Estimating the health and economic effects of the proposed US FDA voluntary sodium reformulation: microsimulation cost-effectiveness analysis

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# Abstract

## Background

Sodium consumption is a modifiable risk factor for higher blood pressure and cardiovascular disease (CVD). The United States (US) Food & Drug Administration (FDA) has proposed voluntary sodium reduction goals targeting processed and commercially prepared foods. We aimed to quantify the potential health and economic impact of this policy.

## Methods/Findings

We used a microsimulation approach of a close-to-reality synthetic population (US IMPACT Food Policy Model) to estimate CVD deaths and cases prevented or postponed, Quality Adjusted Life Years (QALYs), and cost-effectiveness from 2017-2036 of three scenarios:

1. Optimal, 100% compliance of 10-year reformulation targets
2. Modest, 50% compliance of 10-year reformulation targets
3. Pessimistic, 100% compliance of 2-year reformulation targets with no further progress

We used NHANES and high quality meta-analyses to inform model inputs. Costs included government costs to administer and monitor the policy, industry reformulation costs, and CVD-related healthcare, productivity and informal care costs.

Between 2017 and 2036, the optimal reformulation scenario achieving the FDA sodium reduction targets could prevent approximately 450,000 CVD cases (95% UI: 240,000-740,000), gain ~2.1 million discounted QALYs (1.7m-2.4m), and produce discounted cost savings (health savings minus policy costs) of approximately $41billion ($14bn-$81bn). In the modest and pessimistic scenarios health gains would be 1.1m and 0.7m QALYS, and savings of $19bn and $12bn respectively. All the scenarios were estimated with more than 80% probability to be cost-effective (incremental $/QALY<$50,000) by 2021 and to become cost saving by 2031. Limitations include only evaluating diseases mediated through BP, while decreasing sodium consumption could have beneficial effects upon other health burdens such as gastric cancer. Further, the effect estimates in the model use interventional and prospective observational studies. They are therefore subject to biases and confounding that may have influenced also our model estimates.

## Conclusions

Implementing and achieving the FDA sodium reformulation targets could generate substantial health gains and net cost savings.

# Author Summary

## Why was this study done?

* Sodium consumption is a leading modifiable risk factor for high blood pressure and cardiovascular disease in the US and worldwide. The US Food and Drug Administration (FDA) has proposed voluntary sodium reduction targets for processed foods.
* The potential health and economic effects of successful implementation of the FDA’s voluntary reformulation proposal have not been quantified and would be of great interest to policy makers.

## What did the researchers do and find?

* We modelled and compared the potential health and economic effects of three scenarios of differing implementation of the FDA’s proposed voluntary sodium reformulation policy over a 20-year period.
* We found that the optimal scenario, 100% compliance of the 10-year FDA targets, could prevent approximately 450,000 CVD cases, gain 2.1 million Quality Adjusted Life Years (QALYs) and produce discounted cost savings of approximately $41 billion. In contrast, the modest scenario, 50% compliance of the 10-year FDA targets, and the pessimistic scenario, 100% compliance of the 2-year targets but no further progress, could yield health and economic gains half and a quarter as large respectively.
* All three scenarios had greater than 80% probably of being cost-effective by 2021, (incremental cost effectiveness ratio <$50,000 per QALY) and cost saving by 2031.

## What do these findings mean?

* Implementing the FDA’s sodium reformation targets could generate substantial health gains and cost savings.
* Efforts should focus on ensuring high compliance, if FDA targets are implemented, to yield maximum health and economic gains for the US population.

# Introduction

Sodium consumption is a leading modifiable risk factor for higher blood pressure and cardiovascular disease (CVD)[1]. The excess risk associated with sodium consumption appears to be mainly mediated through the deleterious effect of excess sodium consumption on blood pressure[2]. CVD remains the leading cause of mortality and morbidity in the United States (US), generating approximately 800,000 deaths and 6 million hospital admissions annually[3]. These CVD burdens cost $318bn annually in healthcare costs and an additional $237bn in in lost productivity, with further costs of informal care[4]. Average sodium intake in the US is approximately 3,400 milligrams per person per day (mg/day), or 8.6 grams of salt, approximately 50% above recommended consumption levels of 2,300 mg/day[5]. About 75% of sodium intake comes from processed and commercially produced foods, making industry reformulation a major priority for reducing population intake[6,7].

Consistent with World Health Organization (WHO) recommendations and other voluntary reformulation policies that have effectively lowered sodium in Finland, Turkey and the United Kingdom (UK)[8], the US Food and Drug Administration (FDA) in 2016 proposed short-term (2 year) and long-term (10 year) voluntary, category-specific sodium reformulation targets for commercially processed, packaged, and prepared foods across 155 food categories.7 This proposal was designed to support the 2015-2020 US Dietary Guidelines by encouraging food reformulation and new product development.

However, the potential health and economic effects of these proposed targets have not been quantified. In addition, in both the 2017 congressional budget and the current proposed 2018 House Agriculture appropriations bill, Congress has instructed the FDA not “to develop, issue, promote or advance final guidance applicable to food manufacturers for long term population-wide sodium reduction”, at least in part related to uncertainty on potential health effects. Recent studies have estimated the potential health gains of general sodium reduction in the US population, but without mapping the effects of the specific FDA proposed policies for industry or taking a wider, societal perspective[9]. In this study, we quantified the potential reductions in CVD and economic impact of different levels of compliance with the 2016 proposal over a 20-year period. This investigation was performed as part of the Food-PRICE (Policy Review and Intervention Cost-Effectiveness) Project.

# Methods

We used and extended the previously validated US IMPACT Food Policy model[10,11] to assess the potential health and economic effects of the proposed FDA sodium voluntary reformulation policy over a 20-year period (2017­ to 2036). We simulated three scenarios;

1) Optimal implementation of the proposed FDA policy, assuming all processed foods will be reformulated to the FDA proposed 2- and 10-year sodium targets;

2) Modest scenario, assuming 50% compliance with the proposed upper bound of the 2- and 10-year targets and 50% compliance with the main 2- and 10-year targets;

3) Pessimistic scenario, assuming all processed foods will be reformulated to the 2-year target but with no further reformulation.

We compared these three scenarios with a counterfactual ‘no intervention’ scenario. For this, we assumed that the recent observed slow declining trends in sodium consumption[12] will continue in the future.

In addition, we modelled a very low compliance scenario (7.5% of applicable foods) of the 10-year reformulation targets and present these results in **S1 Appendix** (Extra Scenario, p28).

## The US IMPACT Food Policy model

Our extended US IMPACT Food Policy model is a stochastic dynamic microsimulation model that simulates the life course of synthetic individuals in a ‘close-to-reality’ synthetic population under different policy scenarios. Compared to previous versions of the model, it allows for more detailed and flexible simulation of food policies in a competing risk framework, taking into account population heterogeneity and lag times between exposures and outcomes.

Specifically, the model simulates first the life courses of synthetic individuals aged 30 to 84 under the ‘no intervention’ scenario and records their sodium consumption, systolic blood pressure (SBP), the first episode of coronary heart disease (CHD) and/or stroke, quality adjusted life years (QALYs), costs, and death from these or any other cause. Then it calculates the life courses of the same synthetic individuals under each of the three modelled sodium reformulation scenarios (optimistic, modest, and pessimistic) and records the differences in the aforementioned outcomes (**Fig 1**). Model data sources are outlined in **Table 1**. We further describe the model inputs, structure, key assumptions, and outputs below. Detailed description of the model, input sources and key assumptions are detailed in **S1 Appendix** (throughout the text and Table A and Table D).

**Fig 1.** Simplified model structure. CHD, coronary heart disease; QALYs, quality adjusted life years.

**Table 1** The US Sodium Policy model data sources.

| Parameter | Outcome | Details | Comments | Source |
| --- | --- | --- | --- | --- |
| Population size estimates[13] | Population | July 1 US resident population from the Vintage 2014 postcensal series, the revised 2000-2009 intercensal series, and the 1990-1999 intercensal series | Stratified by year, age, sex, bridged-race, and Hispanic origin | United States Department of Health and Human Services (US DHHS), Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). Bridged-race population estimates 1990–2014, United States July 1st resident population by age, sex, bridged-race, and Hispanic origin, on CDC WONDER on-line database [Internet]. 2016 [cited 2017 Feb 11];Available from: <https://wonder.cdc.gov/Bridged-Race-v2014.HTML> |
| Population projections[14] | Population | 2014–2060 US population projections produced by the Census Bureau in 2014 | Stratified by year, age, sex, race, and ethnicity | U.S. Census Bureau. National population projections: United States by age, gender, ethnicity and race for years 2014–2060, released by the U.S. Census Bureau on December 10, 2014, on CDC WONDER on-line database [Internet]. 2015 [cited 2017 Feb 11];Available from: <https://wonder.cdc.gov/population-projections-2014-2060.html> |
| Mortality[15] | Deaths from CHD, stroke, and any other non-modelled causes | Underlying cause of death 1999–2015 | Stratified by year, age, sex, race, ethnicity, and cause of death | United States Department of Health and Human Services (US DHHS), Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). Underlying cause of death 1999–2015 on CDC WONDER online database. Data are compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program [Internet]. 2016 [cited 2017 Apr 18];Available from: <https://wonder.cdc.gov/ucd-icd10.html> |
| Exposure to sodium[16] | Exposure of individuals | National Health and Nutrition Examination Survey (NHANES) | Anonymized, individual-level data sets. Years 2009–2014. | Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 1999–2014 [Internet]. [cited 2016 Nov 15];Available from: <https://wwwn.cdc.gov/nchs/nhanes/ContinuousNhanes/> |
| Exposure to systolic blood pressure [16] | Exposure of individuals | National Health and Nutrition Examination Survey (NHANES) | Anonymized, individual-level data sets. Years 1999–2014. | Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey data. Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 1999–2014 [Internet]. [cited 2016 Nov 15];Available from: <https://wwwn.cdc.gov/nchs/nhanes/ContinuousNhanes/> |
| Effect of sodium consumption on systolic blood pressure[2] | Systolic blood pressure change | Meta-analysis/meta- regression of 103 trials | Only trials with duration > 7 days were analyzed. | Mozaffarian D, Fahimi S, Singh GM, *et al*. Global sodium consumption and death from cardiovascular causes. New England Journal of Medicine 2014;371(7):624–34. (**S1 Appendix**, Text S1) |
| Setting reference level of sodium consumption[2] | Ideal sodium consumption below which no risk was considered | Evidence from ecologic studies randomized trials and meta-analyses of prospective cohort studies | Intake levels associated with the lowest risk ranged from 614 to 2391 mg/day. In large, well-controlled, randomized feeding trials, the lowest tested intake for which blood pressure reductions were clearly documented was 1500 mg/day. | Mozaffarian D, Fahimi S, Singh GM, *et al*. Global sodium consumption and death from cardiovascular causes. New England Journal of Medicine 2014;371(7):624–34. (**S1 Appendix**, Text S4 and Table C) |
| Relative risk for systolic blood pressure[1,17] | CHD and stroke (ICD10: I20–I25 and I60–I69) | Pooled analysis of two individual level meta-analysis | Stratified by age and sex. Adjusted for regression dilution and total blood cholesterol and, where available, lipid fractions (HDL and non-HDL cholesterol), diabetes, weight, alcohol consumption, and smoking at baseline. | Micha R, Peñalvo JL, Cudhea F, Imamura F, Rehm CD, Mozaffarian D. Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. JAMA 2017;317(9):912–24. (**S1 Appendix**, Table E) |
|  | Any other mortality (excluding CHD and stroke) | Individual level meta-analysis of 48 prospective cohort studies | Adjusted for age, sex, race or ethnicity, deprivation, smoking, diabetes, inactivity, alcohol, obesity | Stringhini S, Carmeli C, Jokela M, *et al*. Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1·7 million men and women. The Lancet 2017;389(10075):1229–37. (**Fig 2**) |
| Setting reference level of systolic blood pressure[18] | Ideal systolic blood pressure below which no risk was considered | Evidence from evidence from randomized trials of antihypertensive drugs and the Intersalt study  | There may be health benefits by lowering systolic blood pressure down to 110mmHg | Singh GM, Danaei G, Farzadfar F, *et al*. The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. PLOS ONE 2013;8(7):e65174. |
| Health state utility values[19] | For CHD, stroke, hypertension, and their combinations | Uses EQ-5D-3L data from the Medical Expenditure Panel Survey (MEPS) 2000-2002 | We used the published regression coefficients to estimate utility values by age, sex, race, ethnicity, income, education, and the number of chronic conditions | Sullivan PW, Ghushchyan V. Preference-Based EQ-5D Index Scores for Chronic Conditions in the United States. Medical Decision Making 2006;26(4):410–20. (**Tables 2 and 3**) |
| Disease costs[20-22] | Medical, mortality, and morbidity costs for CHD, stroke, and hypertension | Based on the Medical Expenditure Panel Survey (MEPS) | Stratified by age, sex, and race, adjusted for comorbdities | Khavjou O, Phelps D, Leib A. Projections of cardiovascular disease prevalence and costs: 2015–2035. Technical Report [Internet]. RTI International; 2016 [cited 2017 Jul 10]. Available from[https://www.heart.org/idc/groups/heart-public/@wcm/@adv/documents/downloadable/ucm\_491513.pdf](https://www.heart.org/idc/groups/heart-public/%40wcm/%40adv/documents/downloadable/ucm_491513.pdf) |
|  | Informal care costs for CHD |  | Costs were extrapolated for US settings  | Leal J, Luengo-Fernández R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. Eur Heart J 2006;27(13):1610–9. (**S1 Appendix**, Table E) |
|  | Informal care costs for stroke | Difference-in-differences technique to propensity score-matched populations |  | Joo H, Dunet DO, Fang J, Wang G. Cost of informal caregiving associated with stroke among the elderly in the United States. Neurology 2014;83(20):1831–7. (**Table 3**) |
| Government costs to administer the policy[23] |  | Administration costs for new restaurant menu and vending machine labeling regulation, including cost for outreach, education, review of regulatory issues, developing training for inspectors, and related functions | We assumed sodium reformulation to have same administrative costs | Food and Drug Administration (FDA), Department of Health and Human Services (DHHS). Food and Drug Administration justification of estimates for appropriations committees. Fiscal year 2012 [Internet]. Food and Drug Administration (FDA); 2012 [cited 2017 Jul 10]. Available from: [https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/­Reports/BudgetReports/UCM243370.pdf](https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM243370.pdf) |
| Government costs to monitor and evaluate the policy[24] |  | UK Food Standards Agency impact assessment of UK salt reduction strategy | Costs converted to equivalent US dollars | Collins M, Mason H, O’Flaherty M, Guzman-Castillo M, Critchley J, Capewell S. An economic evaluation of salt reduction policies to reduce coronary heart disease in England: a policy modeling study. Value Health 2014;17(5):517–24. |
| Industry costs to reformulate products[25] |  | Spreadsheet model | The model accounted for variations in product formula complexity, company size, reformulation type, compliance period and other factors | Mary K. Muth, Samantha Bradley, Jenna Brophy, *et al*. Reformulation Cost Model. Contract No. HHSF-223-2011-10005B, Task Order 20. 2015 |

All data sources are available in Table S4.

Fig 2. Cost-effectiveness plane by the end of simulation (year 2036). Each colored dot is the result of a stochastic Monte Carlo iteration. The black dots are the median combinations of cumulative discounted net costs (2017 US Dollars) and discounted net QALYs for each simulated scenario, and the ellipses depict the 95% UI. Negative costs represent savings.

**Table 2**. Health related model estimates over the 20-year simulation period from 2017 to 2036, for US adults age 30 to 84 years. Values are the median estimate (95% UI). Results are rounded to first decimal for SBP, and second significant digit for other outcomes. CHD, coronary heart disease; CVD, cardiovascular disease; QALYs, quality adjusted life years; SBP, systolic blood pressure; UI, uncertainty intervals.

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|  | Optimal policy scenario | Modest policy scenario | Pessimistic policy scenario |
| Median sodium consumption in 2036 (mg/d) | 2,224(2,214 to 2,233) | 2,524 (2,500 to 2,550) | 2,789 (2,779 to 2,800) |
| Median SBP in 2036 (mmHg) | 114.0 (113.8 to 114.1) | 114.5 (114.4 to 114.7) | 115.0 (114.9 to 115.2) |
| CHD cases prevented or postponed | 260,000(110,000 to 490,000) | 120,000(48,000 to 240,000) | 63,000(17,000 to 130,000) |
| Stroke cases prevented or postponed | 180,000(78,000 to 340,000) | 93,000(33,000 to 180,000) | 52,000(11,000 to 110,000) |
| CHD deaths prevented or postponed | 22,000(-3,700\* to 54,000) | 11,000(-13,000\* to 37,000) | 7,400(-15,000\* to 32,000) |
| Stroke deaths prevented or postponed | 13,000(-3,700\* to 32,000) | 7,400(-9,000\* to 22,000) | 5,600(-9,000\* to 20,000) |
| Non-CVD deaths prevented or postponed | 48,000 (13,000 to 85,000) | 24,000 (-5,500\* to 54,000) | 7,400 (-19,000\* to 37,000) |
| All deaths prevented or postponed | 83,000(50,000 to 120,000) | 41,000(17,000 to 71,000) | 22,000(0 to 45,000) |
| Life years gained | 530,000 (290,000 to 830,000) | 260,000 (87,000 to 480,000) | 180,000 (26,000 to 370,000) |
| Discounted QALYs gained (million) | 2.1m (1.7m to 2.4m) | 1.1m(0.91m to 1.3m) | 0.69m (0.54m to 0.86m) |
| \* Negative number of deaths prevented or postponed for specific causes of death is a direct consequence of the mortality competing risk framework we implemented in the model. They represent synthetic individuals that the prevention of their death from a specific disease (i.e. CHD) due to the policy led to their death from another competing cause (i.e. non-CVD) in the same year. |

**Table 3**. QALYs gained and costs per 100,000  person-years. Negative costs represent savings. Readers can calculate similar estimates for other outputs by dividing with 4.7bn (the number of person-years over the 20-year simulated period)

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|   | **Optimal** | **Modest** | **Pessimistic** |
| **QALYs gained per 100,000 person-years (undiscounted)** | 61 | 33 | 19 |
|  | (50 to 71) | (27 to 40) | (14 to 24) |
| **Net cost per 100,000  person-years (undiscounted, medical perspective)** | -550,000 | -240,000 | -120,000 |
|  | (-1,200,000 to -28,000) | (-570,000 to 69,000) | (-350,000 to 73,000) |
| **Net cost per 100,000  person-years (undiscounted, societal perspective)** | -1,400,000 | -680,000 | -410,000 |
|   | (-2,700,000 to -640,000) | (-1,400,000 to -240,000) | (-880,000 to -89,000) |

## Model inputs and structure

**Demographics, sodium intake, and blood pressure:**The model synthesizes information regarding population structure by age, sex, and race/ethnicity[13] and the most recent two National Health and Nutrition Examination Survey (NHANES) cycles (2011–2014[12]) regarding exposures to sodium and SBP to prime a ‘close-to-reality’ synthetic population. For this, the model draws the traits of the synthetic individuals from conditional distributions that were estimated from multinomial models fitted in the original survey data. The statistical framework of this method and its extension to modeling has been described elsewhere[26,27] and a detailed description and validation can be found in **S1 Appendix**. Then, the model projects the recent observed trends in SBP and sodium intake into the future, and uses the projections to evolve the traits of the synthetic individuals over time. We used NHANES 1999–2014 for the SBP projections and NHANES 2009–2014 for sodium intake projections[12]. The inclusion of exposure trends in our analysis ensures more conservative estimates for the potential impact of the proposed FDA targets compared to an analysis assuming no trends.

**CVD endpoints:**We used the CDC Wonder database[13] to extract CHD (ICD10: I20-25), stroke (ICD10: I60-69), and any other cause mortality rates for years 1999–2015, stratified by age, sex, and race/ethnicity. We forecasted these trends to 2036, again providing a more appropriate and conservative estimate of the potential impact of the proposed FDA targets. Then, we used WHO DisMoD II model, to model the incidence and prevalence rates for CHD and stroke for 2014[28]. To account for future trends in CHD and stroke incidence rates that are not attributable SBP trends, we assumed that half of the forecasted annual change in CHD and stroke mortality rates are attributed to changes in incidence rates. We based this assumption on observational evidence from England, and modelling studies in England and the US[29-32], and we included this assumption in our probabilistic sensitivity analysis (see below). Using a population attributable risk approach, the model calculates the annual risk of the synthetic individuals to develop CHD and stroke based on their SBP and incidence rate forecasts using published relative risks. Finally, the model calibrates the annual case fatality for CHD, stroke and any other cause, to the forecasted mortality rates in a competing risk framework. Specifically, for ‘any other cause’ mortality we assumed that hypertensive synthetic individuals have higher mortality rates to account for diseases other than CHD and stroke that we did no explicitly model but are causally related to hypertension[17].

## Summary of evidence regarding the risks of excess sodium consumption

Excess dietary sodium consumption has been linked to an increased risk of cardiovascular disease (CVD)[33]. For CVD, the excess risk appears to be mainly mediated through the deleterious effect of excess sodium consumption on blood pressure[2]. Our methods for evaluating the causality of effects of sodium reduction on BP and of BP reduction on CVD have been previously described[2].

There is some controversy regarding the optimal level of sodium consumption[34]. Some researchers claim that sodium consumption lower than 3,000 mg/d can actually increase the risk of CVD and overall mortality[35,36]. However, it appears that this argument is based on biased measurement methodology[37]. A recent discussion on the subject can be found in Mozaffarian *et al*. who concluded that the optimal level of sodium consumption below which no health gains have been observed is somewhere in the range of 614 mg/d to 2391 mg/d[2]. In our study we have incorporated the uncertainty around the ideal sodium consumption in our probabilistic sensitivity analysis.

Evidence that directly links sodium risk reversibility to CVD mortality or morbidity outcomes is lacking. A meta-analysis of several randomized control trials that tested low sodium diets was underpowered and therefore inconclusive[38]. In comparison, a plethora of evidence exists supporting the effect of low sodium diet on blood pressure which appears to happen within weeks[2,39]. Finally, the cardiovascular risk reversibility of blood pressure has been evident in several randomized control trials and appears to occur within a 5-year period[40].

## Policy effects

The FDA proposed sodium reformulation policy included specific mean and upper bound sodium concentration targets at 2 and 10 years for 155 food categories[41]. In addition, the FDA also provided data to map these 155 food categories to the NHANES 2009–2010 24-hour recall dietary questionnaire[41]. This enabled the model to estimate the potential impact of the modelled policies on every synthetic individual based on their age, sex, race/ethnicity, and sodium consumption in the ‘no intervention’ scenario. The model then uses the estimated reduction in sodium consumption of the synthetic individuals and calculates the effect upon their SBP using a published meta-regression equation[42]. We assumed a gradual reformulation to targets and immediate change in sodium intake according to reformulation. We also assumed that the reformulated products will sustain their sodium concentration thereafter. Although changes in sodium intake influence SBP within weeks[42], we conservatively assumed a median duration of five years from change in SBP to health outcomes.

## Model outputs

For each scenario, the model generated the total numbers of relevant events and reports cases and deaths prevented or postponed (CHD, stroke (CVD) or other), QALYs, life years gained (LYG) and disaggregated disease costs. We present the results for U.S. adults age 30 to 84 from 2017 to 2036 (simulation horizon of 20 years), rounded to the second significant digit.

## Medical costs and health state utility analysis

We calculated the health state utility values (preference weights) using published equations[19] which used EQ-5D-3L data from the Medical Expenditure Panel Survey (MEPS) 2000-2002[19]. The disease medical, mortality, and morbidity costs per person year were derived from a Research Triangle Institute (RTI) International report which was based on MEPS[43]. We estimated informal care costs using published data[21,22]. All costs were stratified by age, sex, and ethnicity/race except informal care costs. The health state utility values were additionally stratified by income and education.

## Policy costs

Policy costs included government costs to administer and monitor the policy as well as industry costs incurred through reformulating products. By taking this societal perspective, we aimed to understand the impact of sodium reduction on the entire US economy. Specifically, for industry costs we used a reformulation cost model developed by the RTI under contract with the FDA[25]. The model accounted for variations in product formula complexity, company size, reformulation type, compliance period and other factors, which produces a more accurate cost estimate compared to a standard per-product cost approach. Administrative costs were assumed to occur every year, with monitoring and evaluation costs occurring every year after full policy implementation at year 3. We assumed the industry cost was equal in the two rounds of reformulation (2 and 10 year targets) except for the pessimistic scenario, and divided the costs over the policy implementation years (intervention years 1–3 for the first round, and intervention years 4–10 for the second round). All costs were inflated to 2017. We assumed no policy costs after intervention year 10.

## Cost-effectiveness analysis

To inform cost-effectiveness from different relevant perspectives, we evaluated both societal and healthcare cost perspectives, closely adhering to the recommendations from the second panel on cost effectiveness[44]. All costs were inflated to 2017 US dollars using consumer price index (CPI) and discounted at a 3% annual rate. We also discounted QALYs at the same rate. We assumed a willingness to pay of $100,000 per QALY[45].

## Sensitivity and uncertainty analyses

We used probabilistic sensitivity analysis via a second-order Monte Carlo approach that allowed the estimated uncertainty of different model parameters and population heterogeneity to be propagated to the outputs[46]. The sources of uncertainty we considered were the sampling errors of the baseline sodium intake, baseline SBP, and the relative risks of SBP on CHD and stroke; the uncertainties around the lowest exposure to sodium and SBP below which no risk is observed; the uncertainty around the effect of sodium on SBP; the uncertainty around the true incidence of CHD and stroke; the uncertainty of mortality forecasts; the uncertainty around which foods will be reformulated; the uncertainty around the quality of life decrements used to calculate QALYs; and the uncertainty of all the costs. We summarize the output distributions by reporting the medians and 95% uncertainty intervals (UI). We also plotted the annual probability that a scenario was cost effective or cost saving over the simulation period. Finally, both discount rate and willingness to pay values were included in one-way sensitivity analysis and allowed to vary in steps between 0–9% and $50,000–$150,000, respectively. Please refer to **S1 Appendix** (specifically Tables D, E and F) for more information.

# Results

## Health related outcomes

In the baseline scenario, median sodium consumption might modestly decline from 3,150 mg/d in 2017 to 2,974 mg/d in 2036. In the optimistic, modest and pessimistic scenarios, sodium consumption would be projected to fall to 2,224 mg/day, 2,524 mg/day and 2,789 mg/day respectively (**Table 2**, **Fig 6**). The resulting difference in median sodium between the optimal and pessimistic scenarios would result in a 1.0 mmHg difference in resulting median SBP. These differences were larger in specific subgroups, for example older adults, those with hypertension, and blacks.

**Fig 3**. Median US sodium consumption among adults age 30–84 years under the baseline projection and three modelled scenarios. The dashed horizontal line depicts the 2015 Dietary Guidelines for Americans recommended target of 2300 mg/d.

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Optimal implementation, achieving the FDA national target of 2,300 mg/d sodium consumption, could potentially prevent or postpone approximately 35,000 CVD deaths (95% UI: 3,700 to 78,000), 450,000 cases of CVD from 2017 to 2036 (95% UI: 240,000 to 740,000), and potentially generate discounted QALYs of 2.1m (95% UI: 1.7m to 2.4m) QALYs between 2017 and 2036 (61 QALYs per 100,000 (**Table 3**). The modest and pessimistic scenarios might potentially prevent or postpone approximately half as many (220,000 cases) and a quarter (120,000) as many total cases respectively. Both could still substantially improve the health of the US population with proportional findings for CVD deaths and QALYs.

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The absolute health benefits from the optimistic scenario would be approximately 50% stronger among men than in women, reflecting their higher sodium intake and higher CVD burden. The benefit would also be higher among non-Hispanic blacks than in non-Hispanic whites, reflecting their higher SBP, higher CVD burden and sensitivity to sodium changes.17 Finally, the largest number of CVD cases would be prevented in the oldest age group (70-84 years), while middle-aged groups (50-69 years) would gain most QALYs (please see **S1 Appendix**, Tables G–I).

## Costs and cost-effectiveness

From a healthcare perspective (government and private payers), the optimal scenario would result in approximately $31bn (95% UI: $20bn to $48bn) reduction in total net costs, a substantial saving over the 20-year period (**Table 4**, **Fig 4**). The pessimistic scenario would still yield one third of the savings, some $9.7bn (95% UI: $5.9bn to $16bn). From the societal perspective, the net savings from 2017–2036 would be even larger; approximately $41bn (95% UI: $14bn to $81bn) reduction in net costs in the optimal scenario. More than 95% of policy costs would be attributed to industry costs of reformulation, with less than 5% attributable to government costs. The largest health-related cost savings for all scenarios would be generated from hypertension medical and productivity costs. The optimal scenario would yield more than three times as much healthcare and societal savings per 100,000 than the pessimistic scenario (**Table 3**).

**Fig 4**. Estimated disaggregated discounted cumulative costs for the simulated period 2017 to 2036. Negative costs represent savings. The shaded areas depict 95% uncertainty intervals.

**Table 4**. Impact Inventory and cost-effectiveness analysis of model output for ages 30 to 84, cumulatively over the 20-year simulation period from 2017 to 2036. Results are rounded to the second significant digit. Costs are median of each distribution so may not add up to totals. Negative costs represent savings. Costs are presented in discounted 2017 Billion US Dollars. Dominant = less costly and more effective than the alternative. CHD, coronary heart disease; QALYs, quality-adjusted life years.

|  |   | Optimal policy scenario | Modest policy scenario | Pessimistic policy scenario |
| --- | --- | --- | --- | --- |
| **Change in health-related costs:** | -57bn (-97bn to -38bn) | -30bn(-50bn to -18bn) | -19bn (-35bn to -9.9bn) |
|  | Hypertension medical costs | -18bn (-24bn to -12bn) | -9.3bn (-13bn to -6.4bn) | -4.4bn (-6.4bn to -3bn) |
|  | Hypertension productivity costs | -12bn (-16bn to -8.1bn) | -6.4bn (-8.8bn to -4.4bn) | -3.5bn (-5bn to -2.3bn) |
|  | CHD medical costs | -7.1bn (-16bn to -2.4bn) | -3.3bn (-8bn to -1bn) | -2.8bn (-6.5bn to -0.76bn) |
|  | CHD mortality productivity costs | -4.8bn (-26bn to 0.92bn) | -2.3bn (-13bn to 3.3bn) | -1.8bn (-12bn to 4.1bn) |
|  | CHD morbidity productivity costs | -1.3bn (-3.4bn to -0.34bn) | -0.64bn (-1.7bn to -0.14bn) | -0.5bn (-1.3bn to -0.1bn) |
|  | CHD informal care costs | -1.5bn (-3.5bn to -0.51bn) | -0.69bn (-1.7bn to -0.2bn) | -0.58bn (-1.4bn to -0.16bn) |
|  | Stroke medical costs | -5.4bn (-13bn to -1.9bn) | -2.9bn (-6.9bn to -0.81bn) | -2.4bn (-5.8bn to -0.64bn) |
|  | Stroke mortality productivity costs | -2.3bn (-12bn to 1.2bn) | -1.3bn (-7.8bn to 2.3bn) | -1.0bn (-7.3bn to 2.5bn) |
|  | Stroke morbidity productivity costs | -0.76bn (-1.9bn to -0.23bn) | -0.41bn (-1.1bn to -0.09bn) | -0.33bn (-0.87bn to -0.051bn) |
|  | Stroke informal care costs | -3.1bn (-8.1bn to -0.91bn) | -1.5bn (-4.4bn to -0.35bn) | -1.2bn (-3.5bn to -0.26bn) |
| **Change in policy costs:** | 17bn (6.3bn to 34bn) | 10bn (4.0bn to 21bn) | 7.3bn (2.9bn to 15bn) |
|  | Policy admin costs | 0.16bn (0.12bn to 0.22bn) | 0.16bn (0.12bn to 0.22bn) | 0.16bn (0.12bn to 0.22bn) |
|  | Policy monitoring costs | 0.029bn (0.021bn to 0.039bn) | 0.029bn (0.021bn to 0.039bn) | 0.029bn (0.021bn to 0.039bn) |
|  | Policy industry costs | 16bn (6.1bn to 34bn) | 10bn (3.8bn to 21bn) | 7.2bn (2.7bn to 15bn) |
| **Total net cost (medical perspective)** | -31bn (-48bn to -20bn) | -16bn (-25bn to -10bn) | -9.7bn (-16bn to -5.9bn) |
| **Total net cost (societal perspective)** | -41bn (-81bn to -14bn) | -19bn (-41bn to -3.4bn) | -12bn (-28bn to 0.39bn) |
| **Net monetary benefit (valuing QALYs at $100,000)** | 250bn (190bn to 300bn) | 130bn (100bn to 170bn) | 81bn (59bn to 110bn) |
| **Incremental cost-effectiveness ratio (2017 US Dollars per QALY)** | Dominant (dominant to dominant) | Dominant (dominant to dominant) | Dominant (dominant to 540) |

All scenarios would be cost effective, with the optimal and modest scenarios being dominant, i.e. cost saving and producing more health than the baseline case. The optimal scenario would be approximately twice and three times as cost effective as the modest and pessimistic scenarios (**Fig 2**, **S1 Animation**), generating a net monetary benefit of approximately $250bn (95% UI: $190bn to $300bn), with each QALY gained valued at $100,000.

## Probability of cost-effectiveness and sensitivity analysis

Including costs, we estimated a probability of near 100% that the scenarios would become cost-effective by 2021 for the optimal and pessimistic scenarios, and by 2023 for the modest scenario. All scenarios were likely to be cost saving by 2036 (99.9%, 99.0% and 97.1% probability for optimal, modest, and pessimistic scenarios, respectively). The optimal and pessimistic scenarios would have more than 80% probability of becoming cost saving by 2029, and the modest scenario by 2031 (**Fig 5**). In a set of one-way sensitivity analyses, net monetary benefit remained positive when willingness to pay for a QALY was varied down from $100,000 to $50,000, and when annual discount rates were varied up from 3% to 9% (see **S1 Appendix**, Tables E and F).

**Fig 5**. Estimated probability of cost saving and cost-effective policy over the 20-year simulated period. Cost effectiveness at the $100,000 per QALY Willingness to pay.

# Discussion

We used a microsimulation approach of a close-to-reality synthetic population (US IMPACT Food Policy Model) to estimate the potential health and economic effects, over a 20-year period, of the FDA’s proposed voluntary sodium reformulation targets proposal under three scenarios of differing compliance. Our study suggests that implementation and full compliance with the FDA voluntary sodium reformulation targets, would result in substantial decreases in CVD incidence and mortality whilst also offering impressive cost savings to the health payers and the wider economy. The optimal scenario saved most lives, and generated the most QALYs and economic savings. However, even lower compliance to just the 2-year targets or 50% of the 10-year targets yielded health and costs savings. This highlights the substantial health and economic opportunity costs of inaction or poorly sustained efforts.

Sub-optimal diet is a leading cause of mortality and morbidity in the US and worldwide, with excess sodium being a significant contributor[1]. The burden of hypertension continues to grow despite advances in screening and evidence-based medications[47], emphasizing the importance of population initiatives to reduce BP. Due to their well-documented effects on BP, sodium reduction policies have been characterized as a “best buy” government intervention by the WHO. Despite this and many efforts, sodium remains overconsumed in the US, highlighting the challenging nature of dietary behavior change. To date, the largest population-wide reductions in sodium consumption have been achieved in Finland, Japan, and the UK via comprehensive “upstream” strategies involving population-wide, multicomponent policies. In contrast, more “downstream” approaches such as individual approaches and worksite or community interventions are much weaker[8], again demonstrating the effectiveness hierarchy of public health interventions[48]. These declines in population sodium have corresponded with expected reductions in population BP, supporting our findings. In addition, long-term follow-up from the largest RCTs of sodium reduction demonstrated expected reductions in risk of CVD events[49]. Gradual sodium reduction achieves mean population sodium intake reductions without noticeable changes to consumers and their palates[50-52]. This is unlikely to trigger compensatory behvaiours resulting in additional sodium used by the consumer at the table of in cooking[53-55]. Together with prior results, our investigation therefore supports the potential health and economic benefits of implementing the proposed FDA voluntary sodium guidelines.

 When stratified by population subgroup, our results suggest the largest beneficial effects in non-Hispanic black populations, based on higher BP responsiveness, and CVD mortality rates[56]. These findings suggest additional benefits in reducing disparities, consistent with previous evidence demonstrating that upstream population interventions are more equitable than downstream individual-focused strategies[57].

Our findings are consistent with previous analyses quantifying potential benefits of general population reduction of sodium[9,58-61] and build upon them significantly. A previous modelling study estimated 194,000 to 392,000 QALYS gained annually in the US with a reduction in salt consumption of 3g/day[9], whilst another simulation study found 312,000 QALYs could be generated annually by reducing sodium consumption to the recommended level of 2,300mg/day[59]. These previous findings are reassuringly consistent with our study which averages 305,000 QALYs generated each year of the study. However, our analysis includes several notable advances. For example, we evaluated and incorporated background trends in sodium intakes, SBP, and CVD, which reduces the estimated potential benefits of our policy interventions, providing the most conservative estimation of benefits. In addition, we specifically modelled the 2016 FDA proposal, providing direct relevance to current policy considerations in the US. Furthermore, we evaluated cost-effectiveness from distinct relevant perspectives, including societal and healthcare perspectives. We were thus able to provide policy makers and health advocacy groups with more accurate and timely real-world estimations of the likely effects of the proposed policy, and the foregone opportunity costs if the desired reformulations are not achieved. By including industry costs, the present study aimed to include all relevant costs and provide objective results for all stakeholders.

This study has potential limitations. The effect estimates in the model use interventional and prospective observational studies. They are therefore subject to biases and confounding that may have influenced also our model estimates. However, the etiological effects of dietary changes were estimated from meta-analyses with confirmatory validity analyses, including from randomised clinical trials. Our estimates may be conservative and underestimate the full health and economic benefits of sodium reformulation, as: 1) our baseline scenario assumed that recent observed declines in sodium intake would continue into the future, moderating the benefit of all scenarios; 2) we only evaluated diseases mediated through BP, while decreasing sodium consumption could have beneficial effects upon other health burdens such as gastric cancer[62,63]; and 3) reductions in sodium consumption achieved through the proposed policy might additionally increase potassium intake though substitution of NaCl with KCl[64]; but we did not include this potential beneficial effect in our model. We do not include unrelated medical costs in a sensitivity analysis as this study focuses only on costs for CVD. Our modeling results cannot replace evidence from evaluating the actual policy intervention over time in the US, indicating that any implementation of the FDA guideline should be accompanied by robust independent assessment.

In conclusion, our findings suggest that the proposed FDA voluntary sodium reformulation could result in substantial health benefits and cost savings across the US population. However, sub-optimal compliance or a delay in reaching these targets could result in a significant number of preventable CVD cases, CVD deaths and costs to the wider economy.

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# Supporting Information

**S1 Appendix:** Supplementary material

**S1 Animation:** Model animation