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Despite medical, dietary, and lifestyle recommendations and drug advancements, hypertension persists as among the most prevalent noncommunicable diseases in the US population, and control remains elusive. Uncontrolled hypertension may increase the risk of serious illness from various other health challenges, including cardiovascular and renal responses. Adoption of a healthy diet is a consistent core element of lifestyle modifications that are recommended for mitigation of hypertension. The dietary sodium-to-potassium ratio is recognized as having promising potential in the regulation of blood pressure. In fact, the understanding of the relation between this ratio and blood pressure was documented as a key evidence gap in the 2019 National Academies of Sciences, Engineering, and Medicine report that revised recommended intake levels for both sodium and potassium. Although notable animal and human evidence supports this point, fundamental to developing a specific dietary recommendation for a sodium-to-potassium ratio is a well-designed human intervention trial. The successful translatability of such a trial will require careful consideration of study elements, including the study population, duration, blood pressure measurement, and dietary intervention, among other factors. This paper addresses these decision points and serves as supporting documentation for a research group or organization with the interest and means to address this important data gap, which will undoubtedly be foundational for advancing dietary guidance and would inform the next iteration of Dietary Reference Intakes for sodium and potassium. *Adv Nutr* 2021;00:1–9.

: Altering the sodium-to-potassium ratio (Na:K) of the diet has potential for blood pressure management. This paper addresses a key evidence gap identified in the 2019 National Academies of Sciences, Engineering, and Medicine (NASEM) Sodium and Potassium Dietary Reference Intakes report by providing considerations and recommendations for the design of a human intervention trial critical for understanding the relation between dietary Na:K and blood pressure.

: hypertension, sodium, potassium, sodium-to-potassium ratio, Na:K ratio, Dietary Reference Intakes

Background and Hypothesis

On 7 October 2020, Surgeon General VADM Jerome M Adams issued a Call to Action urging Americans to recognize and address hypertension control as a national public health priority, noting that uncontrolled hypertension increases the risk of numerous chronic diseases and may increase risk of serious illness from coronavirus disease 2019 (COVID-

potassium intake of Americans consistently is below the level that is recommended (3).

The mechanisms of potassium and sodium interaction to impact blood pressure and the amount of dietary potassium that would be required to improve blood pressure given a designated level of dietary sodium intake are not well understood. Characterization of the relation between the dietary sodium-to-potassium ratio (Na:K) and health was identi ed as a key research gap in the 2019 Sodium and Potassium Dietary Reference Intakes (DRI) report, which set revised recommended intake levels for both nutrients for the United States and Canada (2).

Intakes of sodium and potassium at recommended DRI levels, as compared with lower intake of potassium at the same sodium intake level, moderate blood pressure in prehypertensive individuals (4). Gijsbers et al. (5) showed that supplemental potassium combined with a relatively low-sodium diet bene ted blood pressure among individuals with prehypertension. In comparison, the investigators in the Prospective Urban Rural Epidemiology (PURE) Study concluded that a signi cant relation between estimated intakes of sodium and potassium and blood pressure was nonlinear and most often observed in study participants consuming a high-sodium diet, having hypertension, and of increased age (6). The latter study should, however, be interpreted with caution, because estimations of individual cation intakes were based on spot urine samples and may, as such, have introduced signi cant bias (7), whereas Gijsbers et al. validated intake using 24-h urine collection. Compared with regular salt (i.e., 100% d4

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Blood pressure measurement

Criteria should be established a priori for de ning valid assessments for blood pressure measurements because data often are missing for part of the measurement period. Lack of standardization and quality control in research and clinical blood pressure measurement has contributed to the current controversy about the relation between dietary salt and blood pressure/hypertension.

Advisories o er recommendations on various aspects of blood pressure measurement. The TRUE (inTernational consoRtium for qUality research) Consortium recommended standards for assessing blood pressure in-o ce and out-of-o ce in human research with blood pressure outcomes (18). TRUE recommendations apply to human clinical and epidemiological research on blood pressure or hypertension where blood pressure is thought to be a major mediator of the research outcome. The American Heart Association's Scienti c Statement on Blood Pressure Measurement includes recommendations on frequency and methodology of blood pressure measurement and on standards for monitoring (19). A systematic evidence review for the US Preventive Services Task Force suggests that ambulatory blood pressure monitoring better predicts long-term cardiovascular outcomes and should be the standard for evaluating noninvasive blood pressure measurements (20). Regardless of the method used, initial and ongoing training of technicians and health care providers on the use of validated and calibrated devices is critical to obtaining accurate blood pressure measurements.

Additional controllable factors that contribute to blood pressure variations include physiology, demographics, ethnicity, medications, underlying medical conditions, sta ng, and "white coat" anxiety (21).

Determining the Na:K ratio in intervention diets

Several speci c factors come into consideration when designing a trial evaluating the dietary Na:K ratio. The rst is the methodology for achieving the desired ratio(s), whether by reducing sodium, increasing potassium, or both, and whether by increasing potassium solely through speci c food choices or through partial ingredient replacement for sodium chloride.

Sodium intake and blood pressure have been shown to have a linear relation in some studies but a nonlinear relation in others. A 2014 meta-analysis of 103 sodium-reduction trials demonstrated that greater sodium reduction resulted in greater lowering of blood pressure, but that age, hypertension status, and race impact the relation (22).

In contrast, the relations between dietary potassium and blood pressure have been shown to be nonlinear (23). Most studies have utilized a crossover design and studied people with untreated hypertension (23). Studies typically provided potassium as potassium chloride, with dosages of 30–120 mmol/d (1200–4700 mg/d) (23). The greatest reduction in blood pressure was observed at a potassium intake of 30–40 mmol/d (1200–1500 mg/d) and/or 90–120 mmol/d urinary potassium excretion (23). The dose–response relation between potassium supplementation and blood pressure appeared to be stronger in study populations with lower urinary potassium excretion (<75 mmol/d) at baseline (23). Similarly, the blood pressure e ects of potassium supplementation were greatest in study populations with high sodium excretion at baseline (23). Stratifying based on hypertension status, potassium supplementation was associated with greater blood pressure reduction in those with untreated hypertension (23); few studies were conducted in normotensive participants. Data suggest that the impact on blood pressure can be optimized across a range of potassium

In a later study, Svetkey et al. (

require adjustment to account for lapses in adherence and to estimate a treatment e ect if subjects were perfectly adherent.

A crossover design o ers the presumed advantage of requiring fewer study subjects. It is statistically e cient because participants serve as their own control, reducing random variability (38). Shortfalls include the potential for order and/or carryover e ects, the need for a washout period between treatments, challenges in switching diets, possible unblinding from di erent tastes (i.e., saltiness) between treatments, and di erential dropout between arms. This design is appropriate only if little dropout is expected.

A parallel-design study is simpler to carry out because it does not require a washout period, eliminates confusion around switching diets, and may be faster depending on the length of the recruitment and study periods. It requires a larger overall sample size, but each participant completes just 1 treatment period rather than 2 plus a washout period and therefore may be less prone to drop out before study completion.

In a parallel-group design, regression analysis o ers more statistical power. A study that examines the expected di erence in follow-up value between 2 individuals who start with the same value and are treated with A versus B favors regression analysis of nal measurements, with control for baseline values (39). Regardless of design, any study should

Any public health education component based on study

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