Potential effect of salt reduction in processed foods on health

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ABSTRACT
Background: Excessive salt intake has been associated with hypertension and increased cardiovascular disease morbidity and mortality. Reducing salt intake is considered an important public health strategy in the Netherlands.

Objective: The objective was to evaluate the health benefits of salt-reduction strategies related to processed foods for the Dutch population.

Design: Three salt-reduction scenarios were developed: 1) substitution of high-salt foods with low-salt foods, 2) a reduction in the sodium content of processed foods, and 3) adherence to the recommended maximum salt intake of 6 g/d. Health outcomes were obtained in 2 steps: after salt intake was modeled into blood pressure levels, the Chronic Disease Model was used to translate modeled blood pressures into incidences of cardiovascular diseases, disability-adjusted life years (DALYs), and life expectancies. Health outcomes of the scenarios were compared with health outcomes obtained with current salt intake.

Results: In total, 4.8% of acute myocardial infarction cases, 1.7% of congestive heart failure cases, and 5.8% of stroke cases might be prevented if salt intake meets the recommended maximum intake. The burden of disease might be reduced by 56,400 DALYs, and life expectancy might increase by 0.15 y for a 40-y-old individual. Substitution of foods with comparable low-salt alternatives would lead to slightly higher salt intake reductions and thus to more health gain. The estimates for sodium reduction in processed foods would be slightly lower.

Conclusion: Substantial health benefits might be achieved when added salt is removed from processed foods and when consumers choose more low-salt food alternatives. Am J Clin Nutr 2014;99:446–53.

INTRODUCTION
Cardiovascular disease (CVD) is the second main cause of mortality in the Netherlands (1). In 2007, ~40,000 people died of CVD (1). Although the absolute CVD mortality figure will decrease in the future, the number of years people will live with CVD is expected to increase. This is attributed to the decline in mortality rate from CVD since the 1970s (2).

Hypertension is a main risk factor for CVD (3). Higher sodium intakes have been shown to be associated with higher blood pressure levels (4, 5) and thus have been linked to CVD. Therefore, it is assumed that salt reduction will lead to lower blood pressure levels and consequently to lower incidences of CVD.

In the Netherlands, >85% of the population exceeds the recommended maximum intake of 6 g/d (6). About 80% of the Dutch salt intake results from processed foods (6). Therefore, the Health Council of the Netherlands emphasized the need to reduce the amount of salt used in commercially manufactured foods as an important measure to reduce the salt intake (7).

Recently, several studies have assessed the potential effect of salt reduction on population health (8–12). For example, Bibbins-Domingo et al (8) projected that an average of 3 g salt reduction per individual would lead to a substantial reduction in cardiovascular events (60,000–120,000 cases of coronary heart disease in the US population) and direct medical costs ($10 billion to $24 billion) over a 10-y period. Several studies assessed the health effects in case current salt intakes would be reduced to levels recommended by the WHO or national authorities, but only a few examined the potential health effects of more specified salt-reduction strategies. For example, Cobiac et al (13) compared the health effects of several salt-reduction strategies, including those that are related to the current voluntary salt reductions by food manufacturers and to governmental legislation aimed at more moderate salt levels in foods. Cobiac et al concluded that although voluntary salt-reduction goals by the food industry may improve public health, more regulatory actions from the government are needed to achieve relevant improvements in population health.

In the current study, the expected health effects of 2 specified salt-reduction strategies and of adherence to the recommended intake have been evaluated for the Dutch situation. One salt-reduction strategy relates to nutritional behavior and reflects the substitution of high salt products by comparable low-salt alternatives that are already commercially available. The other strategy relates to the effect of salt reduction in processed foods and represents a major reduction in sodium levels in processed foods.

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4 Abbreviations used: AMI, acute myocardial infarction; CHF, congestive heart failure; CVA, cerebrovascular accident; CVD, cardiovascular disease; DALY, disability-adjusted life year; DNFCs, Dutch National Food Consumption Survey; MORGEN, Monitoring project on Chronic Disease Risk Factors; RIVM-CDM, National Institute for Public Health and the Environment Chronic Disease Model; SBP, systolic blood pressure.

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SUBJECTS AND METHODS

The simulated health outcomes of 2 different salt-reduction scenarios and of the scenario reflecting the recommended maximum salt intake of 6 g/d for all individuals have been compared with the health outcomes obtained with the current salt intake.

Current salt intake

The current salt intake estimate was based on the food-consumption data from the Dutch National Food Consumption Survey 2007–2010 (DNFCS 2007–2010) (14). A representative sample of the population aged 6–69 y ($n = 3819$) was interviewed twice on nonconsecutive days to report their 24-h food intake on the previous day, including foods that were eaten out-of-home. Participants reported their discretionary salt use in additional questionnaires. Food-consumption data were combined with sodium contents of foods in the Dutch National Food Composition Table 2011 (15). This version of the food-composition table includes recent analyses on several foods (e.g., bread). The amount of discretionary salt was estimated by using a probabilistic model (16, 17). Application of this model resulted in usual total salt intake distributions stratified by age and sex (see Supplemental Tables 1–3, paragraph 1, under “Supplemental data” in the online issue). We assumed that the salt intake of individuals older than 69 y would be equal to the salt intake of individuals aged 60–69 y. The estimated total salt intake was compared with 24-h sodium excretions in the Netherlands (18), which indicated the validity of our 24-h recall method.

Salt-reduction strategies and resulting salt intake distributions

The first salt-reduction strategy concerned food choice behavior to adopt a healthier diet. In this scenario, foods with the lowest salt content substituted for foods with a higher salt content within the same food group. The sodium contents of processed foods were taken from the 2011 food-composition table and were classified into food (sub)categories. Within each food (sub)category, the food item with the lowest sodium content was used to replace all the other foods within the same food category (e.g., all canned vegetables by freshly boiled equivalent).

The second strategy concerned salt reduction in processed foods. We virtually reduced the content of sodium in processed foods, taking into account that in some foods major sodium reductions are possible and in others hardly any are. On average, we virtually reduced sodium contents in processed foods by 50%. This salt reduction processed foods scenario reflects major sodium reductions in processed foods. For the 2 salt-reduction strategies, data from the DNFCS 2007–2010 and the specially prepared strategy-specific food-composition tables were combined to calculate usual salt intakes (including estimated use of discretionary salt, as described before). In the recommended maximum intake scenario, each individual from the DNFCS 2007–2010 with a usual salt intake $>6$ g/d was set back to an intake of 6 g/d exactly (recommended maximum intake). We compared the reduction scenarios with the current salt intake scenario, in which salt intake distribution characterized by age and sex was the same as the current salt intake.

From salt intake distributions to systolic blood pressure distributions

Baseline age- and sex-specific measured systolic blood pressure distributions of the Dutch population were taken from the Monitoring project on Chronic Disease Risk Factors (MORGEN) study (19) and the Rotterdam Study (20). The MORGEN study is a large monitoring study in the Netherlands and consists of a general population sample of men and women ($n = 22,654$) aged 20–59 y from 3 Dutch towns (Amsterdam, Maastricht, and Doetinchem). Systolic blood pressure distributions for subjects older than 55 y were taken from the Rotterdam Study. This cohort consists of 7983 subjects aged $\geq 55$ y from a suburb of Rotterdam. The measured blood pressure distributions in the general population were adjusted to usual blood pressure values by using the variance of the measured values (see Supplemental Table 4, paragraph 2.1, under “Supplemental data” in the online issue).

The association between salt intake reduction and systolic blood pressure reduction was derived from a meta-analysis of He and MacGregor (4). This meta-analysis included intervention studies of $\approx 4$ wk, studies with a range of salt reductions, and studies with no concomitant interventions (e.g., no use of antihypertensive medication). He and MacGregor showed that the dose-response relation between salt intake and blood pressure is different between normotensive and hypertensive subjects, i.e., the reduction in systolic blood pressure per gram of salt depends on initial blood pressure levels. They estimated that a 6-g salt reduction leads to a 7.2–mm Hg reduction among hypertensive subjects and a 3.6–mm Hg reduction among normotensive subjects. On the basis of the dose-response relation of this meta-analysis (4) and the current Dutch salt intake and systolic blood pressure distribution, we derived the following dose-response relation between salt intake (SI) and systolic blood pressure (SBP):

$$SBP = c \ e^{b \ SI} - a$$ (I)

The regression coefficients $a$ (−105) and $b$ (0.03) were estimated by using data from the meta-analysis of He and MacGregor (4) (see Supplemental Tables 3 and 5, paragraph 2.2, under “Supplemental data” in the online issue). The variation in blood pressure was affected by more factors than just salt intake (e.g., overweight). Therefore, we assumed that $c$ was a random variable that is log-normal distributed, which depends on sex and age. We estimated the mean and variance of $c$ with the use of usual salt intake and blood pressure data from the DNFCS 2007–2010 and MORGEN study and Rotterdam Study, respectively. We assumed that individuals, who take antihypertensive medications had a response similar to that of individuals who did not take antihypertensive medications but were otherwise similar.

With the use of Equation I, the usual salt intake distributions of our scenarios were converted into usual SBP distributions for each scenario. These usual blood pressure distributions were input parameters of the National Institute for Public Health and the Environment Chronic Disease Model (RIVM-CDM) (see the next section).
From blood pressure distributions to health outcomes

RIVM-CDM

The effects of the change in blood pressure distributions on the incidence of diseases and mortality were calculated by RIVM-CDM version 5.1. A detailed overview of the model was published elsewhere (21) (also see Supplemental Tables 6–8, paragraph 2.3, under “Supplemental data” in the online issue). Briefly, the RIVM-CDM is a Markov-type multistate transition model. It simulates the life course of Dutch population cohorts in terms of changing risk factor classes and disease states. Time is modeled in discrete intervals of 1 y. In the current study, the health benefits of a closed cohort were simulated.

Model inputs

The input data consisted of initial distributions of the risk factors in classes and of diseases in disease states, transition rates between risk factor classes and disease states, RRs, and disability weights. All parameters were age and sex specific. Parameter values were derived from statistical data representing the Dutch population. The usual SBP distribution resulting from salt intake scenarios were divided into 4 classes ($<$120, 120–139, 140–159, and $\geq$160 mm Hg) and were the main model input. We simulated the age-related change in systolic blood pressure through 1-y transition probabilities that conserved the age-specific distribution of usual blood pressure over time (see Supplemental Table 9, paragraph 2.4, under “Supplemental data” in the online issue). RRs for the effect of usual blood pressure on acute myocardial infarction (AMI) and cerebrovascular accident (CVA) were derived from Lewington et al (3) and were defined for unit changes of blood pressure. RRs for congestive heart failure (CHF) were calculated by combining RR values presented in the literature (see Supplemental Table 10, paragraph 2.5, under “Supplemental data” in the online issue). Mortality rates attributable to AMI, CVA, and CHF were estimated by using aggregated cross-sectional data on the incidence and prevalence of current mortality from CVD (22). The risk of mortality from CVD was independent of systolic blood pressure or salt intake levels.

Model outputs

The incidence of CVD events (AMI, CHF, and CVA) and all-cause mortality rates were model output variables. To assess the long-term effect of the salt-reduction strategies, the fate of the adult population aged $\geq$20 y was simulated over a 20-y period. Output variables were the cumulative incidence of AMI, CHF, and CVA and the cumulative all-cause mortality over this 20-y period.

The burden of disease of a particular scenario was calculated as the difference in disability-adjusted life years (DALYs) lived between that particular scenario and the current salt intake (see supplemental material, paragraph 2.6, under “Supplemental data” in the online issue). The disability weights are from the Dutch Disease Weights Study (23). Cumulative DALYs lived were calculated over lifetime for a cohort of 40-y-old individuals. Finally, the effect of the salt-reduction strategies on life expectancy was evaluated for 40-y-old individuals by extending the simulation period until the last individual had died (24).

Uncertainty analysis

To test the sensitivity of the dose-response relation between salt intake and blood pressure, alternative dose-response relations parameters were estimated based on the lower and the upper bound of the dose-response relation reported in the study by He and MacGregor (4) for both normotensive and hypertensive subjects. The uncertainty interval for $\alpha$ was $-92$ to $-109$ and for $\beta$ 0.2–0.3 (see supplemental material, paragraph 2.7, under “Supplemental data” in the online issue).

RESULTS

Salt intake and blood pressure reductions

The median current salt intake of the Dutch population aged $\geq$20 y was 8.4 g/d and the age-standardized mean current systolic blood pressure was 128.2 mm Hg (Table 1). In the salt reduction processed foods scenario, the median salt intake would decrease by 28% and blood pressure by 1.2%. The substitution processed foods scenario would result in a salt reduction of 35% and in a blood pressure reduction of 1.5%, whereas the recommended maximum intake scenario (6 g/d) required a median salt intake reduction of 29% and would reduce the systolic blood pressure by 1.3% (Table 1 and Figure 1).

Reduction in CVD and mortality from these diseases

When the salt intake in the Netherlands remained the same throughout the coming 20 y (current salt intake scenario), 667,600 cases of AMI, 902,900 cases of CHF, and 896,500 cases of CVA were projected to occur (Table 2). If salt intake is reduced to the recommended maximum salt intake (6 g/d), 4.8% of cases of AMI, 1.7% of cases of CHF, and 5.8% of cases of CVA might be prevented. Similar percentages were found in the salt reduction in processed foods scenario, and slightly higher reductions would be found in the substitution scenario, as shown in Table 2. The reductions in disease incidences would not be stable throughout the 20-y period. The annual estimates of the differences in incidences of AMI, CHF, and CVA between the salt-reduction scenarios and the current salt intake scenario are shown in Figure 2. The difference in incidence of AMI, CHF, and CVA

<p>| TABLE 1 |
| Current salt intake and SBP in the Netherlands and in the salt-reduction scenarios $^1$ |</p>
<table>
<thead>
<tr>
<th>Salt-reduction scenario</th>
<th>Median salt intake</th>
<th>Age-standardized mean SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g/d</td>
<td>mm Hg</td>
</tr>
<tr>
<td>Salt-reduction processed foods</td>
<td>−2.3</td>
<td>−1.5</td>
</tr>
<tr>
<td>Substitution processed foods</td>
<td>−3.0</td>
<td>−1.9</td>
</tr>
<tr>
<td>Recommended maximum intake</td>
<td>−2.5</td>
<td>−1.6</td>
</tr>
</tbody>
</table>

$^1$ Current salt intake scenario: median salt intake: 8.4 g/d; age-standardized mean SBP: 128.2 mm Hg. SBP, systolic blood pressure.
might be more pronounced after the initial years of the implementation of the strategies, and in the hypothetical situation of 70 y of implementation, the incidence of all AMI, CVA, and CHF would be similar in the reference scenario.

All-cause mortality might be reduced by 0.7% when salt intake was reduced to the recommended maximum salt intake (Table 2). The same percentage would be found for the salt reduction in processed foods scenario, and a slightly higher reduction would be found for the substitution processed foods scenario.

The reduction in mortality was also not stable throughout the 20-y period. The annual estimates of the differences in all-cause mortality between the salt-reduction scenarios and the current salt intake scenario are shown in Figure 3. In the first 25 y of the implementation of the salt-reduction scenarios and the scenario representing the recommended maximum intake, the mortality would be reduced. However, because this was a fixed cohort, the total population eventually died and, after 25 y, all-cause mortality would increase until the total cohort has died.

**Health gain in DALYs and life expectancy**

A 40-y-old individual would increase the number of DALYs lived by 0.5% (56,400 DALYs) if he would equal his salt intake to the recommended maximum intake for the rest of his life (Table 3). The

<table>
<thead>
<tr>
<th>Salt-reduction scenario</th>
<th>AMI Cases averted</th>
<th>AMI %</th>
<th>CHF Cases averted</th>
<th>CHF %</th>
<th>CVA Cases averted</th>
<th>CVA %</th>
<th>Cumulative all-cause mortality</th>
<th>Cumulative all-cause mortality %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salt-reduction processed foods</td>
<td>29,200 (20,800-37,600)</td>
<td>4.4</td>
<td>16,600 (11,800-21,400)</td>
<td>1.8</td>
<td>53,400 (36,600-70,200)</td>
<td>6.0</td>
<td>25,150 (17,600-32,700)</td>
<td>0.7</td>
</tr>
<tr>
<td>Substitution processed foods</td>
<td>35,500 (25,400-45,600)</td>
<td>5.3</td>
<td>20,000 (14,300-25,700)</td>
<td>2.2</td>
<td>64,300 (44,100-84,400)</td>
<td>7.2</td>
<td>30,400 (21,300-39,500)</td>
<td>0.9</td>
</tr>
<tr>
<td>Recommended maximum intake</td>
<td>31,800 (22,500-41,100)</td>
<td>4.8</td>
<td>15,300 (10,800-19,900)</td>
<td>1.7</td>
<td>51,900 (34,900-68,900)</td>
<td>5.8</td>
<td>25,300 (17,500-33,200)</td>
<td>0.7</td>
</tr>
</tbody>
</table>

1 Current salt intake scenario: AMI, n = 667,600 total cases; CHF, n = 902,900 total cases; CVA, n = 896,500 total cases; cumulative all-cause mortality: n = 3,423,000 cases. Numbers in parentheses represent the lower and upper bounds of the sensitivity analyses. AMI, acute myocardial infarction; CHF, congestive heart failure; CVA, cerebrovascular accident.
reduced incidence in CVD and the decrease in mortality may prolong life expectancy. Life expectancy for a 40-y-old individual would increase by 0.4% (0.15 y) in the recommended maximum intake scenario. Similar health gains were found for the salt reduction in processed foods scenario and for the substitution of processed foods scenario (Table 3).

**DISCUSSION**

This study showed that if salt intake in the Dutch population would be reduced about 30%, systolic blood pressure would decrease by ~1.6 mm Hg and, consequently, substantially less CVD and mortality would occur. If all people would keep to the maximum of 6 g/d, there would be a 4.8% reduction in new cases of AMI. For CHF and CVA these reductions would be 1.7% and 5.8%, respectively, and mortality rates would decrease by 0.7%.

An important strength of our study was that we relied on a recent and extensive food-consumption survey, which included individual food-consumption patterns and foods eaten out-of-home and on a sodium-updated food-composition table, while preparing the salt-reduction scenarios. In the scenarios, the change in salt intake varied among individuals, i.e., individuals with a high salt intake could reduce more than individuals with a low salt intake.

The results of our simulation study were limited by any uncertainty related to the data entered into the model. We did not have national representative blood pressure levels available for individuals older than 69 y and had to estimate the salt intake in older adults. We used blood pressure categories instead of continuous blood pressure levels. In addition, future trends in determinants or treatment of blood pressure or CVD may affect the outcomes of our model, but we did not take these (largely unknown) changes into account.

It has been suggested that there is no compelling evidence from randomized controlled trials that salt restriction will result in lower CVD events (25), but reanalysis of these data showed a significant risk reduction (26). An adverse effect of current
salt intake contents on CVD through blood pressure was recently confirmed by the US Institute of Medicine after combining all available evidence from clinical outcome studies (27). In our 2-step modeling approach, we therefore combined risk estimates from studies of salt intake to blood pressure and blood pressure to CVD. The dose-response association between salt intake and blood pressure was based on a meta-analysis of randomized controlled trials lasting >4 wk (4). We considered reductions obtained with such randomized controlled trials representative for sustained blood pressure reductions. Changes in age-related blood pressure due to successful salt reduction, however, were unknown and are therefore assumed unchanged. This may have caused on overestimation of the potential health gain in our study. We simulated a stronger effect of salt reduction in hypertensive than in normotensive individuals, although stronger estimates may also be valid for other subgroups (eg, obese individuals or individuals taking antihypertensive medications) (28–30). The partial sensitivity analysis showed that the variation in health gain depending on the dose-response association between salt intake and blood pressure only slightly affected our findings.

The risk estimates from blood pressure to CVD from a meta-analysis of long-term observational studies including more than one million adults (3) were considered representative of the general population as opposed to estimates obtained from a meta-analysis of randomized controlled trials (31). Apart from effects on CVD, salt reduction may lower the risk of other diseases, such as renal and gastric disease (32, 33). Our model was not designed for these diseases; therefore, the overall potential effect of salt reduction may be underestimated.

Salt reduction to the recommended maximum intake of 6 g/d is challenging. This study modeled 2 maximal potential scenarios related to reduce salt intake through either behavioral change (substitution processed foods scenario) or food reformulation (salt reduced processed foods scenario). Both approaches yielded roughly similar estimates and are close to the recommended maximum intake. It should be stressed that both scenarios may overestimate the actual salt intake reduction. Presumably not every individual can be persuaded to choose a diet with low-salt alternatives. Likewise, it would require major efforts by food industry to reduce the sodium content in processed foods by 50%. In certain foods sodium can easily be reduced, whereas in other foods sodium reduction will be more challenging. Thus, the health benefits of more realistic versions of our strategies will probably be lower than the projected effects in our study.

The current study showed that achieving the recommended maximum salt intake would reduce the incidence of CVD by roughly 4% and the all-cause mortality rate by 0.7%, and it would increase the life expectancy by 0.15 y. The reduction in all-cause mortality is smaller than simulated by others (8, 12). Possible explanations for why our estimates were somewhat more conservative for mortality than others are discussed below. First, CVD mortality has strongly declined over the past 30 y in the Netherlands (1), and our model made use of recent CVD mortality rates. Second, our model included competing risk and substitute morbidity and mortality: when risks of morbidity of CVD are reduced, more individuals will suffer and die of other diseases. Third, our model assumed no association between salt intake, blood pressure, and mortality: when risks of morbidity of CVD are reduced, more individuals will suffer and die of other diseases. Thus, a reduced salt intake results in fewer people developing CVD, but those who have CVD have the same probability of dying.

Within the past few years, various studies have examined the effects of salt reduction on health (8–13). The main conclusions from these studies are that salt reduction leads to a substantial reduction in incidence of CVD and mortality. The reductions in CVD morbidity in our study are in line with the estimations of the reported studies. However, differences between studies concerning


**TABLE 3**

Projected cumulative DALYs and projected LEs for a cohort of 40-y-old Dutch individuals over a lifetime.  

<table>
<thead>
<tr>
<th>Gain compared with current salt intake</th>
<th>Cumulative DALYs $^2$</th>
<th>LE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salt-reduction processed foods scenario</td>
<td>$-56,000 (-39,700$ to $-72,300)$</td>
<td>0.5</td>
</tr>
<tr>
<td>Substitution processed foods scenario</td>
<td>$-67,900 (-48,300$ to $-87,600)$</td>
<td>0.6</td>
</tr>
<tr>
<td>Recommended maximum intake scenario</td>
<td>$-56,400 (-39,500$ to $-73,200)$</td>
<td>0.5</td>
</tr>
</tbody>
</table>

$^1$Current salt intake scenario: DALYs = 10,611,000, LE = 41.23 y. Numbers in parentheses represent the lower and upper bounds of the sensitivity analyses. DALY, disability-adjusted life year; LE, life expectancy.

$^2$The DALYs were calculated as the difference in DALY between scenarios and the current salt intake scenario. Note that DALYs measure health loss. A negative DALY change reflects a health gain.
the type of model used, salt–blood pressure response, age from which modeling starts and the duration of the modeling period, initial levels of usual salt intake, and blood pressures all affect the outcomes of the simulation and make direct comparisons difficult. Some of these studies evaluated the effects of a 3-g salt reduction on health, leaving aside the question of how to achieve the intended salt reduction (8, 10, 11). Others evaluated the effects of various population strategies to achieve salt reduction (12, 13). It would be worthwhile to consider the wider macroeconomic consequences of salt intake reduction and the costs of our projected scenarios (34). However, these costs should be mapped out and was beyond the scope of the current study.

Various dietary and lifestyle factors affect the prevalence of CVD. Therefore, focus and policies on other dietary and lifestyle factors such as overweight, physical activity, and smoking would also reduce the incidence of CVD and subsequently the burden of disease. In a recent Dutch study, which also used the RIVM-CDM, changes in the incidence of major diseases was simulated when the intake of various nutrients and food groups (fruit and vegetables, SFAs, trans fatty acids, and fish) met dietary recommendations (35). Health gains because of SFA intake, according to the recommendations, were similar to the results of salt reduction. However, the greatest health effects can be obtained by increasing fruit and vegetable and fish consumption to the recommended level (35).

To conclude, our study showed that substantial reductions in salt intake are needed in the Dutch population to reach the recommended maximum intake. Considerable and relevant health gains might be achieved through food reformulation or behavioral change.

The authors’ responsibilities were as follows—MAHH, JMAvR, RTH, JH, and HCB: were involved in the design of the study; MAHH, RTH, JH, and HCB: conducted the research and performed the analyses; JMAvR: had primary responsibility for the final content; and JMAvR, HCB, and JMG: supervised the work and were involved in the data interpretation. All authors contributed to the writing of the manuscript and supplemental material and approved the final version of the manuscript. None of the authors declared a conflict of interest.

REFERENCES


