effect.[31] In the Look AHEAD trial, due to a lower-than-expected event rate, the investigators expanded the primary endpoint to increase the number of potential events and extended the trial by 2 years.[31] Additional concerns with extending study duration include increased costs and lack of adherence to the intervention as the duration increases, particularly among a population which may develop comorbidities that could affect ability to adhere.[31] It is possible we could observe a greater effect size than anticipated given the current plateauing of CVD events and lack of reduction in population sodium intake.[32,33] However, we believe several of our assumptions were optimistic with respect to the potential effect size in real world settings.

A fourth consideration is generalizability, an issue which is relevant to both individual- and cluster-randomized trials. A trial conducted in a high-risk population would likely raise discussion about whether the results are applicable to the general population. While a trial conducted among lower-risk, general population might be proposed to enhance generalizability, the study population would still be highly selected and generalizability would remain a concern. Fifth, it is important to consider the translation of the RCT intervention to policy. An individual approach to sodium reduction, which is most feasible to test in an RCT, is different from an environmental intervention or an intervention that reduces sodium in the food supply.

While it may be possible to reduce the cost of the individually-randomized intervention, for example, by using technology to deliver the intervention remotely, such approaches have not been tested. Thus, there is the risk of a reduced experimental contrast and a false null result.

There are several practical issues related to the feasibility of a cluster-randomized trial. First, a large number of facilities would need to be recruited, for which there is no precedent. We are aware of just one facility-based trial of sodium reduction (using a potassium-enriched salt) on cardiovascular mortality.[34] This study randomized 5 kitchens serving a Taiwanese veterans' home and enrolled 1,982 total participants followed for an average of 31 months.[34] It is unclear which settings in the US or globally would be feasible to recruit in such large numbers. Nursing homes and prisons are two settings which have been mentioned,[9] but there are logistical and ethical issues related to recruitment of facilities and their populations, including the number of facilities needed, length of follow-up required, human subjects considerations, and generalizability of findings.[35,36]

Second, there are issues related to consent. Individual consent would be necessary because some contact with study participants would be required to periodically monitor fidelity to the intervention, including 24-hour urine collection among a subset of participants, measurement of intermediate outcomes such as blood pressure, and determination of clinical outcomes.[37] As individual consent would be obtained after cluster randomization, there is the possibility of selection bias.[37] While randomizing at the cluster level with global consent would theoretically avoid such issues, it is likely unacceptable and infeasible given the need to follow-up with subjects over an extended period. In addition, cluster-randomized trials are susceptible to imbalances across study arms at baseline due to a smaller number of units randomized as compared to an individually-randomized trial.[37] In our scenarios, there are a large number of units, so it is unclear whether this would be an issue. Loss to follow-up is an important factor; 1% loss to follow-up per year is likely conservative depending on the facility type and retention of participants. Lastly, if the ICC is greater than anticipated, the study may be underpowered and require additional study sites and participants.

Based on this case study, a trial using any of the designs considered would require tens of thousands of participants and cost hundreds of millions of dollars. Our estimates may be conservative given potential risks to study integrity such as adherence to the intervention, hypertension co-treatment, and lag-time to effect. Thus, RCTs of sodium reduction with clinical outcomes would be difficult to conduct, costly, and have substantial risk for a spuriously null result.

A Framework to Assess Evidence and Inform Decision-Making on Public Health Interventions

Informed by our findings from the above case study and existing frameworks, we developed a framework to facilitate assessment of evidence for decision-making and development of prevention policy. It is intended for use by policymakers, advocacy and community organizations, and the public health practitioners whom these leaders consult.

Our framework complements existing evidence-grading systems. Some grading systems, including the Grading of Recommendations, Assessment, Development, and Evaluation system (GRADE)[38] prioritize RCT evidence; this may be appropriate for clinical practice recommendations, but there are substantial limitations when GRADE is used to inform decisions about public health interventions.[39] For example, if it is not feasible to conduct an RCT, the lack of available RCTs will result in a lower quality of evidence rating, which may not be well understood. Meanwhile, other systems used by organizations such as the Community Guide to Preventive Services[40] and American Heart Association,[41] and the recently developed Hierarchies of Evidence Applied to Lifestyle Medicine (HEALM) tool,[42] more fully consider other types of evidence, including observational and practice-based evidence. Additionally, other evidence grading systems, such as the Quality and Impact of Component Evidence Assessment[43] and others[44-46] can be used to evaluate the evidence for prevention policy interventions not only in terms of the quality of evidence, but also the potential for their impact on health and equity, scalability, and sustainability. These are just

several examples of evidence grading schemes, but examples which are frequently cited when evaluating and prioritizing cardiovascular prevention policies.[2]

While our framework can be used broadly to guide decision-making about cardiovascular prevention policies, it may be particularly useful in situations where there are calls for an RCT. Calls for RCTs may be made without consideration of their feasibility; the timeframe for designing, conducting and reporting an RCT; and the contribution of RCT evidence to advancing policy deliberations. To our knowledge, there is currently no guidance for policymakers on how to move the debate once someone states an RCT should be done.

The framework (Table 2) includes considerations across stages of weighing evidence and developing prevention policy recommendations. At each stage of the process, we recommend evaluation of data sources and quality *and* consultation with experts and stakeholders. In the 4th stage, there is an explicit step to assess the feasibility of an RCT with 'hard' clinical outcomes (Table 3). This includes estimating sample size and cost for one or more study designs deemed most feasible by experts, assessing threats to validity, and ethical considerations.[47] If an RCT is deemed not feasible, we recommend considering the strength of the evidence currently available from other study designs (e.g. trials with well-accepted surrogate outcomes, high quality cohort studies) using appropriate existing paradigms.[40-42] Additional discussion on applying this framework is available in Appendix 2.

Discussion

In contrast to clinical medicine, in which evidence from trials with hard clinical outcomes is not only expected but often available, few prevention-oriented public health interventions are supported by such evidence. The reason for this dichotomy lies in the distinct nature of public health interventions. In an RCT of a clinical intervention, a participant receives either the drug/procedure or placebo/sham, adherence is generally high, the intervention effect occurs soon after the start of therapy and is often substantial in magnitude. In contrast, public health interventions are often complex with highly variable adherence, especially if the intervention requires substantial behavioral change. Benefits may be significant, but often happen over a longer timeframe, and shorter-term studies may show null results. In this context, we proposed a framework to guide decision makers, including a step that has rarely been considered: a rigorous, published assessment of the feasibility of conducting a trial with hard clinical outcomes.

Our case study on sodium reduction policy as a means to prevent cardiovascular disease illustrates how an assessment could be done. Our findings showed a clinical trial using any of the designs considered, which were those deemed most feasible to implement, would require tens of thousands of participants and cost hundreds of millions of dollars. Our estimates may still be conservative given potential challenges such as sustaining a long-term contrast in sodium intake, differential co-treatment with anti-hypertensive medications, and long lag-time to effect. Thus, despite high costs, there is substantial risk for a spuriously null result.

It is unlikely a funding agency would have sufficient resources to support any trial of the candidate trials. For example, the estimated cost of the NHLBI-funded SPRINT trial was ~ $125m, substantially less than our hypothetical trials. Given the pressure to reduce costs of clinical trials at the NIH, it is doubtful any of the candidate trial designs would be considered, much less funded. Additionally, funding such a trial would reduce resources for other research priorities.

Given these findings, the critical issue remains, *what type of evidence should be used to guide public health policy if a clinical trial with adequate statistical power for hard clinical outcomes cannot be done*? Such decision-making is context-dependent and should be guided by methodologic considerations, which likely differ by public health issue and the available interventions. Such considerations include the availability of accepted surrogate outcomes, availability of appropriate exposures and outcomes in observational studies, and generalizability of the study populations.

There are other questions for which this framework applies. For example, the USPSTF has cited the lack of trials of long-term benefits and harms, including cardiovascular outcomes, as an impediment to making recommendations on childhood cholesterol and hypertension screening.[48,49] RCTs have been proposed for other topics, including the effects of prescribed physical activity or behavioral counseling on cardiovascular outcomes; the effects of pre-conception lifestyle counseling or weight loss before pregnancy on long-term cardiometabolic health in offspring; and the effects of different types of dietary fats (e.g., polyunsaturated fatty acid, mono-unsaturated fatty acid, saturated fatty acid from meat or dairy) on cardiovascular outcomes.[50-52] Our framework can be used to weigh available evidence, assess the feasibility of RCTs, and inform policy solutions.

In conclusion, clinical trials with hard outcomes are unavailable for many public health interventions. Ultimately, policy should be made with an explicit exposition of what evidence is currently available, might become available, or will likely never be available keeping in mind the overall population’s health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Support: Kathryn Foti is supported by Grant Number T32 HL007024 from the National Heart, Lung, and Blood Institute, National Institutes of Health.

References

1. Evidence-Based Policy Making Collaborative. Principles of evidence-based policymaking. 9 2016 https://www.urban.org/sites/default/files/publication/99739/principles_of_evidence-based_policymaking.pdf. Accessed June 1, 2020.
2. Labarthe DR, Goldstein LB, Antman EM, Arnett DK, Fonarow GC, Alberts MJ, Hayman LL, Khera A, Sallis JF, Daniels SR, Sacco RL, Li S, Ku L, Lantz PM, Robinson JG, Creager MA, Van Horn L, Kris-Etherton P, Bhatnagar A, Whitsel LP. Evidence-based policy making: assessment of the

American Heart Association's Strategic Policy Portfolio. Circulation. 2016;133:e615–e653. [PubMed: 27045139]

3. Satija A, Yu E, Willett WC, Hu FB. Understanding nutritional epidemiology and its role in policy. Adv Nutr. 2015; 6:5–18. [PubMed: 25593140]
4. Hyland A, Barnoya J, Corral JE. Smoke-free air policies: past, present and future. Tob Control. 2012; 21:154–161. [PubMed: 22345239]
5. Richardson MB, Williams MS, Fontaine KR, Allison DB. The development of scientific evidence for health policies for obesity: why and how? Int J Obes. 2017; 41:840–848.
6. Woolf SH. A closer look at the economic argument for disease prevention. JAMA. 2009; 301:536–538. [PubMed: 19190319]
7. Alderman M Intersalt data. Data linking sodium intake to subsequent morbid and fatal outcomes must be studied. BMJ. 1997; 315:484–487.
8. Alderman MH. Reducing dietary sodium. JAMA. 2010; 303:448–449. [PubMed: 20124541]
9. Jones DW, Luft FC, Whelton PK, Alderman MH, Hall JE, Peterson ED, Califf RM, McCarron DA. Can we end the salt wars with a randomized clinical trial in a controlled environment? Hypertension. 2018; 72:10–11. [PubMed: 29735638]
10. Institute of Medicine. Dietary Reference Intakes for water, potassium, sodium, chloride, and sulfate. Washington, DC: National Academies Press; 2005 10.17226/10925.
11. Mozaffarian D, Fahimi S, Singh GM, Micha R, Khatibzadeh S, Engell RE, Lim S, Danaei G, Ezzati M, Powles J. Global sodium consumption and death from cardiovascular causes. N Engl J Med. 2014; 371:624–634. [PubMed: 25119608]
12. Fleming TR, Powers JH. Biomarkers and surrogate endpoints in clinical trials. Stat Med. 2012; 31:2973–2984. [PubMed: 22711298]
13. Taylor RS, Ashton KE, Moxham T, Hooper L, Ebrahim S. Reduced dietary salt for the prevention of cardiovascular disease In: Taylor RS, editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2011.
14. O'Donnell M, Mente A, Rangarajan S, McQueen MJ, Wang X, Liu L, Yan H, Lee SF, Mony P, Devanath A, Rosengren A, Lopez-Jaramillo P, Diaz R, Avezum A, Lanas F, Yusoff K, Iqbal R, Ilow R, Mohammadifard N, Gulec S, Yusufali AH, Kruger L, Yusuf R, Chifamba J, Kabali C, Dagenais G, Lear SA, Teo K, Yusuf S. Urinary sodium and potassium excretion, mortality, and cardiovascular events. N Engl J Med. 2014; 371:612–623. [PubMed: 25119607]
15. Cobb LK, Anderson CAM, Elliott P, Hu FB, Liu K, Neaton JD, Whelton PK, Woodward M, Appel LJ. Methodological issues in cohort studies that relate sodium intake to cardiovascular disease outcomes: a science advisory from the American Heart Association. Circulation. 2014; 129:1173–1186. [PubMed: 24515991]
16. He FJ, MacGregor GA. Salt reduction lowers cardiovascular risk: meta-analysis of outcome trials. Lancet. 2011;378:380–382. [PubMed: 21803192]
17. Trials of Hypertension Prevention Collaborative Research Group. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. JAMA. 1992; 267:1213–1220. [PubMed: 1586398]
18. Trials of Hypertension Prevention Collaborative Research Group. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. Arch Intern Med. 1997; 157:657–667. [PubMed: 9080920]
19. Cook NR, Cutler JA, Obarzanek E, Buring JE, Rexrode KM. Long term effects of dietary sodium reduction on of the trials of hypertension prevention (TOHP). BMJ. 2007; 55:1–8.
20. Writing Group of the PREMIER Collaborative Research Group. Effects of comprehensive lifestyle modification on blood pressure control. JAMA. 2003; 289:2083–2093. [PubMed: 12709466]
21. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER, Simons-Morton DG, Karanja N, Lin P-H, Aickin M, Most-Windhauser MM, Moore TJ, Proschan MA, Cutler JA. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med. 2001; 344:3–10. [PubMed: 11136953]
22. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015; 373:2103–2116. [PubMed: 26551272]

23. Estruch R, Ros E, Salas-Salvadó J, Covas M-I, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV., Martínez JA, Fitó M, Gea A, Hernán MA, Martínez-González MA. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med. 2018; 378:e34. [PubMed: 29897866]
24. Manson JE, Bassuk SS, Lee I, Cook NR, Albert MA, Gordon D, Zaharris E, Macfadyen JG, Danielson E, Lin J, Zhang SM, Buring JE. The VITamin D and OmegA-3 TriaL (VITAL): rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. Contemp Clin Trials. 2012; 33:159–171. [PubMed: 21986389]
25. Howard BV, Van Horn L, Hsia J, Manson JE, Stefanick ML, Wassertheil-Smoller S, Kuller LH, LaCroix AZ, Langer RD, Lasser NL, Lewis CE, Limacher MC, Margolis KL, Mysiw WJ, Ockene JK, Parker LM, Perri MG, Phillips L, Prentice RL, Robbins J, Rossouw JE, Sarto GE, Schatz IJ, Snetselaar LG, Stevens VJ, Tinker LF, Trevisan M, Vitolins MZ, Anderson GL, Assaf AR, Bassford T, Beresford SAA, Black HR, Brunner RL, Brzyski RG, Caan B, Chlebowski RT, Gass M, Granek I, Greenland P, Hays J, Heber D, Heiss G, Hendrix SL, Hubbell FA, Johnson KC, Kotchen JM. Low-fat dietary pattern and risk of cardiovascular disease. JAMA. 2006; 295:655–666. [PubMed: 16467234]
26. Neal B, Tian M, Li N, Elliott P, Yan LL, Labarthe DR. Rationale, design, and baseline characteristics of the Salt Substitute and Stroke Study (SSaSS)—A large-scale cluster randomized controlled trial. Am Heart J. 2017; 188:109–117. [PubMed: 28577665]
27. Institute of Medicine (US) Committee to Review the NIH Women's Health Initiative; Thaul S, Hotra D, editors. An Assessment of the NIH Women's Health Initiative. Washington (DC): National Academies Press (US); 1993 https://www.ncbi.nlm.nih.gov/books/NBK236506/. Accessed June 1, 2020.
28. The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med. 2013; 369:145–154. [PubMed: 23796131]
29. Prentice RL, Aragaki AK, Van Horn L, Thomson CA, Beresford SA, Robinson J, Snetselaar L, Anderson GL, Manson JE, Allison MA, Rossouw JE, Howard B V. Low-fat dietary pattern and cardiovascular disease: results from the Women's Health Initiative randomized controlled trial. Am J Clin Nutr. 2017; 106:35–43. [PubMed: 28515068]
30. Prentice RL, Aragaki AK, Van Horn L, Rossouw JE, Howard BV. Reply to DR Merkle. Am J Clin Nutr. 2018; 107:297–298. [PubMed: 29529155]
31. Brancati FL, Evans M, Furberg CD, Geller N, Haffner S, Kahn SE, Kaufmann PG, Lewis CE, Nathan DM, Pitt B, Safford MM, Look AHEAD Study Group. Midcourse correction to a clinical trial when the event rate is underestimated: the Look AHEAD (Action for Health in Diabetes) Study. Clin Trials. 2012; 9:113–124. [PubMed: 22334468]
32. Sidney S, Quesenberry CP, Jaffe MG, Sorel M, Nguyen-Huynh MN, Kushi LH, Go AS, Rana JS. Recent trends in cardiovascular mortality in the United States and public health goals. JAMA Cardiol. 2016; 1:594–599. [PubMed: 27438477]
33. Brouillard AM, Kraja AT, Rich MW. Trends in dietary sodium intake in the United States and the impact of USDA Guidelines: NHANES 1999-2016. Am J Med. 2019; 132:1199–1206. [PubMed: 31103645]
34. Chang H-Y, Hu Y-W, Yue C-SJ, Wen Y-W, Yeh W-T, Hsu L-S, Tsai S-Y, Pan W-H. Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men. Am J Clin Nutr. 2006;83:1289–1296. [PubMed: 16762939]
35. Angell SY. A diet study of prisoners? Wrong on many levels. The New York Times 6 11, 2018 https://www.nytimes.com/2018/06/11/opinion/diet-study-prisoners.html. Accessed June 1, 2020.
36. Christopher PP, Stein MD. Should a prison salt trial be federally funded? Ann Intern Med. 2019; 170:409–410. [PubMed: 30831598]
37. Weijer C, Grimshaw JM, Eccles MP, Mcrae AD, White A, Brehaut JC, Taljaard M, the Ottawa Ethics of Cluster Randomized Trials Consensus Group. The Ottawa Statement on the ethical design and conduct of cluster randomized trials. PloS Med. 2012; 9:e1001346. [PubMed: 23185138]

38. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schünemann HJ, GRADE Working Group. Going from evidence to recommendations. BMJ. 2008; 336:1049–1051. [PubMed: 18467413]
39. Holger Schünemann Jan Brożek, Guyatt Gordon, Oxman Andrew. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. BMJ. 2013; 332:1089–1092.
40. Briss PA, Zaza S, Pappaioanou M, Fielding J, Wright-De Agüero L, Truman BI, Hopkins DP, Dolan Mullen P, Thompson RS, Woolf SH, Carande-Kulis VG, Anderson L, Hinman AR, Mcqueen DV, Teutsch SM, Harris JR. Developing an evidence-based Guide to Community Preventive Services—Methods. Am J Prev Med. 2000; 18:35–43. [PubMed: 10806978]
41. Mozaffarian D, Afshin A, Benowitz NL, Bittner V, Daniels SR, Franch HA, Jacobs DR, Kraus WE, Kris-Etherton PM, Krummel DA, Popkin BM, Whitsel LP, Zakai NA. Population approaches to improve diet, physical activity, and smoking habits: a scientific statement from the American heart association. Circulation. 2012; 126:1514–1563. [PubMed: 22907934]
42. Katz DL, Karlsen MC, Chung M, Shams-White MM, Green LW, Fielding J, Saito A, Willett W. Hierarchies of evidence applied to lifestyle Medicine (HEALM): introduction of a strength-of-evidence approach based on a methodological systematic review. BMC Med Res Methodol. 2019; 19:1–16. [PubMed: 30611213]
43. Barbero C, Gilchrist S, Schooley MW, Chriqui JF, Luke DA, Eyler AA. Appraising the evidence for public health policy components using the quality and impact of component evidence assessment. Glob. Heart. 2015;10:3111.
44. Brennan L, Castro S, Brownson RC, Claus J, Orleans CT. Accelerating evidence reviews and broadening evidence standards to identify effective, promising, and emerging policy and environmental strategies for prevention of childhood obesity. Annu Rev Public Health. 2011; 32:199–223. [PubMed: 21219169]
45. Brownson RC, Fielding JE, Maylahn CM. Evidence-based public health: a fundamental concept for public health practice. Annu Rev Public Health. 2009; 30:175–201. [PubMed: 19296775]
46. Flay BR, Biglan A, Boruch RF, Castro FG, Gottfredson D, Kellam S, Mościcki EK, Schinke S, Valentine JC, Ji P. Standards of evidence: criteria for efficacy, effectiveness and dissemination. Prev Sci. 2005; 6:151–175. [PubMed: 16365954]
47. U.S. Department of Health and Human Services. The Belmont Report. Ethical principles and guidelines for the protection of human subjects of research. 4 18, 1979 https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html#xjust. Accessed June 1, 2020.
48. Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW, García FAR, Gillman MW, Kemper AR, Krist AH, Kurth AE, Landefeld CS, LeFevre M, Mangione CM, Owens DK, Phillips WR, Phipps MG, Pignone MP, Siu AL. Screening for lipid disorders in children and adolescents. JAMA. 2016; 316:625–633. [PubMed: 27532917]
49. Thompson M, Dana T, Bougatsos C, Blazina I, Norris SL. Screening for hypertension in children and adolescents to prevent cardiovascular disease. Pediatrics. 2013; 131:490–525. [PubMed: 23439904]
50. Patnode CD, Evans CV., Senger CA, Redmond N, Lin JS. Behavioral counseling to promote a healthful diet and physical activity for cardiovascular disease prevention in adults without known cardiovascular disease risk factors. JAMA. 2017; 318:175–193. [PubMed: 28697259]
51. Stang J, Huffman LG. Position of the Academy of Nutrition and Dietetics: obesity, reproduction, and pregnancy outcomes. J Acad Nutr Diet. 2016; 116:677–691. [PubMed: 27017177]
52. Jacobs DR, Petersen KS, Svendsen K, Ros E, Sloan CB, Steffen LM, Tapsell LC, Kris-Etherton PM. Considerations to facilitate a US study that replicates PREDIMED. Metabolism. 2018; 85:361–367. [PubMed: 29733820]

Table 1.

Study design parameters for a case study of sodium reduction on cardiovascular outcomes among adults

Parameter	Estimate	Rationale
Randomization	***Individual***	
Type I error	0.05	Commonly accepted value
Power	0.9	Common among major trials
Hazard ratio	0.85	Based on the hazard ratio of cardiovascular disease among follow-up responders in the TOHP* study (0.75; 95% CI: 0.57–0.99)[19] and expert opinion of the plausible net effect after accounting for intervention lag and hypertension co-treatment among controls. A hazard ratio of 0.80 is often used in planning major trials (e.g., SPRINT*[22]); however, these are generally drug treatment trials as opposed to lifestyle intervention trials and we expect adherence to the lifestyle intervention may wane over time.
Primary outcome	Composite of: myocardial infarction, other acute coronary syndromes, stroke, heart failure, and death from cardiovascular causes	Same primary outcome used in SPRINT*[22]
Annual event rate (among controls)	High-risk population: 2.25% per year Lower-risk (general) population: 1.0% per year	Based on event rate in the high-risk population in SPRINT* (2.2% event rate per year among controls)[22] Based on event rate parameters established for the low-risk group in the VITAL* study (estimated 0.8% event rate per year among controls in trial planning)[24]
Accrual time	2 years	Determined to be feasible based on investigators' clinical trial experiences. Assumes uniform accrual.
Follow-up time (average)	5 years	Based on PREDIMED* which is a long-term dietary intervention trial in which participants were followed for a median of 4.8 years over a 6-year study period[23]
Loss to follow-up	1% per year	Assumes 5% loss to follow-up at 5 years and that losses are uniform and unrelated to the intervention. Rate was determined by the investigators, roughly based on WHI* DM which had 4.7% loss to follow-up among the intervention group and 4.0% loss to follow-up among usual diet group after an average follow-up of 8.1 years.[25]
Treatment allocation ratio	1:1	Based on standard practice and investigators' clinical trial experiences
Randomization	***Cluster*** *(same parameters as individually-randomized trial except where noted below)*	
Hazard ratio	0.80	Based on the hazard ratio of cardiovascular disease among follow-up responders in TOHP* study (0.75; 95% CI: 0.57–0.99)[19] and investigators' opinion of the plausible net effect in a facility-based trial with an environmental intervention.
Cluster size	100	Determined based on investigators' experiences and practical considerations.
Intracluster correlation coefficient (ICC)	0.05	Determined based on investigators' experiences. The SSaSS* trial, a community-based, cluster-randomized trial of sodium substitution, estimated its sample size using an ICC of 0.04.[26] Because we anticipate increased clustering in a facility-based environmental intervention (i.e., with greater control over dietary intake) as compared with an intervention among free-living populations in community-based settings, we assumed an ICC of 0.05. This may still be conservative.

* Abbreviations: TOHP, Trials of Hypertension Prevention; SPRINT, Systolic Blood Pressure Intervention Trial; VITAL, VITamin D and OmegA-3 TriaL; PREDIMED, Prevención con Dieta Mediterránea; WHI DM, Women's Health Initiative Randomized Controlled Dietary Modification Trial; ICC, intracluster correlation coefficient; SSaSS, Salt Substitute and Stroke Study.

Table 2.

Framework for reviewing prevention-related public health evidence and determining when it is appropriate to use an existing body of evidence for policy-making or intervention

Stage 1. Identify the problem: ***What is the public health concern?***	
Data sources and quality	• Does evidence exist that describes the problem? • What is the level of evidence? • Is there an equity impact?
Expert consultation	• Does the public health concern warrant policy or intervention? • Will it improve health equitably across populations? • Would policy action feasibly address the problem or its related/more proximal health issues?
Stage 2. Define the scope of the problem: ***What is the impact of the problem on public health?***	
Data sources and quality	• What data exist which describe the magnitude of the problem? • Do these data adequately describe the population of interest?
Expert consultation	• Is there a strong perceived need for a policy or intervention? • Are authoritative agencies concerned?
Stage 3. Identify policy scenarios: ***What types of policies should be considered to solve the problem?***	
Data sources and quality	• Are there lessons learned from success stories? • Do process evaluation or outcomes data exist? • Is there any demonstrated implementation evaluation? • If an RCT were designed, could proposed policy options be translated into arms of an RCT?
Expert consultation	• Is there precedence locally or internationally for relevant policies or interventions? • What have authoritative bodies concluded?
Stage 4. Review existing data: ***What data exist which describe the problem and/or potential solutions?***	
Data sources and quality	• How does each source of data contribute to decision-making? • What intermediary results are available? • If an RCT with clinical outcomes has been suggested, has its feasibility been evaluated? When would results become available? (**See** Table 3) • What type of evidence is likely to become available and what type of evidence is unlikely to become available? • If an RCT with clinical outcomes is deemed not feasible, what is the level of evidence currently available based on accepted paradigms? • Is it possible to model different courses of action and the potential impact?
Expert consultation	• Are the data being reviewed relevant, of high-quality, and complete? • Do the data represent the state of the science? • Would an RCT advance evidence of effectiveness and advance policy discussions? • What do experts conclude given the available evidence?
Stage 5. Summarize results for policymakers: ***Does the preponderance of evidence support action?***	
Data sources and quality	• What are the strengths and limitations of the existing data?

	• Does the state of the science support action?
Expert consultation	• What are the advantages and disadvantages of implementing a policy or intervention? • Who are the potential government agency, non-governmental organization, coalition, and other stakeholder partners?

Table 3.

Assessing the feasibility of a randomized controlled trial.

When assessing the feasibility of an RCT, consider one or more possible study designs and their strengths and weaknesses. Consider varying the parameters used to estimate sample size and costs to provide ranges. Inputs will come from the literature and investigator experience.

- **Designing candidate trials**
  - Study design: What study design(s) will most closely align with the desired intervention? What study design(s) are best suited to achieving the necessary effect size?
  - Population: Who is the target population? Can you recruit a study population for whom the results will be generalizable to the target population?
  - Intervention: What is the intervention of interest for policymaking? How can it be implemented in an RCT?
  - Comparison: What is the appropriate comparison group? What is the potential for bias if participants or physicians (if appropriate) decline to participate in the control group?
  - Outcome: How is the clinical outcome of the trial defined?
  - Event rate: What is the expected rate of events among your study population?
  - Effect size: What is an effect size of public health significance? What is a plausible effect size among the study population based on relevant literature?
  - Timeline: How long will it take to recruit your participants? How long do you anticipate participants will adhere to the intervention and is there sufficient time for events to accrue? What is the duration of study close out?
  - Setting: In what setting will the intervention be implemented? Is the chosen setting relevant for future policymaking?
  - Power: What is an acceptable level of power for a major RCT?
  - Sample size: What is the sample size needed based on the study parameters above?
  - Threats: Assess possible threats to internal validity, such as contamination, co-treatment, or non-adherence. Assess threats to external validity based on the population under study.
- **Estimating the cost of the trial**
  - Intervention delivery: How and where will the intervention be implemented? What are the associated costs?
  - Baseline and follow-up measurements: What measurements will be needed among your study population and how frequently?
  - Staffing: What is the level of staffing needed to implement the intervention with fidelity?
  - Data analysis: What are the costs associated with data analysis?
  - Planning: What costs will accrue during the planning phase?
  - Closeout: What costs are there during study closeout?
  - Costs and benefits: Assess whether the costs are reasonable relative to the expected benefits and with respect to the potential threats to achieving valid results. Assess whether potential funders might be willing to fund the trial given the costs and benefits and competing funding priorities.
- **Ethical considerations**[47]
  - Respect for persons: How will you obtain consent? How will you provide information about the study to participants? Is participation truly voluntary?
  - Beneficence: What are the risks and benefits of the study to participants?
  - Justice: Will participants who bear the burden stand to benefit from the intervention? Is it appropriate to include certain vulnerable or institutionalized populations in the study?
  - Risks and benefits: Assess whether a trial could be ethically conducted, among whom, and how the risks and benefits of study participation will be communicated.