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Non-alcoholic fatty liver disease as a mediator of detriments of dietary sugar consumption: implications for the health and economic benefits of interventions in the United States

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Abstract

Objectives: Excessive consumption of added sugars in the human diet has been associated with obesity, type 2 diabetes (T2D), coronary heart disease (CHD), and other elements of the metabolic syndrome. Recent studies have shown that non-alcoholic fatty liver disease (NAFLD) is a critical pathway to metabolic syndrome. This model assesses the health and economic benefits of interventions aimed at reducing intake of added sugars.

Methods: Using data from U.S. National Health Surveys and current literature, we simulated an open cohort, for the period 2015 to 2035. We constructed a microsimulation model with Markov chains for NAFLD (including steatosis, non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC)), body mass index (BMI), T2D, and CHD. We assessed reductions in population disease prevalence, disease-attributable disability-adjusted life years (DALYs), and costs, with interventions that reduce added sugars consumption by either 20% or 50%.

Findings: The model estimated that a 20% reduction in added sugars intake will reduce prevalence of hepatic steatosis, NASH, cirrhosis, HCC, obesity, T2D, and CHD. Incidence of T2D and CHD would be expected to decrease by 19.9 (95% CI: 12.8 – 27.0) and 9.4 (95% CI: 3.1 — 15.8) cases per 100,000 people after 20 years, respectively. A 20% reduction in consumption is also projected to annually avert 0.767 million (M) DALYs (95% CI: 0.757M — 0.777M), and a total of 10.3 billion (B) USD (95% CI: 10.2B — 10.4B) in discounted direct medical costs by 2035. These effects increased proportionally when added sugars intake were reduced by 50%.

Conclusions: The decrease in incidence and prevalence of disease is similar to results in other models, but averted costs and DALYs were higher, mainly due to inclusion of NAFLD and CHD. Based on this model, societal efforts to reduce consumption of added sugars could result in significant public health and economic benefits.

Strengths and limitations of this study

- No previous model has captured the full effects of added sugars through non-alcoholic fatty liver disease, obesity, type 2 diabetes and coronary heart disease.
- This model is applicable to each intervention that is aimed at reducing added sugars.
- The model is based on input parameters from multiple studies who were not always of excellent quality. We have used large intervals around these parameters to ensure reliable results.

Introduction

The social and economic burdens of chronic metabolic disease have been increasing in the United States for the last three decades. Two-thirds of the adult population in the United States is now overweight, and morbid obesity affects 9.9% of all adult women [1]. Prevalence of Type 2 diabetes (T2D) in the U.S. is at 9.3%.[2,3] Coronary heart disease (CHD) prevalence increased concurrently from 13 to 15.5 million over the last ten years.[4,5] More than 15% of all deaths are attributable to CHD and more than 3% to diabetes.[6] Costs have simultaneously increased; and costs for CHD are expected to double over the next two decades.[7,8] Though these figures are stunning, they underestimate the magnitude of the problem. Non-alcoholic fatty liver disease (NAFLD) has recently been found to be present in over 30% of the population, and is thought to play an important role in metabolic pathophysiology.[9,10] NAFLD is defined by the presence of liver fat in absence of primary causes such as alcohol and hepatitis C.[11] NAFLD is further categorized into: a) hepatic steatosis, which is a reversible fat accumulation in the liver defined by an occupation of steatotic hepatocytes of more than 5.5% of the liver parenchyma; and b) non-alcoholic steatohepatitis (NASH), which is defined as the presence of hepatic steatosis plus necroinflammation with hepatocyte injury (ballooning) with or without scarring.[9,11,12] NASH can cause scarring and fibrosis to develop (cirrhosis), which is an irreversible process. Cirrhosis can further progress to hepatocellular carcinoma (HCC).[13] NASH is projected to become the leading cause of liver transplantation in the USA by 2020,[14,15] and 30-40% of NASH-cirrhotic patients succumb to a liver-related death within 10 years.[16,17] Hospitalizations for NAFLD have increased 97% between 2000 and 2012.[18] NAFLD has also been suggested as an important driver of T2D in lean individuals, as liver fat accumulation can cause insulin resistance.[10,19-21] Furthermore, NAFLD has been shown to regularly precede the metabolic syndrome, and scientists now argue that NAFLD is the hepatic manifestation of metabolic syndrome, and should be included in its definition.[22-25] It is important to identify determinants of these metabolic diseases and assess the effectivity of upstream policy interventions to curb the national and the global epidemic of metabolic syndrome.

Added sugars

The excessive amount of added sugars (glucose + fructose) in our food supply has been associated with NAFLD and each of the elements in the metabolic syndrome.[26,27,28] Fructose is metabolized into fat in the liver through the process of *de novo* lipogenesis [29**]**, which can result in hepatic steatosis and lead to insulin resistance, causing weight gain and predisposing to T2D. This effect appears to be specific for sugar, and independent of calories consumed or BMI.[29-33, 51] Added sugars consumption has increased in the U.S. over the years 1977-2000, decreased slightly between 2000—2008, and seems to have stabilized in the years thereafter.[34-36] Over 55% of all American adults consumed more than 50 grams of added sugars per day between 2005—2012, which is thought to be the cut-off value for added risk of metabolic derangement, and more than the advised maximum according to the American Heart Association (25 - 37.5 grams). Furthermore, U.S. adolescents during this period averaged 94.0 grams per day.[3,37,38]

Intervention effectiveness

Several studies have modeled the effects of different interventions to reduce added sugars intake. A popular suggestion is the implementation of a sugar-sweetened beverage (SSB) tax. Though this does not affect all added sugars in the food supply, SSB's are the main single contributor to overall added sugars intake, and a tax on SSB's is easier to implement than an added sugars tax.[39] A 20% SSB tax is projected to reduce prevalence of obesity anywhere from 1.5 — 10%, based on different studies.[40-42] Annual diabetes cases would be expected to decline concurrently between 1.8% and 3.4%, and CHD cases by 0.5 —1.0%.[41,43] Additional research has focused on other strategies to lower added sugars consumption. Banning SSB's from the U.S. Supplemental Nutrition Assistance Program (SNAP) is expected to result in a 0.89% lower obesity prevalence within 10 years, while lowering the amount of sugars in the food supply through a cap and trade approach by 1% annually is expected to lower the prevalence of obesity by 1.7% after 20 years.[44,45]

An important limitation of all these studies is that none of these models incorporate the effects and costs related to sugar-induced NAFLD. Because NAFLD explains a part of the incidence of diabetes in lean individuals and is expected to contribute significantly to overall healthcare burden and costs, it is necessary that modeling incorporate all of these diseases.

Our goal is to predict the health and economic effects of interventions that are designed to reduce added sugars consumption either by 20% or 50%, respectively. We describe the process of creating, calibrating and validating a microsimulation model. We clarify the relevant interactions that determine progression within this model in Markov chains for NAFLD (including cirrhosis and HCC), obesity, T2D, and CHD, and we describe the creation of a simulated open cohort representative of the US population. We allow the model to run for 20 years into the future to predict effectiveness. We report the outcomes of these simulations in future incidence, prevalence and mortality of disease, and in disability-adjusted life years (DALYs) and costs averted.

Methods

The Methods section is constructed according to the recommendations by the ISPOR taskforce for good modelling practice, and completeness is checked according to the CHEERS statement.[46,47]

Summary

We constructed an individual based model consisting of a base cohort of 22,400 people. New people entered the model each year at age 20, the youngest age group. Individuals get assigned a state at initialization in each 'chain' of the model.

These include age, sex, ethnicity, sugar consumption, NAFLD, BMI, T2D, and CHD. The current states of each individual at the beginning of a cycle form a risk profile, and the presence in a risk inducing state in one of the chains can influence the probability of transitioning between states in a different chain, according to literature-based odds ratios. We simulated 20 annual cycles for each individual, counting events, incurred direct medical costs, and DALYs for each cycle, as well as the overall prevalence for the total cohort. We discounted the costs and DALYs by 3.0% annually, and costs were presented in 2015 USD. Two interventions were simulated: one that reduced each individual's added sugars consumption by 20%, and one that reduced it by 50%. We used identical random numbers for the base case scenario and each of the interventions, to reduce variance. We calibrated the model to other studies reporting historic trends and predicting future prevalence, and validated the model via face validation, cross-validation, and sensitivity analyses. Deterministic sensitivity analysis was used to determine the influence of individual input parameters. Probabilistic sensitivity analysis was used to generate mean results and 95% confidence intervals.

Model type

An individual-based stochastic Markov model (microsimulation) was used. The model contained a chain for each of four separate diseases which interact. Because each of these diseases has a minimum of 3 states, and the transitions between these states are based on the presence or absence of a set of risk factors, the state-space explosion phenomenon prohibits us from using traditional Markov cohort simulation. A microsimulation approach makes it possible to use individual-specific transition rates, capturing the effect of interventions on individual risk factor profiles, thereby reducing states and allowing for complex relationships between several risk factors within a single individual.[48] It also opens up potential for future analyses among subgroups.

Population and setting

The model is based on the adult population (age 20+) of the United States. Outcomes are reported from a healthcare perspective. This includes direct medical costs and DALYs averted. Indirect medical or non-medical costs are excluded. Because this model is meant to assess the benefits of reducing added sugars intake, unrelated to the type of intervention, costs of implementing any specific intervention and possible revenues (e.g. in the case of an excise or general services tax) are also excluded.

Model structure and input parameters

A simplified model transition diagram is presented in Figure 1. Individuals will reside in a state within each chain at any given point in time. The probability of staying within a state or moving to another state in each cycle is determined by a set of defined transition probabilities, which are influenced by the risk profile (the current state in the other chains) of the individual. Events in different chains can occur in parallel. The simulation starts when the specific individual gets assigned a state for his or her age (A), sex (S) and ethnicity (E). Age states are based on the population distribution that is provided by the Bureau of the Census, and are specified for each age from 20 to 84 and a cumulative age group for anyone above 85. We simulate an open cohort. New individuals with age 20 will enter each year.[49] Ethnicities incorporated into the model are Hispanic, non-Hispanic black, and non-Hispanic-white. Data availability did not allow us to incorporate Asians and Native Americans as separate groups and therefore they were grouped with the non-Hispanic whites. When the individual is assigned an age, sex and ethnicity, these determine the state that this individual will be assigned to in each of the chains for NAFLD, BMI, T2D and CHD at the start of the simulation. Because each chain has its own healthy state, but this does not mean that this person is actually healthy (e.g. a person can have cirrhosis but not diabetes), these healthy states will be referred to as non-disease states (e.g. non-T2D). The NAFLD chain includes a non-NAFLD state, and states for hepatic steatosis, NASH, cirrhosis, and NASH- or cirrhosis-related hepatocellular carcinoma. A person is defined as having NAFLD when his or her current state is steatosis, NASH or cirrhosis. This is different from common terminology, where cirrhosis is excluded. We chose this definition for easy reference, because these three states infer extra risk for progression within other chains. It is important to note that modeled cirrhosis and hepatocellular carcinoma are specifically related to steatosis and NASH, and do not include all cirrhosis and HCC cases within the population, irrespective of cause. Transition directly from the non-NAFLD state to either one is therefore not possible. The BMI chain includes states for healthy weight, overweight and obesity. The T2D chain includes a non-T2D state and a T2D state. The CHD chain includes a non-CHD state and a CHD state. The individual also gets assigned an added sugars consumption. There are two states in the sugar chain — high consumption (≥50g of added sugars per day), and low consumption (< 50g of added sugars per day). The distribution of these states among the study population reflects the data of the NHANES 2005-2012 and is specified per sex and ethnicity group.[3,37] Sugar consumption is fixed throughout the simulation for each person. Each chain has a death state, called 'non-disease related death'. Three disease chains also have a disease-specific death state (e.g. T2D-death), to easily calculate disease-attributable death. Transitions to death states are "synchronized" between chains, meaning that death in one chain forces an instant transition to the death state in other chains.

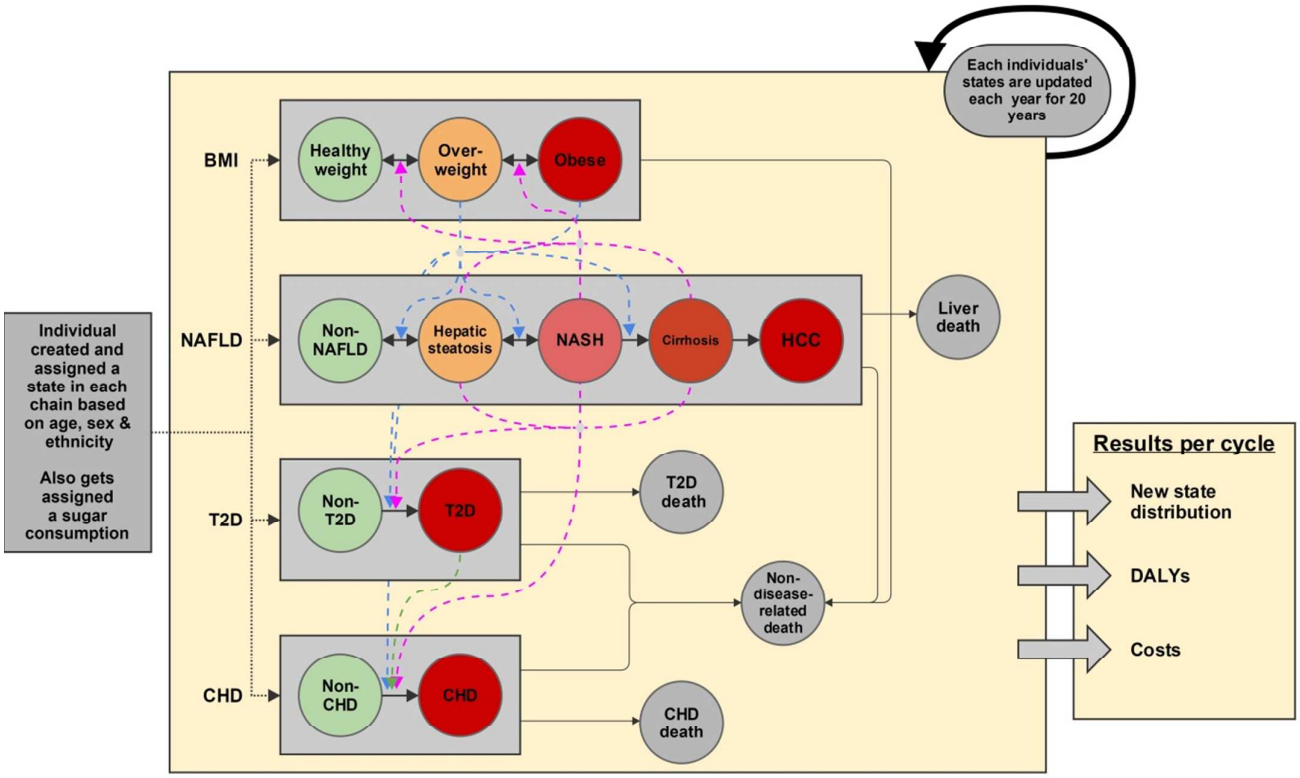


Figure 1. *Model structure.*
Dotted lines indicate the assignment of a state in each chain at the start of the simulation. Solid lines indicate a possible transition pathway between states. Striped lines indicate how being in a state within one chain can affect the value of the transition probability between two states in another chain. Pink striped lines indicate the effect of NAFLD on progression in the BMI, T2D and CHD chains. Blue striped lines indicate the effect of overweight and obesity on progression in the NAFLD, T2D and CHD chains. The green striped line indicates the effect of T2D on progression in the CHD chain.
BMI: body mass index, NAFLD: non-alcoholic fatty liver disease, T2D: type 2 diabetes, CHD: coronary heart disease, NASH: non-alcoholic steatohepatitis, HCC: hepatocellular carcinoma, DALYs: disability-adjusted life years

Final transition probabilities per chain are compared to a pseudo-random number to determine state-transitions each cycle. These final transition probabilities are derived from a baseline probability that gets corrected for applicable risk factors and annual regression rates. The baseline transition probabilities for HCC incidence, and for T2D and CHD incidence and mortality are age-specific. The correction formula for the baseline transition probabilities is a multiplicative function of all applicable values for present risk factors (odds ratios). The presence of a risk factor, which is determined by the current state in each chain, indicates that there is an "interaction". Ethnicity interacts with progression in the NAFLD chain up to cirrhosis. Steatosis, NASH, and cirrhosis disease states (collectively defined as NAFLD) interact with progression within the BMI chain, and with the incidence rate in the T2D chain and the CHD chain (pink arrows). Overweight and obesity interact with progression within the NAFLD chain up to cirrhosis, and with incidence rates in the T2D and CHD chains (blue arrows). T2D interacts with the incidence rate of CHD (green arrow). High added sugars consumption interacts with progression between states in the NAFLD chain up to cirrhosis, and with progression within the BMI chain. To determine whether there were temporal trends in incidence or death rates, we plotted the available historic data (1999-2013) and projected this to the future. [5,6,50] These annual "regression rates" were found to be present for the incidence and mortality rate of CHD, and for the non-disease specific mortality rate. We incorporated these regression rates into the model by adjusting the respective baseline transition probabilities before each cycle. To remove confounding because of calculation order, chain calculation order was randomized.

Interventions
Two interventions were simulated: a reduction of 20%, and a reduction of 50% in individual added sugars consumption. A 20% reduction in added sugars was simulated because this is the percentage reduction assessed in several studies.[40-42] In addition, a 50% reduction was simulated because the American Heart Association advises 6-9 teaspoons of added sugar (for females and males respectively) as a maximum per day which is approximately 50% of the current average consumption.[3,37,38] The individual added sugars consumption distribution was then split into a dichotomous variable; with people consuming less than or equal to 50 grams of added sugars being considered low consumers, and people consuming more than 50 grams per day being considered high consumers. This model did not incorporate substitutions to other food categories, but it did incorporate the overall added sugars reduction, rather than a sole reduction in SSB consumption used in other studies.[41,43] This makes it possible to capture the overall effects of added sugars, contrary to

the solitary effect of SSB's. The effects of changes in food consumption to other food groups (e.g. proteins, fat) are not modeled. Detrimental effects of these food categories are less well documented and inferior to the effects of added sugars. Our expected effect was based on a reduction in overall calories as well as a reduction in the directly detrimental effects of added sugars, as recent (non-industry sponsored) studies clarify that there appears to be a detrimental effect even irrespective of calories.[26-33, 51] NHANES data was used to reduce individual added sugars consumption by the specified amount. From these data, new distributions were calculated to reflect subgroup consumption patterns. These distributions determined the ratio between individuals in the high and the low risk group, and therefore determine progression within disease chains. Identical random numbers were used between interventions to reduce variance, as described by Stout and Goldie.[52]

Time horizon, cycle length

The model had a time horizon of 20 years, modelling the calendar years 2015 to 2035. This duration was chosen to make sure effects within chronic diseases (T2D, CHD) were sufficiently visible. Cycle length was 1 year, to ensure accurate modeling of disease progression. Individuals could exit the model through each death state, or live until the end of the simulation.

Outcomes

Outcomes were incidence, prevalence and mortality of disease, and direct medical costs and DALYs averted. Costs were calculated by multiplying prevalence by discounted disease-attributable costs. DALYs were calculated by adding years lived with disability (YLD) and years of life lost (YLL). YLD was calculated as the product of the prevalence of disease times the discounted disability weight. YLL was calculated by multiplying the discounted health-adjusted life expectancy at death by the amount of people that died in that specific year, given a certain age and sex. The discount rate for costs, disability weights, and life expectancy was 3.0% annually. Health-adjusted life expectancy and discounted life expectancy for males and females for the United States, reported by the Institute for Health Metrics and Evaluation (IHME), are provided in the online supplement.[53]

Input parameter determination

Model input parameters, their distribution ranges, and their sources are presented in Tables 1 and 2. The parameters that determined demographics and the distribution of risk factors and disease at the start of the simulation are mainly derived from NHIS and NHANES data. If data were not sufficient, current literature was consulted. Baseline transition probabilities were derived from literature data, and where necessary, via calibration. Also when necessary, we used logistic conversion to adjust transition rates to reflect annual probabilities. Interaction values were derived from literature data. For interactions between chains, we used conservative data when possible, to ensure no overestimation of effect size. We took special care to ensure these odds ratios reflect the case for our model, i.e. reflect increased risk due to a reduction in overall added sugars intake, not just a reduction in sugar-sweetened beverage intake, which is more commonly investigated. Regression rates were determined by historic and projected trends reported by the CDC and the American Heart Association.[3,5,49] Costs were derived from American population-based studies and, where necessary, were inflated by the inflation calculator of the United States Department of Labor Statistics to 2015 USD.[54] Costs were calculated as specific disease-attributable costs (i.e. costs for CHD due to diabetes were counted as costs due to CHD rather than costs due to diabetes). This was necessary to prevent overlapping costs. Disability weights were adopted from World Health Organizations' burden of disease estimates and current literature. Specific sources are provided in the tables.

Table 1. Model input values and ranges for disease characteristics. Costs are population based, meaning that they include those who do not get care.

	Prevalence at simulation start				Costs (annual)			Disability weights			
Disease state	***Mean***	***Min***	***Max***	**Ref.**	***Mean***	***SD***	***Ref.***	***Mean***	***Min***	***Max***	**Ref.**
Steatosis	27.955%#	18.637%	41.933%	8,14,16	134	50	53	0.000	0.000	0.000	50-52
NASH	3.141%#	2.094%	4.712%	8,14,16	267	100	53	0.033	0.017	0.066	50-52
Cirrhosis	0.314%#	0.209%	0.471%	54-56	2,861	1073	58	0.194	0.127	0.273	10,57
HCC	0.025%#	0.017%	0.038%	59,60	42,644	15,992	61,62	0.294	0.199	0.411	57,59,60
CHD	6.544%#	-	-	1,6	13,233	4962	6,63	0.066	0.043	0.095	57
T2D	9.447%#	-	-	1	8,170	3064	65	0.150	0.080	0.220	57,64
Overweight	33.473%#	-	-	1	343	129	67	0.000	0.000	0.000	66
Obesity	37.391%#	-	-	1	916	344	67	0.012	0.001	0.022	66

SD: standard deviation, NASH: non-alcoholic steatohepatitis, HCC: hepatocellular carcinoma, CHD: coronary heart disease, T2D: type 2 diabetes. CHD, T2D, overweight, and obesity prevalence are not varied in the sensitivity analyses.
Age, sex and/or ethnicity specific values are specified in the online supplement.

Table 2. Selected model input parameter values and ranges.

Parameter				
Initialization	**Mean**	**Min**	**Max**	**Source**
Age distribution	OS1*	-	-	[68]
Sex distribution	OS2**	-	-	[68]
Ethnicity distribution	OS3***	-	-	[68]
High sugar consumption	57.278%#	38.186%	85.917%	[2,32]
Baseline transition probabilities##	**Mean chance**	**Min**	**Max**	**Source**
Non-NAFLD -> steatosis	0.0100	0.006700	0.01500	[69-77]
Non-NAFLD -> NASH	0.0003	0.000201	0.00045	[69-77]
Steatosis -> NASH	0.0060	0.004020	0.00900	[69-77]
Steatosis -> cirrhosis	0.0002	0.000134	0.00030	[69-77]
NASH -> cirrhosis	0.0020	0.001340	0.00300	[69-77]
NASH -> HCC	0.0001#	0.000067	0.00015	[69-80]
NASH -> liver death	0.0038	0.002546	0.00570	[81-84]
Cirrhosis -> HCC	0.0200#	0.013400	0.03000	[69-80]
Cirrhosis -> liver death	0.0340	0.022780	0.05100	[81-84]
HCC -> liver death	0.5000	0.335000	0.75000	[81-84]
Non-CHD -> CHD	0.0045#	0.003015	0.00675	[85,86]
CHD -> CHD death	0.0100#	0.006700	0.01500	[5,85,86]
Non-T2D -> T2D	0.0045#	0.003015	0.00675	[45,87]
T2D -> T2D death	0.0100#	0.006700	0.01500	[5,45,87]
Healthy weight -> overweight	0.0500	0.033500	0.07500	[88-91]
Healthy weight -> obese	0.0060	0.004020	0.00900	[88-91]
Overweight -> obese	0.0180	0.012060	0.02700	[88-91]
Each alive state -> non-disease related death	0.0100#	0.006700	0.01500	[5]
Risk factors (odds ratios)	**Mean value**	**Min**	**Max**	**Source**
NHB ethnicity for progression within NAFLD	0.93	0.70	1.00	[92]
Hispanic ethnicity for progression within NAFLD	1.67	1.22	2.22	[92]
Overweight for progression within NAFLD	2.19	1.60	3.38	[70,93-98]
Obesity for progression within NAFLD	3.14	2.07	5.28	[70,93-98]
High sugar consumption for progression within NAFLD	2.00	1.50	3.00	[27,99]
NAFLD for TP non-CHD -> CHD	2.31	1.66	3.62	[100-104]
Overweight for TP non-CHD -> CHD	1.22	1.12	1.32	[105-112]
Obesity for TP non-CHD -> CHD	1.60	1.43	1.79	[105-112]
T2D for TP non-CHD -> CHD	2.24	1.64	3.06	[113]
NAFLD for TP non-T2D -> T2D	2.73	1.87	4.46	[114-120]
Overweight for TP non-T2D -> T2D	2.18	1.59	3.36	[121-127]
Obesity for TP non-T2D -> T2D	3.36	2.18	5.72	[121-127]
NAFLD for progression within the BMI chain	2.19	1.60	3.38	[70,93-98]
High sugar consumption for progression within the BMI chain	2.60	1.20	6.00	[128,129]

SD: standard deviation, NAFLD: non-alcoholic fatty liver disease (steatosis, NASH & cirrhosis), NASH: non-alcoholic steatohepatitis, HCC: hepatocellular carcinoma, CHD: coronary heart disease, T2D: type 2 diabetes, NHB: non-Hispanic black.
* See online supplement table 1. ** See online supplement table 2. *** See online supplement table 3.
# Age, sex and/or ethnicity specific values are specified in the online supplement.
Transition probabilities for regression to less severe disease are specified in the online supplement.

Calibration

Incidence, prevalence, mortality and costs of overweight and obesity, T2D, and CHD were calibrated to reflect historic data from the CDC and projections from the American Heart Association (AHA) and several individual studies predicting future disease.[3,7,135-139] NASH- and cirrhosis-related HCC incidence and mortality was calibrated to historic trends reported by the CDC, and future predictions reported by the American Cancer Association.[3,140]

Validation

Validation of the model occurred via face validation, cross-validation and sensitivity analyses. Face validation was performed manually by the authors. Each chain was checked separately for functionality before merging them. Cross-validation was performed by comparing epidemiological outcomes and predictions from our model with reported results from different studies on each subject, as presented in the Discussion.

Uncertainty was assessed using deterministic and probabilistic sensitivity analysis (DSA & PSA). DSA was conducted using a five-point analysis, with the minima and maxima specified in Tables 1 & 2. If a mean and standard deviation (SD) are specified, we used a range of mean ± 1.96*SD. DSA results are only presented for the two main outcomes: total costs and DALYs averted in the year 2035. PSA was conducted using the distributions defined in Tables 1 & 2, to produce a mean and 95% confidence interval for all outcome values by running the simulation 10,000 times (each of which including the base case and two interventions).

Cohort simulation

To produce stable results, limit computational requirements, and have a cohort that remained representative of the U.S. population, we simulated a base cohort of 22,400 people, with new entry of 416 people each year, reflecting CDC population prospects.[44] Because of computational requirements, the model was built in Golang programming language (Google Inc, Mountain View, CA). Model code is publicly available via https://github.com/alexgoodell/go-mdism or can be acquired through the corresponding author. Sensitivity analyses were conducted using a 20-machine cluster (Amazon Web Services, Seattle, WA). Outcome analysis was completed in Excel 2010 (Microsoft, Redmond, WA).

Results

Incidence and mortality

The incidence of T2D, CHD, and HCC and the corresponding death rates in the year 2035 are stated in Table 3. Diabetes incidence is expected to rise over the next 20 years, resulting in an incidence rate of 1035 cases per 100,000 people. The interventions are expected to reduce this by 19.9 and 83.5 respectively. CHD incidence is expected to rise to 665 cases per 100,000 people by 2035. This can be reduced by 9.4 and 39 cases by the 20% and the 50% intervention respectively. NASH- or cirrhosis-related hepatocellular carcinoma incidence will rise to 4.4 cases per 100,000 people. Interventions could reduce this amount by 0.3 and 1.3 respectively. Liver death can be due to HCC, or it can be related to NASH or cirrhosis in the absence of HCC. Liver-related deaths will rise substantially, to 19.8 deaths per 100,000 people by 2035. This can be reduced by 1.4 or 5.8 deaths per 100,000 people by the 20% and 50% intervention, respectively.

Table 3. Annual occurring and averted events in 2035

Per 100,000 people

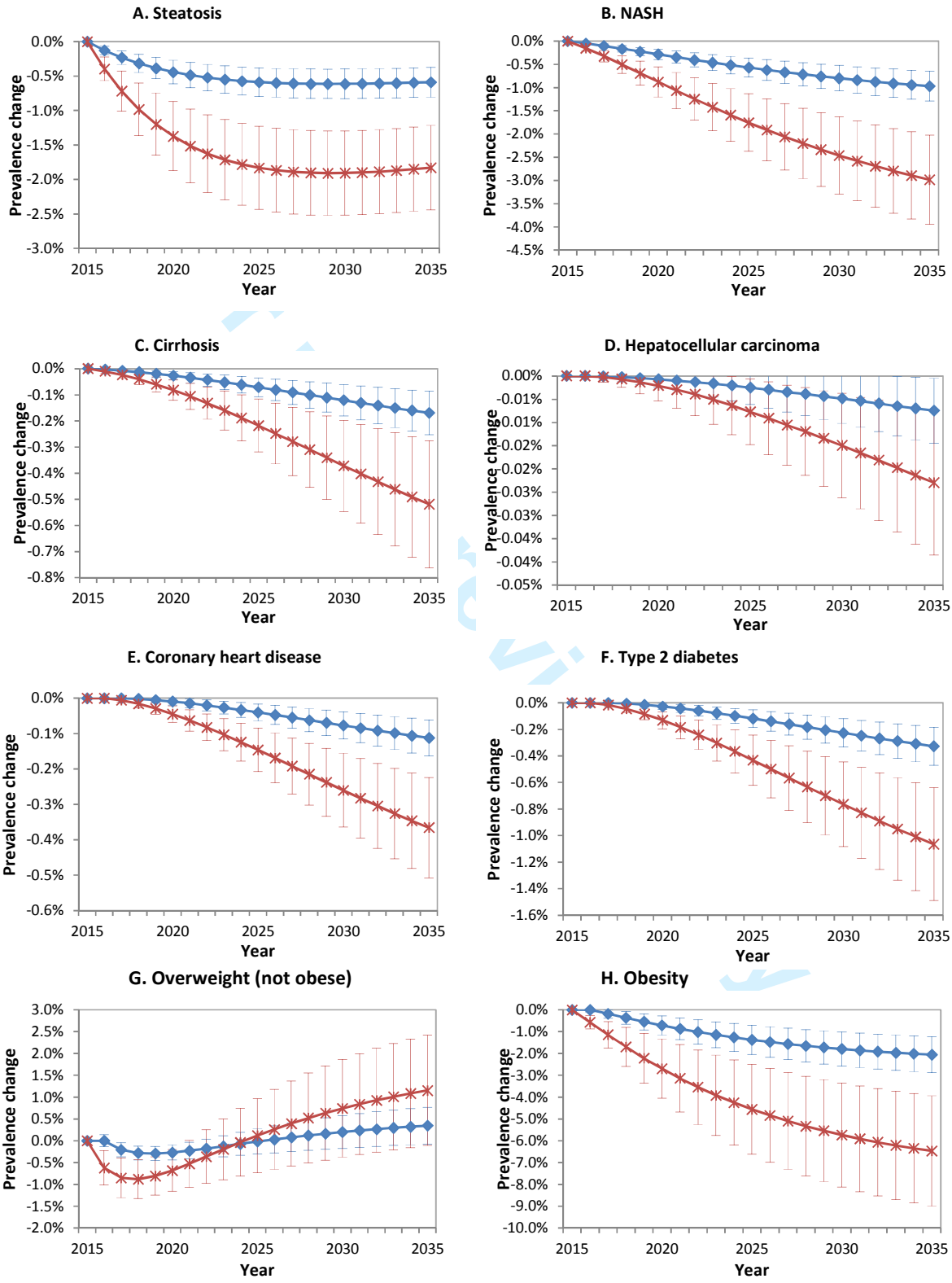
Events	No intervention (CI)	20% red. (CI)	Difference (CI)	50% red. (CI)	Difference (CI)
T2D cases	1034.6 (1031.0-1038.2)	1014.7 (1011.3-1018.2)	19.9 (12.8-27.0)	951.2 (947.9-954.4)	83.5 (76.7-90.3)
T2D deaths	576.6 (574.2-578.9)	569.3 (567.0-571.6)	7.2 (2.7-11.8)	546.4 (544.2-548.6)	30.2 (25.7-34.6)
CHD cases	665.1 (661.9-668.2)	655.6 (652.5-658.8)	9.4 (3.1-15.8)	626.1 (623.1-629.1)	39.0 (32.8-45.2)
CHD deaths	203.6 (202.2-205.0)	201.9 (200.5-203.3)	1.6 (-1.2-4.4)	197.2 (195.9-198.6)	6.3 (3.6-9.1)
HCC cases	4.4 (4.32-4.41)	4.0 (3.95-4.05)	0.3 (0.24-0.39)	3.1 (3.02-3.18)	1.3 (1.24-1.38)
Liver deaths	19.8 (19.65-20.02)	18.5 (18.29-18.63)	1.4 (1.02-1.73)	14.1 (13.94-14.21)	5.8 (5.44-6.08)

NASH: non-alcoholic steatohepatitis; HCC: hepatocellular carcinoma; CHD: coronary heart disease; T2D: type 2 diabetes mellitus; CI: 95% confidence interval. Numbers might not add up due to rounding.

Prevalence

Figure 2, graphs A-H show the reduction in prevalence of disease due to the two intervention strategies. A 20% reduction in added sugars consumption is expected to decrease prevalence of each disease state significantly after 20 years, except for overweight prevalence, which does not change significantly. A 50% reduction in added sugars consumption will proportionally affect prevalence. Effects on T2D and CHD prevalences are starting to accumulate after an initial 3-year lag period. Overweight prevalence is not reduced because people that regress to the normal weight group are replaced by others that were obese. This effect is clarified by the drop in obesity prevalence.

Figure 2, graphs A to H. reduction in population prevalence of disease due to interventions. Lines represent mean values +/- one standard deviation. 0% is the baseline, representing no intervention. The blue lines with diamonds indicate a reduction of added sugar of 20%. The red lines with crosses represent a reduction of 50%. NASH; non-alcoholic steatohepatitis.



Costs & DALYs

An overview of economic findings is presented in Table 4. Overall costs for the modeled disease states could be reduced by 2.26% (95% CI 2.23% — 2.29%) by the year 2035 with an intervention that reduces added sugars intake by 20%. The 50% intervention will reduce overall costs by 6.99% (95% CI: 6.91 — 7.08). DALY burden and averted DALYs are presented in Table 5. Total amount of DALYs could be reduced by 4.32% (95% CI: 4.27% — 4.38%) or 13.37% (95% CI: 13.24% — 13.51%) respectively. The majority of averted DALYs are due to reduced mortality.

Table 4. Annual costs spent and averted per disease state in 2035

In billions 2015 USD, discounted by 3.0% annually

State	No intervention (CI)	20% reduction (CI)	Difference (CI)	50% reduction (CI)	Difference (CI)
Steatosis	6.48 (6.43-6.53)	6.40 (6.35-6.45)	0.08 (0.080-0.082)	6.23 (6.18-6.28)	0.25 (0.248-0.255)
NASH	5.26 (5.22-5.30)	4.89 (4.85-4.93)	0.37 (0.368-0.375)	4.11 (4.08-4.14)	1.15 (1.139-1.162)
Cirrhosis	7.00 (6.93-7.07)	6.22 (6.16-6.28)	0.78 (0.772-0.791)	4.60 (4.56-4.65)	2.40 (2.371-2.429)
HCC	5.10 (5.04-5.16)	4.55 (4.50-4.60)	0.55 (0.537-0.558)	3.40 (3.36-3.44)	1.70 (1.669-1.721)
CHD	162.2 (160.9-163.6)	160.1 (158.8-161.5)	2.09 (2.06-2.12)	155.7 (154.4-157.0)	6.51 (6.43-6.58)
T2D	200.0 (198.4-201.6)	195.9 (194.3-197.5)	4.07 (4.02-4.12)	187.4 (185.9-188.9)	12.59 (12.46-12.73)
Overweight	16.4 (16.3-16.5)	16.6 (16.5-16.8)	-0.25 (-0.26 - -0.25)	17.2 (17.1-17.3)	-0.79 (-0.81 - -0.78)
Obesity	52.7 (52.3-53.1)	50.1 (49.7-50.5)	2.59 (2.57-2.62)	44.7 (44.3-45.0)	8.03 (7.95-8.12)
Total	**455.1** (451.4-458.9)	**444.9** (441.2-448.5)	**10.3** (10.2-10.4)	**423.3** (419.8-426.8)	**31.8** (31.5-32.2)

NASH: non-alcoholic steatohepatitis; HCC: hepatocellular carcinoma; CHD: coronary heart disease; T2D: type 2 diabetes mellitus; CI: 95% confidence interval. Numbers might not add up due to rounding.

Table 5. Annual occurring and averted DALYs in 2035

In millions

State	No intervention (CI)	20% reduction (CI)	Difference (CI)	50% reduction (CI)	Difference (CI)
NASH	2.97 (2.955-2.988)	2.76 (2.746-2.777)	0.210 (0.209-0.212)	2.32 (2.309-2.334)	0.650 (0.645-0.655)
Cirrhosis	0.48 (0.475-0.482)	0.42 (0.422-0.428)	0.053 (0.053-0.054)	0.31 (0.312-0.316)	0.164 (0.162-0.165)
HCC	3.06 (3.046-3.084)	2.78 (2.765-2.799)	0.283 (0.279-0.283)	2.19 (2.180-2.206)	0.872 (0.863-0.881)
CHD	2.32 (2.305-2.330)	2.29 (2.276-2.302)	0.028 (0.028-0.029)	2.23 (2.217-2.242)	0.088 (0.086-0.090)
T2D	8.21 (8.180-8.248)	8.06 (8.023-8.089)	0.158 (0.155-0.160)	7.72 (7.690-7.752)	0.492 (0.487-0.498)
Obesity	0.69 (0.689-0.700)	0.66 (0.655-0.666)	0.034 (0.034-0.035)	0.59 (0.584-0.593)	0.106 (0.105-0.107)
Total	**17.74** (17.65-17.83)	**16.97** (16.89-17.06)	**0.767** (0.757-0.777)	**15.37** (15.29-15.44)	**2.372** (2.348-2.396)
From mortality	11.94	11.50	0.439	10.58	1.357
From morbidity	5.80	5.47	0.328	4.78	1.015

NASH: non-alcoholic steatohepatitis; HCC: hepatocellular carcinoma; CHD: coronary heart disease; T2D: type 2 diabetes mellitus; CI: 95% confidence interval. Numbers might not add up due to rounding.

Sensitivity analyses

We show tornado diagrams for the two most important outcomes: annual costs and DALYs averted by the year 2035 due to an intervention that reduces sugar consumption by 20%. The diagrams show the impact that specific input parameters had on selected results. The ten variables that caused the widest range in results are shown. When varying individual variables, the annual savings by the year 2035 range from 7.9 to 17.1 billion 2015 USD. The tornado diagram (Figure 3) shows that the interaction between high added sugars consumption and the progression within the NAFLD and BMI chains had the greatest impact on total costs averted. In the tornado diagram for total annual DALYs averted by the 20% intervention in the year 2035 (Figure 4), assigned disability weights had the greatest impact. Total DALYs averted ranged between 0.36 and 1.41 million.

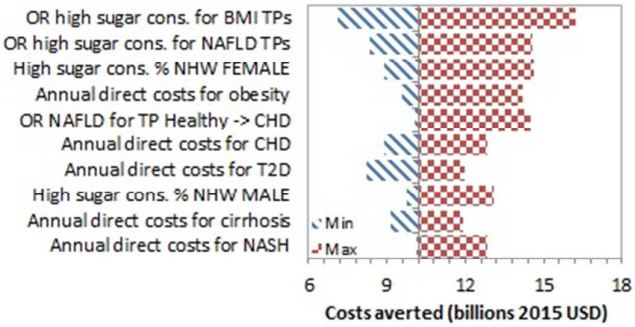


Figure 3. Tornado diagram of the ten most critical variables on total costs averted in the year 2035.

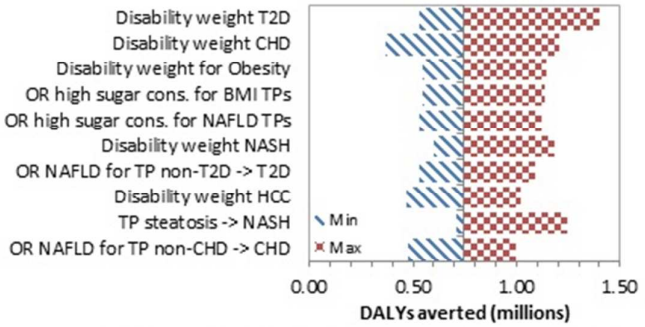


Figure 4. Tornado diagram of the ten most critical variables on total DALYs averted in the year 2035.

Discussion

This model shows clear and significant benefits for interventions that reduce consumption of added sugars. A reduction by 20% will reduce annual direct medical costs for U.S. adults by more than 10 billion USD (2015 dollars) by the year 2035. A 50% reduction will save an additional 21 billion. Together with these economic benefits, population health will significantly improve. A total of 770,000 DALYs could be averted with a 20% reduction in consumption. A 50% reduction in consumption will avert another 1.6 million DALYs. These health and economic benefits are the direct result of lower incidence, prevalence, and mortality of disease in U.S. adults due to lower added sugars consumption.

Fit with current knowledge

The estimate for health and economic benefit of this model is similar to a number of previously performed economic evaluations. Basu et al. found a reduction in diabetes incidence of 21.7 cases per 100,000 people with a reduction of 20% of added sugars through a cap and trade approach, limiting the amount of sugars in the food supply.[45] We found a reduction of 19.9 cases per 100,000 people, indicating a similar absolute effect size. CHD incidence reduction is estimated to be about 1.5-fold higher than found in a similar study, but we argue that this is mainly because the other study simulated a 20% tax on sugar-sweetened beverages, and therefore the overall added sugars consumption reduction was smaller than the 20% reduction we simulated.[41] In an econometric analysis looking backward in time, Basu et al. found a delay of 3 years between changes in sugar consumption and prevalence of diabetes.[31] Similarly, we found a delay of 3 years going forward in time between reduction of consumption and reduction in prevalence of disease. Prevalence of obesity has been reported to drop by 1.5% — 10% due to a reduction of added sugars by 10% — 20%.[40-42] Our result of 2.1% reduction in obesity prevalence seems to reflect our conservative approach in determining input parameter values.

Costs savings are bigger in our model compared to other models.[41,43,44] This was for three reasons. First, some other models do not use added sugars as a whole but use SSB's, resulting in a smaller effect. Second, our overall prevalence of T2D and CHD is higher than most other models. We have calibrated our model to historic trends reported by the CDC and to future projections of the AHA, ADA and separate studies predicting future prevalence, and therefore argue that our estimate is valid. Third, and perhaps most importantly, no other studies predict future NAFLD prevalence. We present the first model that estimates the effects of sugar interventions on NAFLD prevalence and associated costs and DALYs.

Strengths and limitations

This study is the first of its kind to model the effect of added sugars on NAFLD as well as on BMI, and therefore it captures a more complete picture of the possible health and economic benefits of interventions that reduce intake of added sugars. Though taxing sugar-sweetened products, mainly beverages, has been widely suggested as a public health strategy, other approaches, e.g. a cap and trade approach, have also been suggested.[39-45] We have constructed this model to be applicable with each of these interventions, so that it does not rely on any consumption statistics other than added sugars as a whole. A limitation to this approach is that our model does not incorporate a possible change to non-sugared caloric products, containing protein, fat, or other carbohydrates. It is important that effort is put into investigating self- and cross-elasticity of sugar-sweetened products to determine the effect of these caloric replacements. Though this is a limitation, research has clearly shown that the contribution of added sugars in relation to their excessive intake is likely the most important consumption factor for metabolic derangement. Furthermore, added sugars consumption was fixed throughout the simulation for each individual (though specified per sex and ethnic group). We could not find sufficient data on changes in sugar consumption related to incident disease and therefore could not model these changes accurately enough. We argue that keeping the sugar consumption fixed is likely more accurate than modeling changing sugar consumption based solely on age. The main limitation of this model is the uncertainty of input parameters. The pathophysiology of NAFLD and its associations with other metabolic diseases is still widely under investigation. Therefore, baseline transition probabilities and interaction (OR) values are still somewhat uncertain. Many studies report associations, but very few studies report plausible quantitative causal relationships. There are several reasons that explain this low number of studies. First, it is hard to accurately determine the individual components in an individuals' diet. Second, there is no cheap, accurate way to determine the presence of individual NAFLD states. Commonly used ultrasonography possibly underestimates the prevalence of NAFLD and does not differentiate between steatosis and NASH, while up to 79% of patients may have serum alanine aminotransferase (ALT) levels within the normal reference range of < 40 U/mL.[9,141] We have addressed this uncertainty by taking wide ranges in the probabilistic sensitivity analysis, which determines the SD and 95% confidence interval around the results. Results remain statistically significant, indicating that any minor inaccuracies in input parameter values will not render the effects insignificant. Ultimately, it is desirable to determine incidence of NAFLD states and risk factor relative risks in independent prospective cohort studies, and to assess intervention effectiveness via randomized controlled trials. This model can be refined and updated when new data become available.

It is possible that our results might still underestimate the total effects. We only modeled diagnosed disease, we took a conservative approach when determining input parameter values, and we did not take societal costs into account. Real health, healthcare, and economic benefits are likely larger than estimated.

Implications

This model clarifies the significant health and economic benefits that could be achieved by a public health intervention that reduces consumption of added sugars in U.S. adults. We recommend that health policy makers review their options to implement interventions.

Future research

Future research should focus on establishing a more precise measurement of NAFLD prevalence, incidence, and risk factors. Furthermore, magnitude and effects of switching to different food groups should be assessed. Finally, changes in added sugars consumption related to ageing and incident disease should be more intensively investigated.

Contributor statement

RAV was involved in conceptualizing the study, reviewing literature, conducting the modeling analysis, analyzing the data and writing the manuscript. AJG was involved in conducting the modeling analysis and in editing the paper. LAR and RHL were involved in conceptualizing the model, providing and structuring data inputs and editing the manuscript. JGK was involved in conceptualization of the model, input data review, guiding the modeling process and providing a critical review of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare no direct conflicts of interest. However, Dr. Lustig has received author fees from Hudson Street Press regarding his authorship of: "Fat Chance: Beating the Odds Against Sugar, Processed Food, Obesity, and Disease"; "The Fat Chance Cookbook"; and "Sugar has 56 names: A Shopper's Guide". He is also the unpaid president of the non-profit Institute for Responsible Nutrition.

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Data sharing statement

An online supplement will be made available containing comprehensive tables of used input data. The modeling code is available through github: https://github.com/alexgoodell/go-mdism or can be accessed via the corresponding author.

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Online supplement

Non-alcoholic fatty liver disease as a mediator of sugar effects; implications for the health and economic benefits of interventions in the US

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Table 1. Selected model parameter values and ranges.

Parameter					
Initialization	**Distribution**	**Mean**	**Min**	**Max**	**Source**
Age distribution	Fixed	OS2*1	-	-	[1]
Sex distribution	Fixed	OS3*2	-	-	[1]
Ethnicity distribution	Fixed	OS4*3	-	-	[1]
Steatosis prevalence	Beta	27.955%*4	18.637%	41.933%	[2-4]
NASH prevalence	Beta	3.141%*4	2.094%	4.712%	[2-4]
Cirrhosis prevalence	Beta	0.314%*4	0.209%	0.471%	[5-8]
HCC prevalence	Beta	0.025%*4	0.017%	0.038%	[9,10]
CHD prevalence	Fixed	6.544%*5	-	-	[11]
T2D prevalence	Fixed	9.447%*6	-	-	[11]
Overweight prevalence	Fixed	33.473%*7	-	-	[11]
Obesity prevalence	Fixed	37.391%*8	-	-	[11]
High sugar consumption	Beta	57.278%*9	38.186%	85.917%	[12,13]
Baseline transition probabilities	**Distribution**	**Mean chance**	**Min**	**Max**	**Source**
Non-NAFLD -> steatosis	Beta	0.0100	0.006700	0.01500	[14-22]
Non-NAFLD -> NASH	Beta	0.0003	0.000201	0.00045	[14-22]
Steatosis -> non-NAFLD	Beta	0.0200	0.013400	0.03000	[14-22]
Steatosis -> NASH	Beta	0.0060	0.004020	0.00900	[14-22]
Steatosis -> cirrhosis	Beta	0.0002	0.000134	0.00030	[14-22]
NASH -> non-NAFLD	Beta	0.0010	0.000670	0.00150	[14-22]
NASH -> steatosis	Beta	0.0200	0.013400	0.03000	[14-22]
NASH -> cirrhosis	Beta	0.0020	0.001340	0.00300	[14-22]
NASH -> HCC	Beta	0.0001*10	0.000067	0.00015	[14-25]
NASH -> liver death	Beta	0.0038	0.002546	0.00570	[26-29]
Cirrhosis -> HCC	Beta	0.0200*10	0.013400	0.03000	[14-25]
Cirrhosis -> liver death	Beta	0.0340	0.022780	0.05100	[26-29]
HCC -> liver death	Beta	0.5000	0.335000	0.75000	[26-29]
Non-CHD -> CHD	Beta	0.0045*11	0.003015	0.00675	[30,31]
CHD -> CHD death	Beta	0.0100*12	0.006700	0.01500	[30-32]
Non-T2D -> T2D	Beta	0.0045*13	0.003015	0.00675	[33,34]
T2D -> T2D death	Beta	0.0100*14	0.006700	0.01500	[32-34]
Healthy weight -> overweight	Beta	0.0500	0.033500	0.07500	[35-38]
Healthy weight -> obese	Beta	0.0060	0.004020	0.00900	[35-38]
Overweight -> healthy weight	Beta	0.0500	0.033500	0.07500	[35-38]
Overweight -> obese	Beta	0.0180	0.012060	0.02700	[35-38]
Obese-> healthy weight	Beta	0.0060	0.004020	0.00900	[35-38]
Obese -> overweight	Beta	0.0350	0.023450	0.05250	[35-38]
Each alive state -> non-disease related death	Beta	0.0100*15	0.006700	0.01500	[32]
Risk factors	**Distribution**	**Mean value**	**Min**	**Max**	**Source**
NHB ethnicity for progression within NAFLD	Beta	0.93	0.70	1.00	[39]
Hispanic ethnicity for progression within NAFLD	Beta	1.67	1.22	2.22	[39]
Overweight for progression within NAFLD	Beta	2.19	1.60	3.38	[15,40-45]
Obesity for progression within NAFLD	Beta	3.14	2.07	5.28	[15,40-45]
High sugar consumption for progression within NAFLD	Beta	2.00	1.50	3.00	[46,47]
NAFLD for TP non-CHD -> CHD	Beta	2.31	1.66	3.62	[48-52]
Overweight for TP non-CHD -> CHD	Beta	1.22	1.12	1.32	[53-60]
Obesity for TP non-CHD -> CHD	Beta	1.60	1.43	1.79	[53-60]
T2D for TP non-CHD -> CHD	Beta	2.24	1.64	3.06	[61]
NAFLD for TP non-T2D -> T2D	Beta	2.73	1.87	4.46	[62-68]
Overweight for TP non-T2D -> T2D	Beta	2.18	1.59	3.36	[69-75]
Obesity for TP non-T2D -> T2D	Beta	3.36	2.18	5.72	[69-75]
NAFLD for progression within the BMI chain	Beta	2.19	1.60	3.38	[15,40-45]
High sugar consumption for progression within the BMI chain	Beta	2.60	1.20	6.00	[76,77]
Regression rates	**Distribution**	**Mean value**	**Min**	**Max**	**Source**
CHD incidence regression rate/year	Beta	0.985	0.970	1.00	[78-81]
CHD mortality regression rate/year	Beta	0.979	0.958	1.00	[78-81]
Non-disease mortality regression rate/year (20-30)	Beta	1.000	0.990	1.00	[32]
Non-disease mortality regression rate/year (30-55)	Beta	0.980	0.960	1.00	[32]
Non-disease mortality regression rate/year (55+)	Beta	0.970	0.940	1.00	[32]

Table 1. Continued

Costs (annual direct medical, in 2015 USD)	Distribution	Mean value	SD		Source
Steatosis	Gamma	134	50		[82-85]
NASH	Gamma	267	100		[82-85]
Cirrhosis	Gamma	2861	1073		[86]
HCC	Gamma	42644	15992		[87,88]
CHD	Gamma	13233	4962		[89]
T2D	Gamma	8170	3064		[90]
Overweight	Gamma	343	129		[91]
Obesity	Gamma	916	344		[91]
Disability weights	**Distribution**	**Mean value**	**Min**	**Max**	**Source**
NASH	Beta	0.033	0.017	0.066	[3,84]
Cirrhosis	Beta	0.194	0.127	0.273	[92]
HCC	Beta	0.294	0.199	0.411	[92]
CHD	Beta	0.066	0.043	0.095	[92]
T2D	Beta	0.150	0.080	0.220	[92]
Obesity	Beta	0.012	0.001	0.022	[93]

SD: standard deviation, CHD: coronary heart disease, T2D: type 2 diabetes, NAFLD: non-alcoholic fatty liver disease (steatosis, NASH & cirrhosis), NASH: non-alcoholic steatohepatitis, HCC: hepatocellular carcinoma, Hisp: Hispanic, NHW: non-Hispanic white, NHB: non-Hispanic black, TP: transition probability, OR: odds ratio

*1 See online supplement table 2. *2 See online supplement table 3. *3 See online supplement table 4. *4 See online supplement table 5. *5 See online supplement table 6. *6 See online supplement table 7. *7 See online supplement table 8. *8 See online supplement table 9. *9 See online supplement table 10. *10 See online supplement table 11. *11 See online supplement table 12. *12 See online supplement table 13. *13 See online supplement table 14. *14 See online supplement table 15. *15 See online supplement table 16.

Table 2. Age distribution.[1]

Age	Percentage
20	1.9194
21	1.9194
22	1.9194
23	1.9194
24	1.9194
25	1.8701
26	1.8701
27	1.8701
28	1.8701
29	1.8701
30	1.7749
31	1.7749
32	1.7749
33	1.7749
34	1.7749
35	1.7757
36	1.7757
37	1.7757
38	1.7757
39	1.7757
40	1.8487
41	1.8487
42	1.8487
43	1.8487
44	1.8487
45	2.0018
46	2.0018
47	2.0018
48	2.0018
49	2.0018
50	1.9767
51	1.9767
52	1.9767
53	1.9767
54	1.9767
55	1.7505
56	1.7505
57	1.7505
58	1.7505
59	1.7505
60	1.5024
61	1.5024
62	1.5024
63	1.5024
64	1.5024
65	1.1073
66	1.1073
67	1.1073
68	1.1073
69	1.1073
70	0.8256
71	0.8256
72	0.8256
73	0.8256
74	0.8256
75	0.6473
76	0.6473
77	0.6473
78	0.6473
79	0.6473
80	0.5093
81	0.5093
82	0.5093
83	0.5093
84	0.5093
85+	2.4517

Table 3. Sex distribution.[1]

Sex	Percentage
Male	48.4388
Female	51.5612

Table 4. Ethnic distribution.[1]

Age	Percentage
Hispanic	14.0377
Non-hispanic White	74.3771
Non-hispanic Black	11.5852

Table 5. Non-alcoholic fatty liver disease prevalence percentage at start of simulation.[2-10]

Ethnicity	Steatosis	NASH	Cirrhosis	Hepatocellular carcinoma
Hispanic	40.05	4.5	0.45	0.0363
NH-White	26.70	3.0	0.30	0.0242
NH-Black	21.36	2.4	0.24	0.0194

Table 6. Coronary heart disease prevalence percentage at the start of the simulation.[11]

Sex	Ethnicity	Age	Percentage with CHD
Male	Hispanic	20-35	0.00
Male	Hispanic	35-44	1.30
Male	Hispanic	45-54	3.90
Male	Hispanic	55-64	10.60
Male	Hispanic	65-74	19.20
Male	Hispanic	75-84	23.50
Male	Hispanic	85+	23.80
Male	NH-White	20-35	0.00
Male	NH-White	35-44	1.20
Male	NH-White	45-54	6.00
Male	NH-White	55-64	13.80
Male	NH-White	65-74	23.30
Male	NH-White	75-84	31.80
Male	NH-White	85+	38.60
Male	NH-Black	20-35	0.00
Male	NH-Black	35-44	1.70
Male	NH-Black	45-54	7.50
Male	NH-Black	55-64	14.20
Male	NH-Black	65-74	16.90
Male	NH-Black	75-84	22.10
Male	NH-Black	85+	18.80
Female	Hispanic	20-35	0.00
Female	Hispanic	35-44	1.20
Female	Hispanic	45-54	3.00
Female	Hispanic	55-64	6.70
Female	Hispanic	65-74	16.20
Female	Hispanic	75-84	20.30
Female	Hispanic	85+	23.90
Female	NH-White	20-35	0.00
Female	NH-White	35-44	0.90
Female	NH-White	45-54	3.30
Female	NH-White	55-64	6.70
Female	NH-White	65-74	11.20
Female	NH-White	75-84	18.40
Female	NH-White	85+	24.30
Female	NH-Black	20-35	0.00
Female	NH-Black	35-44	1.20
Female	NH-Black	45-54	5.30
Female	NH-Black	55-64	11.20
Female	NH-Black	65-74	17.40
Female	NH-Black	75-84	19.80
Female	NH-Black	85+	21.80

Table 7. Type 2 diabetes prevalence percentage at the start of the simulation.[11]

Sex	Ethnicity	Age	Percentage with T2D
Male	Hispanic	20-24	0.90
Male	Hispanic	25-44	3.50
Male	Hispanic	45-54	14.20
Male	Hispanic	55-64	25.80
Male	Hispanic	65-74	32.80
Male	Hispanic	75-84	31.30
Male	Hispanic	85+	23.80
Male	NH-White	20-24	0.90
Male	NH-White	25-44	2.40
Male	NH-White	45-54	8.20
Male	NH-White	55-64	14.70
Male	NH-White	65-74	20.10
Male	NH-White	75-84	20.50
Male	NH-White	85+	17.90
Male	NH-Black	20-24	1.00
Male	NH-Black	25-44	5.00
Male	NH-Black	45-54	15.00
Male	NH-Black	55-64	24.00
Male	NH-Black	65-74	26.50
Male	NH-Black	75-84	39.00
Male	NH-Black	85+	18.70
Female	Hispanic	20-24	0.90
Female	Hispanic	25-44	3.60
Female	Hispanic	45-54	10.30
Female	Hispanic	55-64	24.00
Female	Hispanic	65-74	34.80
Female	Hispanic	75-84	32.40
Female	Hispanic	85+	22.80
Female	NH-White	20-24	1.20
Female	NH-White	25-44	2.80
Female	NH-White	45-54	7.30
Female	NH-White	55-64	12.10
Female	NH-White	65-74	17.00
Female	NH-White	75-84	17.10
Female	NH-White	85+	12.10
Female	NH-Black	20-24	1.00
Female	NH-Black	25-44	5.20
Female	NH-Black	45-54	10.90
Female	NH-Black	55-64	24.10
Female	NH-Black	65-74	32.60
Female	NH-Black	75-84	31.60
Female	NH-Black	85+	20.20

Table 8. Overweight and obesity prevalence percentages at the start of the simulation.[11]

Sex	Ethnicity	Age	Overweight percentage	Obesity percentage
Male	Hispanic	20-44	39.5	36.8
Male	Hispanic	45-64	43.8	41.0
Male	Hispanic	65+	42.8	44.7
Male	White	20-44	35.7	31.6
Male	White	45-64	40.8	39.0
Male	White	65+	42.5	36.9
Male	Black	20-44	28.7	36.9
Male	Black	45-64	34.3	40.6
Male	Black	65+	37.0	36.7
Female	Hispanic	20-44	33.2	36.8
Female	Hispanic	45-64	32.9	52.9
Female	Hispanic	65+	33.0	49.3
Female	White	20-44	25.3	28.0
Female	White	45-64	32.6	37.4
Female	White	65+	29.5	44.3
Female	Black	20-44	22.3	56.1
Female	Black	45-64	27.1	61.8
Female	Black	65+	25.8	53.7

Table 9. Added sugar consumption distributions.[12,13]

Sex	Ethnicity	Consumption group	% in low vs high risk group
Male	Hispanic	Low sugar consumption	36.40%
Male	Hispanic	High sugar consumption	63.60%
Male	Non-hispanic White	Low sugar consumption	36.40%
Male	Non-hispanic White	High sugar consumption	63.60%
Male	Non-hispanic Black	Low sugar consumption	34.10%
Male	Non-hispanic Black	High sugar consumption	65.90%
Female	Hispanic	Low sugar consumption	52.80%
Female	Hispanic	High sugar consumption	47.20%
Female	Non-hispanic White	Low sugar consumption	49.30%
Female	Non-hispanic White	High sugar consumption	50.70%
Female	Non-hispanic Black	Low sugar consumption	41.70%
Female	Non-hispanic Black	High sugar consumption	58.30%

Table 10. Hepatocellular carcinoma incidence rate from NASH.[14-25]

Age	Incidence rate
40 to 44 years	3.64216E-05
45 to 49 years	4.64842E-05
50 to 54 years	5.93269E-05
55 to 59 years	7.57179E-05
60 to 64 years	9.66373E-05
65 to 69 years	0.000123336
70 to 74 years	0.000157412
75 to 79 years	0.000200902
80 years and over	0.000256408

Table 11. Hepatocellular carcinoma incidence rate from cirrhosis.[14-25]

Age	Incidence rate
40 to 44 years	0.008844339
45 to 49 years	0.011287867
50 to 54 years	0.014406497
55 to 59 years	0.018386746
60 to 64 years	0.023466665
65 to 69 years	0.029950073
70 to 74 years	0.038224725
75 to 79 years	0.048785512
80 years and over	0.062264050

Table 12. Coronary heart disease incidence rate (in %).[30,31]

Year	<35	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
2010	0.0	0.0516	0.0516	0.2007	0.2007	0.3519	0.3519	0.5869	0.5869	1.4447	1.4447	3.0621
2011	0.0	0.0508	0.0508	0.1976	0.1976	0.3466	0.3466	0.5781	0.5781	1.4230	1.4230	3.0162
2012	0.0	0.0501	0.0501	0.1947	0.1947	0.3414	0.3414	0.5694	0.5694	1.4017	1.4017	2.9709
2013	0.0	0.0493	0.0493	0.1918	0.1918	0.3363	0.3363	0.5609	0.5609	1.3806	1.3806	2.9263
2014	0.0	0.0486	0.0486	0.1889	0.1889	0.3312	0.3312	0.5525	0.5525	1.3599	1.3599	2.8825
2015	0.0	0.0478	0.0478	0.1860	0.1860	0.3262	0.3262	0.5442	0.5442	1.3395	1.3395	2.8392
2016	0.0	0.0471	0.0471	0.1833	0.1833	0.3214	0.3214	0.5360	0.5360	1.3194	1.3194	2.7966
2017	0.0	0.0464	0.0464	0.1805	0.1805	0.3165	0.3165	0.5280	0.5280	1.2997	1.2997	2.7547
2018	0.0	0.0457	0.0457	0.1778	0.1778	0.3118	0.3118	0.5201	0.5201	1.2802	1.2802	2.7134
2019	0.0	0.0450	0.0450	0.1751	0.1751	0.3071	0.3071	0.5123	0.5123	1.2610	1.2610	2.6727
2020	0.0	0.0444	0.0444	0.1725	0.1725	0.3025	0.3025	0.5046	0.5046	1.2420	1.2420	2.6326
2021	0.0	0.0437	0.0437	0.1699	0.1699	0.2980	0.2980	0.4970	0.4970	1.2234	1.2234	2.5931
2022	0.0	0.0430	0.0430	0.1674	0.1674	0.2935	0.2935	0.4896	0.4896	1.2051	1.2051	2.5542
2023	0.0	0.0424	0.0424	0.1649	0.1649	0.2891	0.2891	0.4822	0.4822	1.1870	1.1870	2.5159
2024	0.0	0.0418	0.0418	0.1624	0.1624	0.2848	0.2848	0.4750	0.4750	1.1692	1.1692	2.4781
2025	0.0	0.0411	0.0411	0.1600	0.1600	0.2805	0.2805	0.4679	0.4679	1.1516	1.1516	2.4410
2026	0.0	0.0405	0.0405	0.1576	0.1576	0.2763	0.2763	0.4608	0.4608	1.1344	1.1344	2.4043
2027	0.0	0.0399	0.0399	0.1552	0.1552	0.2721	0.2721	0.4539	0.4539	1.1174	1.1174	2.3683
2028	0.0	0.0393	0.0393	0.1529	0.1529	0.2681	0.2681	0.4471	0.4471	1.1006	1.1006	2.3328
2029	0.0	0.0387	0.0387	0.1506	0.1506	0.2640	0.2640	0.4404	0.4404	1.0841	1.0841	2.2978
2030	0.0	0.0381	0.0381	0.1483	0.1483	0.2601	0.2601	0.4338	0.4338	1.0678	1.0678	2.2633
2031	0.0	0.0376	0.0376	0.1461	0.1461	0.2562	0.2562	0.4273	0.4273	1.0518	1.0518	2.2293
2032	0.0	0.0370	0.0370	0.1439	0.1439	0.2523	0.2523	0.4209	0.4209	1.0360	1.0360	2.1959
2033	0.0	0.0364	0.0364	0.1417	0.1417	0.2485	0.2485	0.4146	0.4146	1.0205	1.0205	2.1630
2034	0.0	0.0359	0.0359	0.1396	0.1396	0.2448	0.2448	0.4084	0.4084	1.0052	1.0052	2.1305
2035	0.0	0.0354	0.0354	0.1375	0.1375	0.2411	0.2411	0.4022	0.4022	0.9901	0.9901	2.0986

Table 13. Coronary heart disease mortality rate (in %).[30-32]

Year	<35	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
2010	0.0000	0.5067	0.8506	0.9493	1.3778	1.4767	1.4179	1.1071	2.1109	2.2865	3.9970	9.4859
2011	0.0000	0.4960	0.8327	0.9293	1.3489	1.4457	1.3881	1.0839	2.0665	2.2385	3.9130	9.2867
2012	0.0000	0.4856	0.8152	0.9098	1.3205	1.4153	1.3590	1.0611	2.0231	2.1914	3.8309	9.0917
2013	0.0000	0.4754	0.7981	0.8907	1.2928	1.3856	1.3304	1.0388	1.9807	2.1454	3.7504	8.9007
2014	0.0000	0.4654	0.7813	0.8720	1.2657	1.3565	1.3025	1.0170	1.9391	2.1004	3.6717	8.7138
2015	0.0000	0.4557	0.7649	0.8537	1.2391	1.3280	1.2751	0.9956	1.8983	2.0563	3.5946	8.5308
2016	0.0000	0.4461	0.7489	0.8358	1.2131	1.3002	1.2484	0.9747	1.8585	2.0131	3.5191	8.3517
2017	0.0000	0.4367	0.7331	0.8182	1.1876	1.2728	1.2221	0.9543	1.8195	1.9708	3.4452	8.1763
2018	0.0000	0.4275	0.7177	0.8010	1.1626	1.2461	1.1965	0.9342	1.7812	1.9294	3.3728	8.0046
2019	0.0000	0.4186	0.7027	0.7842	1.1382	1.2199	1.1714	0.9146	1.7438	1.8889	3.3020	7.8365
2020	0.0000	0.4098	0.6879	0.7677	1.1143	1.1943	1.1468	0.8954	1.7072	1.8492	3.2326	7.6719
2021	0.0000	0.4012	0.6735	0.7516	1.0909	1.1692	1.1227	0.8766	1.6714	1.8104	3.1648	7.5108
2022	0.0000	0.3927	0.6593	0.7358	1.0680	1.1447	1.0991	0.8582	1.6363	1.7724	3.0983	7.3531
2023	0.0000	0.3845	0.6455	0.7204	1.0456	1.1207	1.0760	0.8402	1.6019	1.7352	3.0332	7.1987
2024	0.0000	0.3764	0.6319	0.7053	1.0236	1.0971	1.0534	0.8225	1.5683	1.6987	2.9695	7.0475
2025	0.0000	0.3685	0.6187	0.6905	1.0021	1.0741	1.0313	0.8052	1.5353	1.6631	2.9072	6.8995
2026	0.0000	0.3608	0.6057	0.6760	0.9811	1.0515	1.0096	0.7883	1.5031	1.6281	2.8461	6.7546
2027	0.0000	0.3532	0.5929	0.6618	0.9605	1.0294	0.9884	0.7718	1.4715	1.5939	2.7864	6.6128
2028	0.0000	0.3458	0.5805	0.6479	0.9403	1.0078	0.9677	0.7556	1.4406	1.5605	2.7278	6.4739
2029	0.0000	0.3385	0.5683	0.6343	0.9206	0.9867	0.9474	0.7397	1.4104	1.5277	2.6706	6.3380
2030	0.0000	0.3314	0.5564	0.6209	0.9012	0.9659	0.9275	0.7242	1.3808	1.4956	2.6145	6.2049
2031	0.0000	0.3245	0.5447	0.6079	0.8823	0.9457	0.9080	0.7090	1.3518	1.4642	2.5596	6.0746
2032	0.0000	0.3176	0.5332	0.5951	0.8638	0.9258	0.8889	0.6941	1.3234	1.4335	2.5058	5.9470
2033	0.0000	0.3110	0.5220	0.5826	0.8456	0.9064	0.8703	0.6795	1.2956	1.4034	2.4532	5.8221
2034	0.0000	0.3044	0.5111	0.5704	0.8279	0.8873	0.8520	0.6652	1.2684	1.3739	2.4017	5.6998
2035	0.0000	0.2981	0.5004	0.5584	0.8105	0.8687	0.8341	0.6513	1.2417	1.3450	2.3513	5.5801

Table 14. Type 2 diabetes incidence rate.[33,34]

Age	Incidence rate
20-24	0.000447
25-29	0.000762
30-34	0.001090
35-39	0.001625
40-44	0.002880
45-49	0.003575
50-54	0.004957
55-59	0.005071
60-64	0.004662
65-69	0.004450
70-74	0.003925
75-79	0.003609
80+	0.003240

Table 15. Type 2 diabetes mortality rate.[32-34]

Age	Mortality rate
20-24	0.006177
25-29	0.009399
30-34	0.009399
35-39	0.009399
40-44	0.009399
45-49	0.013706
50-54	0.013706
55-59	0.020137
60-64	0.020137
65-69	0.031904
70-74	0.031904
75-79	0.068313
80+	0.068313

Table 16. Non-disease related mortality rate (in %).[32]

Year	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
2010	0.086	0.093	0.105	0.128	0.178	0.275	0.411	0.583	0.822	1.242	1.909	3.038	4.952	11.162
2011	0.086	0.093	0.105	0.125	0.174	0.269	0.403	0.571	0.797	1.205	1.851	2.947	4.804	10.828
2012	0.086	0.093	0.105	0.123	0.171	0.264	0.395	0.560	0.773	1.169	1.796	2.859	4.660	10.503
2013	0.086	0.093	0.105	0.120	0.167	0.259	0.387	0.548	0.750	1.133	1.742	2.773	4.520	10.188
2014	0.086	0.093	0.105	0.118	0.164	0.253	0.379	0.537	0.728	1.099	1.690	2.690	4.384	9.882
2015	0.086	0.093	0.105	0.115	0.161	0.248	0.372	0.527	0.706	1.066	1.639	2.609	4.253	9.586
2016	0.086	0.093	0.105	0.113	0.158	0.243	0.364	0.516	0.685	1.034	1.590	2.531	4.125	9.298
2017	0.086	0.093	0.105	0.111	0.154	0.239	0.357	0.506	0.664	1.003	1.542	2.455	4.002	9.019
2018	0.086	0.093	0.105	0.109	0.151	0.234	0.350	0.496	0.644	0.973	1.496	2.381	3.881	8.749
2019	0.086	0.093	0.105	0.106	0.148	0.229	0.343	0.486	0.625	0.944	1.451	2.310	3.765	8.486
2020	0.086	0.093	0.105	0.104	0.145	0.225	0.336	0.476	0.606	0.916	1.408	2.241	3.652	8.231
2021	0.086	0.093	0.105	0.102	0.142	0.220	0.329	0.467	0.588	0.888	1.365	2.173	3.543	7.985
2022	0.086	0.093	0.105	0.100	0.140	0.216	0.323	0.457	0.570	0.862	1.324	2.108	3.436	7.745
2023	0.086	0.093	0.105	0.098	0.137	0.211	0.316	0.448	0.553	0.836	1.285	2.045	3.333	7.513
2024	0.086	0.093	0.105	0.096	0.134	0.207	0.310	0.439	0.537	0.811	1.246	1.984	3.233	7.287
2025	0.086	0.093	0.105	0.094	0.131	0.203	0.304	0.430	0.521	0.786	1.209	1.924	3.136	7.069
2026	0.086	0.093	0.105	0.092	0.129	0.199	0.298	0.422	0.505	0.763	1.172	1.866	3.042	6.857
2027	0.086	0.093	0.105	0.090	0.126	0.195	0.292	0.413	0.490	0.740	1.137	1.810	2.951	6.651
2028	0.086	0.093	0.105	0.089	0.124	0.191	0.286	0.405	0.475	0.718	1.103	1.756	2.862	6.451
2029	0.086	0.093	0.105	0.087	0.121	0.187	0.280	0.397	0.461	0.696	1.070	1.703	2.776	6.258
2030	0.086	0.093	0.105	0.085	0.119	0.183	0.275	0.389	0.447	0.675	1.038	1.652	2.693	6.070
2031	0.086	0.093	0.105	0.083	0.116	0.180	0.269	0.381	0.434	0.655	1.007	1.603	2.612	5.888
2032	0.086	0.093	0.105	0.082	0.114	0.176	0.264	0.374	0.421	0.635	0.977	1.555	2.534	5.711
2033	0.086	0.093	0.105	0.080	0.112	0.173	0.258	0.366	0.408	0.616	0.947	1.508	2.458	5.540
2034	0.086	0.093	0.105	0.079	0.110	0.169	0.253	0.359	0.396	0.598	0.919	1.463	2.384	5.374
2035	0.086	0.093	0.105	0.077	0.107	0.166	0.248	0.352	0.384	0.580	0.891	1.419	2.313	5.213

Table 17. IHME health-adjusted life expectancy and discounted life expectancy for females. [94,95]

Age of death	WHO HALE	Discounted by 3%
20	51.138	25.981
21	51.138	25.981
22	51.138	25.981
23	51.138	25.981
24	51.138	25.981
25	46.766	24.966
26	46.766	24.966
27	46.766	24.966
28	46.766	24.966
29	46.766	24.966
30	42.466	23.832
31	42.466	23.832
32	42.466	23.832
33	42.466	23.832
34	42.466	23.832
35	38.214	22.560
36	38.214	22.560
37	38.214	22.560
38	38.214	22.560
39	38.214	22.560
40	34.033	21.144
41	34.033	21.144
42	34.033	21.144
43	34.033	21.144
44	34.033	21.144
45	29.960	19.584
46	29.960	19.584
47	29.960	19.584
48	29.960	19.584
49	29.960	19.584
50	26.017	17.884
51	26.017	17.884
52	26.017	17.884
53	26.017	17.884
54	26.017	17.884
55	22.214	16.045
56	22.214	16.045
57	22.214	16.045
58	22.214	16.045
59	22.214	16.045
60	18.574	14.081
61	18.574	14.081
62	18.574	14.081
63	18.574	14.081
64	18.574	14.081
65	15.167	12.042
66	15.167	12.042
67	15.167	12.042
68	15.167	12.042
69	15.167	12.042
70	12.020	9.968
71	12.020	9.968
72	12.020	9.968
73	12.020	9.968
74	12.020	9.968
75	9.169	7.912
76	9.169	7.912
77	9.169	7.912
78	9.169	7.912
79	9.169	7.912
80	6.646	5.942
81	6.646	5.942
82	6.646	5.942
83	6.646	5.942
84	6.646	5.942
85	4.512	4.159
86	4.512	4.159
87	4.512	4.159
88	4.512	4.159
89	4.512	4.159
90	2.915	2.751
91	2.915	2.751
92	2.915	2.751
93	2.915	2.751
94	2.915	2.751
95	1.868	1.789
96	1.868	1.789
97	1.868	1.789
98	1.868	1.789
99	1.868	1.789
100	1.231	1.189
101	1.231	1.189
102	1.231	1.189
103	1.231	1.189
104	1.231	1.189
105	1.000	0.971
106	1.000	0.971
107	1.000	0.971
108	1.000	0.971
109	1.000	0.971
110	1.000	0.971

Table 18. IHME health-adjusted life expectancy and discounted life expectancy for males.[94,95]

Age of death	WHO HALE	Discounted by 3%
20	48.035	25.275
21	48.035	25.275
22	48.035	25.275
23	48.035	25.275
24	48.035	25.275
25	43.802	24.200
26	43.802	24.200
27	43.802	24.200
28	43.802	24.200
29	43.802	24.200
30	39.589	22.989
31	39.589	22.989
32	39.589	22.989
33	39.589	22.989
34	39.589	22.989
35	35.374	21.616
36	35.374	21.616
37	35.374	21.616
38	35.374	21.616
39	35.374	21.616
40	31.217	20.085
41	31.217	20.085
42	31.217	20.085
43	31.217	20.085
44	31.217	20.085
45	27.195	18.412
46	27.195	18.412
47	27.195	18.412
48	27.195	18.412
49	27.195	18.412
50	23.347	16.614
51	23.347	16.614
52	23.347	16.614
53	23.347	16.614
54	23.347	16.614
55	19.705	14.714
56	19.705	14.714
57	19.705	14.714
58	19.705	14.714
59	19.705	14.714
60	16.256	12.716
61	16.256	12.716
62	16.256	12.716
63	16.256	12.716
64	16.256	12.716
65	13.080	10.688
66	13.080	10.688
67	13.080	10.688
68	13.080	10.688
69	13.080	10.688
70	10.208	8.680
71	10.208	8.680
72	10.208	8.680
73	10.208	8.680
74	10.208	8.680
75	7.680	6.767
76	7.680	6.767
77	7.680	6.767
78	7.680	6.767
79	7.680	6.767
80	5.524	5.019
81	5.524	5.019
82	5.524	5.019
83	5.524	5.019
84	5.524	5.019
85	3.723	3.471
86	3.723	3.471
87	3.723	3.471
88	3.723	3.471
89	3.723	3.471
90	2.388	2.269
91	2.388	2.269
92	2.388	2.269
93	2.388	2.269
94	2.388	2.269
95	1.521	1.462
96	1.521	1.462
97	1.521	1.462
98	1.521	1.462
99	1.521	1.462
100	1.000	0.971
101	1.000	0.971
102	1.000	0.971
103	1.000	0.971
104	1.000	0.971
105	1.000	0.971
106	1.000	0.971
107	1.000	0.971
108	1.000	0.971
109	1.000	0.971
110	1.000	0.971

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Additional file 1

EVEREST Statement: Checklist for health economics paper

	Study section	Additional remarks
Study design		
(1) The research question is stated	Introduction	Page 2
(2) The economic importance of the research question is stated	Introduction	Page 2
(3) The viewpoint(s) of the analysis are clearly stated and justified	Introduction, Methods	Page 2 and page 4-5 (interventions)
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Methods	Page 4-5 (interventions)
(5) The alternatives being compared are clearly described	Methods	Page 4-5 (interventions)
(6) The form of economic evaluation used is stated	Methods	Page 3
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Introduction, Methods	Page 3
Data collection		
(8) The source(s) of effectiveness estimates used are stated	Methods; Table 1, Table 2	Page 5 and 6
(9) Details of the design and results of effectiveness study are given (if based on single study)	N/A	Data derived from peer reviewed literature and national health surveys
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	Methods	Page 6
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods	Page 5
(12) Methods to value health states and other benefits are stated	Methods	Page 5; table 1
(13) Details of the subjects from whom valuations were obtained are given	N/A	
(14) Productivity changes (if included) are reported separately	N/A	
(15) The relevance of productivity changes to the study question is discussed	N/A	
(16) Quantities of resources are reported separately from their unit costs	Methods; stated per person; Table 1, Table 2	Page 5 and 6
(17) Methods for the estimation of quantities and unit costs are described	Methods; Table 1, Table 2	Page 5 and 6; Adopted from literature

(18) Currency and price data are recorded	Methods; Table 1, Table 2	Page 5 and 6
(19) Details of currency of price adjustments for inflation or currency conversion are given	Methods	Page 5
(20) Details of any model used are given	Methods	Page 3
(21) The choice of model used and the key parameters on which it is based are justified	Methods	Page 3
Analysis and interpretation of results		
(22) Time horizon of costs and benefits is stated	Methods	Page 5
(23) The discount rate(s) is stated	Methods	Page 5
(24) The choice of rate(s) is justified	Methods	Page 5
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	N/A	
(27) The approach to sensitivity analysis is given	Methods	Page 6
(28) The choice of variables for sensitivity analysis is justified	Methods; Table 1, Table 2	Page 6
(29) The ranges over which the variables are varied are stated	Table 1, Table 2	Page 6
(30) Relevant alternatives are compared	Methods, Results	Page 4 and 5
(31) Incremental analysis is reported	N/A	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	Table 3, 4 and 5	Page 7 and 9
(33) The answer to the study question is given	Discussion, Conclusion	Page 10
(34) Conclusions follow from the data reported	Conclusion	Page 11
(35) Conclusions are accompanied by the appropriate caveats	Discussion, Conclusion	Page 10

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Non-alcoholic fatty liver disease as a mediator of detriments of dietary sugar consumption: implications for the health and economic benefits of interventions in the United States

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Non-alcoholic fatty liver disease as a mediator of detriments of dietary sugar consumption: implications for the health and economic benefits of interventions in the United States

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Abstract

Objectives: Excessive consumption of added sugars in the human diet has been associated with obesity, type 2 diabetes (T2D), coronary heart disease (CHD), and other elements of the metabolic syndrome. Recent studies have shown that non-alcoholic fatty liver disease (NAFLD) is a critical pathway to metabolic syndrome. This model assesses the health and economic benefits of interventions aimed at reducing intake of added sugars.

Methods: Using data from U.S. National Health Surveys and current literature, we simulated an open cohort, for the period 2015 to 2035. We constructed a microsimulation model with Markov chains for NAFLD (including steatosis, non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC)), body mass index (BMI), T2D, and CHD. We assessed reductions in population disease prevalence, disease-attributable disability-adjusted life years (DALYs), and costs, with interventions that reduce added sugars consumption by either 20% or 50%.

Findings: The model estimated that a 20% reduction in added sugars intake will reduce prevalence of hepatic steatosis, NASH, cirrhosis, HCC, obesity, T2D, and CHD. Incidence of T2D and CHD would be expected to decrease by 19.9 (95% CI: 12.8 – 27.0) and 9.4 (95% CI: 3.1 — 15.8) cases per 100,000 people after 20 years, respectively. A 20% reduction in consumption is also projected to annually avert 0.767 million (M) DALYs (95% CI: 0.757M — 0.777M), and a total of 10.3 billion (B) USD (95% CI: 10.2B — 10.4B) in discounted direct medical costs by 2035. These effects increased proportionally when added sugars intake were reduced by 50%.

Conclusions: The decrease in incidence and prevalence of disease is similar to results in other models, but averted costs and DALYs were higher, mainly due to inclusion of NAFLD and CHD. The model suggests that efforts to reduce consumption of added sugars may result in significant public health and economic benefits.

Strengths and limitations of this study

- No previous model has captured the full effects of added sugars through non-alcoholic fatty liver disease, obesity, type 2 diabetes and coronary heart disease.
- This model is applicable to each intervention that is aimed at reducing added sugars.
- The model is based on input parameters from multiple studies who were not always of excellent quality. We have used large intervals around these parameters to ensure reliable results.

Introduction

The social and economic burdens of chronic metabolic disease have been increasing in the United States for the last three decades. Two-thirds of the adult population in the United States is now overweight, and morbid obesity affects 9.9% of all adult women.(1) Prevalence of Type 2 diabetes (T2D) in the U.S. is at 9.3%.(2,3) And the population affected by Coronary heart disease (CHD) increased concurrently from 13 to 15.5 million over the last ten years.(4,5) More than 15% of all deaths are attributable to CHD and more than 3% to diabetes.(6) Costs have simultaneously increased; and costs for CHD are expected to double over the next two decades.(7,8) Though these figures are stunning, they underestimate the magnitude of the problem. Non-alcoholic fatty liver disease (NAFLD) has recently been found to be present in over 45% of Latinos, 33% of Caucasians, and 24% of African-Americans, and is thought to play an important role in metabolic pathophysiology.(9–12) NAFLD is defined by the presence of liver fat in the absence of a primary insult such as alcohol, viral hepatitis, or heavy metal accumulation.(13) NAFLD is further categorized into: a) hepatic steatosis, which is a reversible fat accumulation in the liver defined by an occupation of steatotic hepatocytes of more than 5% of the liver parenchyma; and b) non-alcoholic steatohepatitis (NASH), which is defined as the presence of hepatic steatosis along with lobular and portal inflammation with hepatocyte injury (ballooning). Progressive collagen deposition and vascular remodelling in NASH may lead to cirrhosis, which in turn predisposes one to hepatocellular carcinoma (HCC).(9,13–15) NAFLD is the most common cause of liver disease in the Western world, and NASH is projected to become the leading cause of liver transplantation in the USA by the year 2020.(16,17) Currently 30-40% of NASH-cirrhotic patients succumb to a liver-related death within 10 years.(18,19) Hospitalizations for NAFLD have increased 97% between 2000 and 2012.(20) NAFLD has also been suggested as an important driver of T2D in lean individuals, as liver fat accumulation can cause insulin resistance.(10,21–23) NAFLD can occur as either a cause or consequence of the metabolic syndrome(10), and many now argue that NAFLD is the hepatic manifestation of metabolic syndrome, and should be included in its definition.(24–27) It is important to identify determinants of these metabolic diseases and assess the efficacy of upstream policy interventions to curb the national and the global epidemic of metabolic syndrome.

Added sugars

Added sugars consumption increased in the U.S. over the years 1977-2000, decreased slightly between 2000—2008, and seems to have stabilized in the years thereafter.(28–30) Over 55% of all American adults consumed more than 50 grams of added sugars per day between 2005—2012, which is thought to be the cut-off value for added risk of metabolic derangement, and more than the advised maximum according to the American Heart Association (25 - 37.5 grams). Furthermore, U.S. adolescents during this period averaged 94.0 grams per day.(3,31,32) The European Food and Safety authority does not state an explicit maximum for (added) sugars in their advice, but they do note that a number of authorities have established boundaries of <10% of total energy intake.(33)

The excessive amount of added sugars (glucose + fructose) in the food supply has been associated with NAFLD and with each of the component diseases of the metabolic syndrome.(34–36) Fructose is metabolized by the liver, as it is the only organ with the required Glut5 transporter. Fructose bypasses glycogen, and is metabolized by the glycolytic pathway to acetyl-CoA. From there, excess acetyl-CoA is converted to citrate, diverted from the mitochondria into the cytoplasm via the citrate shuttle, and is then converted into fatty acids through the process of *de novo* lipogenesis(DNL).(37) From there, hepatically-derived excess triglyceride is either packaged with apo-B100 into very-low-density-lipoprotein (VLDL), which is released into the bloodstream and can foment cardiovascular disease; or will precipitate as a lipid droplet, resulting in hepatic steatosis which drives insulin resistance, causing weight gain, and predisposing to T2D. While most early studies of added sugar and chronic disease were correlative and confounded by excess caloric administration, lack of adjustment for total calories, or adiposity, more recent studies demonstrate that the effect is specific for dietary fructose, and independent of calories consumed and BMI.(37–46) For instance, added sugar is directly correlated with risk for metabolic syndrome in adolescents in NHANES even after controlling for total calories and BMI z-score.(31) Added sugar has been associated with elevated uric acid levels and hypertension.(47,48) Two recent studies, both controlled for calories and adiposity and employing a time analysis, support sugar-sweetened beverages as a specific causative agent in the pathogenesis of T2D.(40,49,50) A decade-long global econometric analysis demonstrates that only changes in sugar availability are predictive of changes in diabetes prevalence, unrelated to poverty, urbanization, aging, physical activity, total calories, or obesity.(35) Lastly, in a starch-for-sugar exchange study, our group has documented improvements in metabolic and lipid parameters unrelated to both calories and changes in weight, demonstrating improved metabolic health within 10 days.(38,51) We have demonstrated that the decline in DNL and resultant reduction in liver fat was the primary driver in the metabolic and cardiovascular improvement.(52) By demonstrating that removal of dietary fructose (the macronutrient most closely associated with DNL) commensurately improves liver fat and insulin dynamics irrespective of calories or weight, we are able to infer a causative mechanism of metabolic dysfunction by linking DNL to both liver fat and insulin resistance. We also demonstrated that despite an increase in the glucose (starch) content of the diet, beta-cell insulin secretion reduced, thus protecting against beta-cell exhaustion, thought to be important in the pathogenesis of type 2 diabetes(53); and reducing total body insulin burden, thought to contribute to both obesity and risk for cardiovascular disease.(54,55) Thus, reduction in DNL and liver fat through reduction in consumption of added sugars appears to be a primary goal of both therapy and prevention of chronic metabolic disease, and forms the rationale for our microsimulation model.

Intervention efficacy

Several studies have modeled the effects of different interventions to reduce added sugars intake. One popular intervention is the implementation of a sugar-sweetened beverage (SSB) tax. Though this does not affect all added sugars in the food supply, SSB's are the main single contributor to overall added sugars intake, and a tax on SSB's is easier to implement than an added sugars tax.(56) A 20% SSB tax is projected to reduce prevalence of obesity anywhere from 1.5 — 10%, based on different studies.(57–59) Data from Mexico demonstrate that effects on reduction of consumption are durable, although evidence of mitigation of disease are not yet available.(60) Annual diabetes cases would be expected to decline concurrently between 1.8% and 3.4%, and CHD cases by 0.5 —1.0%.(58,61) Additional research has focused on other strategies to lower added sugars consumption. Banning SSB's from the U.S. Supplemental Nutrition Assistance Program (SNAP) is expected to result in a 0.89% lower obesity prevalence within 10 years, while lowering the amount of sugars in the food supply through a cap and trade approach by 1% annually is expected to lower the prevalence of obesity by 1.7% after 20 years.(62,63)

An important limitation of all these studies is that none of these models incorporate the effects and costs related to sugar-induced NAFLD. Because NAFLD explains a part of the incidence of diabetes in lean individuals and is expected to contribute significantly to overall healthcare burden and costs, it is necessary that models incorporate all of these diseases.

Our goal is to predict the magnitude of the health and economic effects of interventions that are designed to reduce added sugars consumption either by 20% or 50%, respectively. This modelling approach more precisely quantifies the benefits of reducing added sugar consumption. We describe the process of creating, calibrating and validating a microsimulation model. We clarify the relevant interactions that determine progression within this model in Markov chains for NAFLD (including cirrhosis and HCC), obesity, T2D, and CHD, and we describe the creation of a simulated open cohort representative of the US population. We allow the model to run for 20 years into the future to predict effectiveness. We report the outcomes of these simulations in future incidence, prevalence and mortality of disease, and in disability-adjusted life years (DALYs) and costs averted.

Methods

The Methods section is constructed according to the recommendations by the ISPOR taskforce for good modelling practice, and completeness is checked according to the CHEERS statement.(64,65)

Summary

We constructed an individual based model consisting of a base cohort of 22,400 people. New people entered the model each year at age 20, the youngest age group we simulate. Individuals are assigned a state at initialization in each 'chain' of the model. These include age, sex, ethnicity, sugar consumption, NAFLD, BMI, T2D, and CHD. The current health state of each individual at the beginning of a cycle forms a risk profile, and the presence in a risk-inducing state in one of the chains can influence the probability of transitioning between states in a different chain, according to literature-based odds ratios. We simulated 20 annual cycles for each individual, counting events, incurred direct medical costs, and DALYs for each cycle, as well as the overall prevalence for the total cohort. We discounted the costs and DALYs by 3.0% annually, and costs were presented in 2015 USD. Two interventions were simulated: one that reduced each individual's added sugars consumption by 20%, and one that reduced it by 50%. We used identical random numbers for the base case scenario and each of the interventions, to reduce variance. We calibrated the model to other studies reporting historic trends and predicting future prevalence, and validated the model via face validation, cross-validation, and sensitivity analyses. Deterministic sensitivity analysis was used to determine the influence of individual input parameters. Probabilistic sensitivity analysis was used to generate mean results and 95% central coverage intervals.

Model type

An individual-based stochastic Markov model (microsimulation) was used. The model contained a chain for each of four separate diseases. Because each of these diseases has a minimum of 3 states, and the transitions between these states are based on the presence or absence of a set of risk factors, the state-space explosion phenomenon prohibits us from using traditional Markov cohort simulation. An individual-based approach makes it possible to use individual-specific transition rates, capturing the effect of interventions on individual risk factor profiles, thereby avoiding the need to count the number of individuals in all possible states and allowing for complex relationships between several risk factors within a single individual.(66) It also opens up potential for future analyses among subgroups.

Population and setting

The model is based on the adult population (age 20+) of the United States. Outcomes are reported from a healthcare perspective. This includes direct medical costs and DALYs averted. Indirect medical or non-medical costs are excluded. Because this model is meant to assess the benefits of reducing added sugars intake, unrelated to the type of intervention, costs of implementing any specific intervention and possible revenues (e.g. in the case of an excise or general services tax) are also excluded.

Model structure and input parameters

A simplified model transition diagram is presented in **Figure 1.** Individuals will reside in a state within each chain at any given point in time. The probability of staying within a state or moving to another state in each cycle is determined by a set of defined transition probabilities, which are influenced by the risk profile (the current state in the other chains) of the individual. Events in different chains can occur in parallel.

The simulation is initialized by assignment of age (A), sex (S), and ethnicity (E) to each individual. Age states are based on the population distribution that is provided by the Bureau of the Census, and are specified for each age from 20 to 84 and a cumulative age group for anyone above 85. We simulate an open cohort. New individuals with age 20 enter each year.(67) The initial age distribution is specified in supplementary **table 2**. Male and female sex are incorporated with an initial distribution specified in supplementary **table 3**. Ethnicities incorporated into the model are Hispanic, non-Hispanic black, and non-Hispanic-white. Data availability did not allow us to incorporate Asians and Native Americans as separate groups and therefore they were grouped with the non-Hispanic whites. The initial ethnicity distribution is specified in supplementary **table 4**.

When the individual is assigned an age, sex and ethnicity, these determine the state that this individual will be assigned to in each of the chains for NAFLD, BMI, T2D, and CHD at the start of the simulation. Each chain represents a separate disease process, and has its own non-disease state (e.g., non-T2D). This does not mean that this person is actually healthy (e.g. a person can have cirrhosis but not diabetes). The NAFLD chain includes a non-NAFLD state, and states for hepatic steatosis, NASH, cirrhosis, and NASH- or cirrhosis-related HCC. A person is defined as having NAFLD when his or her current state is steatosis, NASH, or cirrhosis. This is different from common terminology, where cirrhosis is excluded. We chose this definition for easy reference, because these three states imply extra risk for progression within other chains. The initial distribution over NAFLD states is specified in supplementary **table 5** and specified per ethnicity group.

It is important to note that modeled cirrhosis and HCC are specifically related to steatosis and NASH, and do not include all cirrhosis and HCC cases within the population, irrespective of cause. Transition directly from the non-NAFLD state to either one is therefore not possible. Baseline transition probabilities are specified in **table 2** and transition rates from NASH and cirrhosis to HCC are specified per age group, as defined in supplementary **table 10 and 11**, starting at age 40. (age groups: 40-44, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79 and 80 years and over), Risk factors for progression are stated in **table 2** and include ethnicity (protective and detrimental factors), being overweight or obese, and high sugar consumption. These risk factors apply for transitions up to the cirrhosis state.

The BMI chain includes states for healthy weight, overweight and obesity. The initial distribution over BMI states is specified in supplementary **table 8,** and specified by sex, ethnicity, and age group (ages 20-35, 35-44, 45-54, 55-64, 65-74, 75-84 and 85+). Baseline transition probabilities are specified in **table 2**. Risk factors for progression are stated in **table 1** and include NAFLD disease states and high sugar consumption.

The T2D chain includes a non-T2D state and a T2D state. The initial distribution over T2D states is specified in supplementary **table 7** and specified by sex, ethnicity, and age group (ages 20-35, 35-44, 45-54, 55-64, 65-74 75-84 and 85+). Average baseline transition probability to T2D is specified in **table 2** and age-specific incidence rates are provided in supplementary **table 14** (age groups: 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79 and 80+). Risk factors for progression to T2D are stated in **table 2** and include NAFLD disease states, overweight, and obesity.

The CHD chain includes a non-CHD state and a CHD state. The distribution over CHD states at simulation start is specified in supplementary **table 6** and specified per sex, ethnicity and age group (ages 20-44, 45-64 and 65+). Average baseline transition probability to CHD is specified in **table 2** and age-specific incidence rates are provided in supplementary **table 12** (age groups: <35, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84 and 85+). Risk factors for progression to CHD are stated in **table 2** and include NAFLD disease states, overweight, obesity, and T2D.

Each individual is assigned a level of consumption of added sugars. There are two states in the sugar chain — high consumption (≥50g of added sugars per day), and low consumption (< 50g of added sugars per day). The distribution of these states among the study population reflects the data of the NHANES 2005-2012, and is specified per sex and ethnicity group, as shown by supplementary **table 9**.(3,31) Sugar consumption is fixed throughout the simulation for each person.

From each state, individuals can transition to a 'non-disease related death' state. Three disease chains also have a disease-specific death state (i.e.. T2D-death, CHD-death, and liver-related death), allowing calculation of disease-attributable death. Mortality rates from causes outside the model were corrected for the competing risks of modeled causes of mortality to ensure valid overall mortality. Death in one chain forces an instant transition to the death state in other chains. Average transition probabilities to disease-related death states are specified in **table 2**. Age specific rates for T2D-related death are specified in supplementary **table 15**. Liver death rates are specified in **table 2**. Deaths were attributed to the disease for which the transition to death was established first. To remove confounding because of calculation order, chain calculation order was randomized. This ensures that deaths are attributed to the right disease, e.g. people with T2D and CHD have a chance to die of T2D, CHD or succumb to a non-disease related death.

To determine whether there were temporal trends in incidence or death rates, we plotted the available historic data (1999-2013) and projected this to the future.(5,6,68) These trends were found to be present for the incidence and mortality rate of CHD, and for the non-disease specific mortality rate. We incorporated these regression rates into the model by adjusting the respective baseline transition probabilities before each cycle. Average baseline transition probabilities for CHD and non-disease related deaths are specified in **table 2**. The CHD-specific death rates by year and age are specified in supplementary **table 13** and the non-disease related death rates per year and age are specified in supplementary **table 16**.

Final transition probabilities per chain are compared to a pseudo-random number to determine state-transitions each cycle. These final transition probabilities were derived from baseline transition probabilities, adjusting for the relative risk of progression observed for applicable risk factors. The correction formula for the baseline transition probabilities is a multiplicative function of all applicable values for present risk factors (odds ratios).

Figure 1

Interventions

Two interventions were simulated: a reduction of 20%, and a reduction of 50% in individual added sugars consumption. A 20% reduction in added sugars was simulated to be consistent with the percentage reduction assessed in several studies.(57–59) In addition, a 50% reduction was simulated because the American Heart Association advises 6-9 teaspoons of added sugar (for females and males respectively) as a maximum per day, which is approximately 50% of the current average consumption.(3,31,32) The individual added sugars consumption distribution was then split into a dichotomous variable; with people consuming less than or equal to 50 grams of added sugars being considered low consumers, and people consuming more than 50 grams per day being considered high consumers. This model did not incorporate substitutions to other food categories, but it did incorporate the overall added sugars reduction, rather than a sole reduction in SSB consumption used in other studies.(58,61) This makes it possible to capture the overall effects of added sugars, contrary to the solitary effect of SSB's. The effects of changes in food consumption to other food groups (e.g. proteins, fat) are not modeled. Detrimental effects of these food categories are less well documented and inferior to the effects of added sugars. NHANES data was used to reduce individual added sugars consumption by the specified amount. From these data, new distributions were calculated to reflect subgroup consumption patterns. These distributions determined the ratio between individuals in the high and the low risk group, and therefore determine progression within disease chains. Identical random numbers were used between interventions to reduce variance, as described by Stout and Goldie.(69)

Time horizon, cycle length

The model had a time horizon of 20 years, modeling the calendar years 2015 to 2035. This duration was chosen to make sure effects within chronic diseases (T2D, CHD) were sufficiently visible. The cycle length was 1 year. Individuals could exit the model through each death state, or live until the end of the simulation.

Outcomes

Outcomes were incidence, prevalence and mortality of disease, and direct medical costs and DALYs averted. Costs were calculated by multiplying prevalence by discounted disease-attributable costs. DALYs were calculated by adding years lived with disability (YLD) and years of life lost (YLL). YLD was calculated as the product of the prevalence of disease times the discounted disability weight. YLL was calculated by multiplying the discounted health-adjusted life expectancy at death by the amount of people that died in that specific year, given a certain age and sex. The discount rate for costs, disability weights, and life expectancy was 3.0% annually. Health-adjusted life expectancy and discounted life expectancy for males and females for the United States were not derived by the model but implemented directly from publications of the Institute for Health Metrics and Evaluation (IHME). They are provided in the online supplement, **table 3 and 4**.

Input parameter determination

The model parameters that determined demographics and the distribution of risk factors and disease at the start of the simulation are mainly derived from NHIS and NHANES data. If data were not sufficient, current literature was consulted. Model input parameters, their distribution ranges, and the sources from which they were acquired are presented in **tables 1 and 2**. Baseline transition probabilities were derived from literature data, and where necessary, via calibration. Also when necessary, we used logistic conversion to adjust transition rates to reflect annual probabilities. Interaction values were derived from literature data. For interactions between chains, we used conservative data when possible, to ensure no overestimation of effect size. We took special care to ensure these odds ratios reflect the case for our model, i.e. reflect decreased risk due to a reduction in overall added sugars intake, not just a reduction in sugar-sweetened beverage intake, which is more commonly investigated. Regression rates were determined by historic and projected trends reported by the CDC and the American Heart Association.(3,5,6) Costs were derived from American population-based studies and, where necessary, were inflated by the inflation calculator of the United States Department of Labor Statistics to 2015 USD.(70) Costs were calculated as specific disease-attributable costs (i.e. costs for CHD due to diabetes were counted as costs due to CHD rather than costs due to diabetes). This was necessary to prevent overlapping costs. Disability weights were adopted from World Health Organizations' burden of disease estimates and current literature. Specific sources are provided in the tables.

Table 1. Model input values and ranges for disease characteristics. Costs are population based, meaning that they include those who do not get care.

	Prevalence at simulation start				Costs (annual)			Disability weights			
Disease state	*Mean*	*Min*	*Max*	Ref.	*Mean*	*SD*	*Ref.*	*Mean*	*Min*	*Max*	Ref.
Steatosis	27.955%#	18.637%	41.933%	(8,16,18)	134	50	(71)	0.000	0.000	0.000	(72–74)
NASH	3.141%#	2.094%	4.712%	(8,16,18)	267	100	(71)	0.033	0.017	0.066	(72–74)
Cirrhosis	0.314%#	0.209%	0.471%	(75,76)	2,861	1073	(77)	0.194	0.127	0.273	(10,71)
HCC	0.025%#	0.017%	0.038%	(78,79)	42,644	15,992	(72,80,81)	0.294	0.199	0.411	(72–74)
CHD	6.544%#	-	-	(1,2,6)	13,233	4962	(6,82)	0.066	0.043	0.095	(72)
T2D	9.447%#	-	-	(1,2)	8,170	3064	(82–84)	0.150	0.080	0.220	(72,85)
Overweight	33.473%#	-	-	(1,2)	343	129	(82,84)	0.000	0.000	0.000	(86)
Obesity	37.391%#	-	-	(1,2)	916	344	(82,84)	0.012	0.001	0.022	(86)

SD: standard deviation, NASH: non-alcoholic steatohepatitis, HCC: hepatocellular carcinoma, CHD: coronary heart disease, T2D: type 2 diabetes. CHD, T2D, overweight, and obesity prevalence are not varied in the sensitivity analyses.
Age, sex and/or ethnicity specific values are specified in the online supplement.

Table 2. Selected model input parameter values and ranges.

Parameter				
Initialization	**Mean**	**Min**	**Max**	**Source**
Age distribution	OS1*	-	-	(87)
Sex distribution	OS2**	-	-	(87)
Ethnicity distribution	OS3***	-	-	(87)
High sugar consumption	57.278%#	38.186%	85.917%	(3,31,40)
Baseline transition probabilities##	**Mean chance**	**Min**	**Max**	**Source**
Non-NAFLD -> steatosis	0.0100	0.006700	0.01500	(88–96)
Non-NAFLD -> NASH	0.0003	0.000201	0.00045	(88–96)
Steatosis -> NASH	0.0060	0.004020	0.00900	(88–96)
Steatosis -> cirrhosis	0.0002	0.000134	0.00030	(88–96)
NASH -> cirrhosis	0.0020	0.001340	0.00300	(88–96)
NASH -> HCC	0.0001#	0.000067	0.00015	(88–99)
NASH -> liver death	0.0038	0.002546	0.00570	(100–103)
Cirrhosis -> HCC	0.0200#	0.013400	0.03000	(88–99)
Cirrhosis -> liver death	0.0340	0.022780	0.05100	(100–103)
HCC -> liver death	0.5000	0.335000	0.75000	(100–103)
Non-CHD -> CHD	0.0045#	0.003015	0.00675	(104,105)
CHD -> CHD death	0.0100#	0.006700	0.01500	(5,6,104)
Non-T2D -> T2D	0.0045#	0.003015	0.00675	(68,106)
T2D -> T2D death	0.0100#	0.006700	0.01500	(6,68,106)
Healthy weight -> overweight	0.0500	0.033500	0.07500	(107–110)
Healthy weight -> obese	0.0060	0.004020	0.00900	(107–110)
Overweight -> obese	0.0180	0.012060	0.02700	(107–110)
Each alive state -> non-disease related death	0.0100#	0.006700	0.01500	(6)
Risk factors (odds ratios)	**Mean value**	**Min**	**Max**	**Source**
NHB ethnicity for progression within NAFLD	0.93	0.70	1.00	(111)
Hispanic ethnicity for progression within NAFLD	1.67	1.22	2.22	(111)
Overweight for progression within NAFLD	2.19	1.60	3.38	(89,112–117)
Obesity for progression within NAFLD	3.14	2.07	5.28	(89,112–117)
High sugar consumption for progression within NAFLD	2.00	1.50	3.00	(36,118)
NAFLD for TP non-CHD -> CHD	2.31	1.66	3.62	(119–123)
Overweight for TP non-CHD -> CHD	1.22	1.12	1.32	(124–131)
Obesity for TP non-CHD -> CHD	1.60	1.43	1.79	(124–131)
T2D for TP non-CHD -> CHD	2.24	1.64	3.06	(132)

NAFLD for TP non-T2D -> T2D	2.73	1.87	4.46	(133–139)
Overweight for TP non-T2D -> T2D	2.18	1.59	3.36	(140–146)
Obesity for TP non-T2D -> T2D	3.36	2.18	5.72	(140–146)
NAFLD for progression within the BMI chain	2.19	1.60	3.38	(89,112–117)
High sugar consumption for progression within the BMI chain	2.60	1.20	6.00	(145,146)

SD: standard deviation, NAFLD: non-alcoholic fatty liver disease (steatosis, NASH & cirrhosis), NASH: non-alcoholic steatohepatitis, HCC: hepatocellular carcinoma, CHD: coronary heart disease, T2D: type 2 diabetes, NHB: non-Hispanic black.
* See online supplement table 1. ** See online supplement table 2. *** See online supplement table 3.
# Age, sex and/or ethnicity specific values are specified in the online supplement.
Transition probabilities for regression to less severe disease are specified in the online supplement.

Calibration

Incidence, prevalence, mortality and costs of overweight and obesity, T2D, and CHD were calibrated to reflect historic data from the CDC and projections from the American Heart Association (AHA) and several individual studies predicting future disease.(6,7,147–151) NASH- and cirrhosis-related HCC incidence and mortality was calibrated to historic trends reported by the CDC, and future predictions reported by the American Cancer Association.(6,152)

Validation

Validation of the model occurred via face validation, cross-validation, and sensitivity analyses. Face validation was performed manually by the authors. Each chain was checked separately for functionality before merging them. Cross-validation was performed by comparing epidemiological outcomes and predictions from our model with reported results from different studies on each subject, as presented in the Discussion.

Uncertainty was assessed using deterministic and probabilistic sensitivity analysis (DSA & PSA). DSA was conducted using a five-point analysis, with the minima and maxima specified in **tables 1 and 2**. If a mean and standard deviation (SD) are specified, we used a range of mean ± 1.96*SD. DSA results are only presented for the two main outcomes: total costs and DALYs averted in the year 2035. PSA was conducted using the distributions defined in **tables 1 and 2**, to produce a mean and 95% central coverage interval for all outcome values by running the simulation 10,000 times (each of which including the base case and two interventions).

Cohort simulation

To produce stable results, limit computational requirements, and have a cohort that remained representative of the U.S. population, we simulated a base cohort of 22,400 people, with new entry of 416 people each year, reflecting CDC population prospects.(67) Because of computational requirements, the model was built in Golang programming language (Google Inc, Mountain View, CA). Model code is publicly available via https://github.com/alexgoodell/go-mdism or can be acquired through the corresponding author. Sensitivity analyses were conducted using a 20-machine cluster (Amazon Web Services, Seattle, WA). Outcome analysis was completed in Excel 2010 (Microsoft, Redmond, WA).

Results

Incidence and mortality

The incidence of T2D, CHD, and HCC and the corresponding death rates in the year 2035 are stated in **table 3**. Diabetes incidence is expected to rise over the next 20 years, resulting in an incidence rate of 1035 cases per 100,000 people. The interventions are expected to reduce this by 19.9 and 83.5 respectively. CHD incidence is expected to rise to 665 cases per 100,000 people by 2035. This can be reduced by 9.4 and 39 cases by the 20% and the 50% intervention respectively. NASH- or cirrhosis-related HCC incidence will rise to 4.4 cases per 100,000 people. Interventions could reduce this amount by 0.3 and 1.3 respectively. Liver death can be due to HCC, or it can be related to NASH or cirrhosis in the absence of HCC. Liver-related deaths will rise substantially, to 19.8 deaths per 100,000 people by 2035. This can be reduced by 1.4 or 5.8 deaths per 100,000 people by the 20% and 50% intervention, respectively.

Table 3. Annual occurring and averted events in 2035

Per 100,000 people						
Events	**No intervention (CI)**	**20% red. (CI)**	**Difference (CI)**	**50% red. (CI)**	**Difference (CI)**	
T2D cases	1034.6 (1031.0-1038.2)	1014.7 (1011.3-1018.2)	19.9 (12.8-27.0)	951.2 (947.9-954.4)	83.5 (76.7-90.3)	
T2D deaths	576.6 (574.2-578.9)	569.3 (567.0-571.6)	7.2 (2.7-11.8)	546.4 (544.2-548.6)	30.2 (25.7-34.6)	
CHD cases	665.1 (661.9-668.2)	655.6 (652.5-658.8)	9.4 (3.1-15.8)	626.1 (623.1-629.1)	39.0 (32.8-45.2)	
CHD deaths	203.6 (202.2-205.0)	201.9 (200.5-203.3)	1.6 (-1.2-4.4)	197.2 (195.9-198.6)	6.3 (3.6-9.1)	
HCC cases	4.4 (4.32-4.41)	4.0 (3.95-4.05)	0.3 (0.24-0.39)	3.1 (3.02-3.18)	1.3 (1.24-1.38)	
Liver deaths	19.8 (19.65-20.02)	18.5 (18.29-18.63)	1.4 (1.02-1.73)	14.1 (13.94-14.21)	5.8 (5.44-6.08)	

NASH: non-alcoholic steatohepatitis; HCC: hepatocellular carcinoma; CHD: coronary heart disease; T2D: type 2 diabetes mellitus; CI: 95% central coverage interval. Numbers might not add up due to rounding.

Prevalence

Figure 2, graphs A-H show the reduction in prevalence of disease due to the two intervention strategies. A 20% reduction in added sugars consumption is expected to decrease prevalence of each disease state significantly after 20 years, except for overweight prevalence, which does not change significantly. A 50% reduction in added sugars consumption will proportionally affect prevalence. Effects on T2D and CHD prevalences start to accumulate after an initial 3-year lag period. Graph G shows that overweight prevalence is not reduced. This is because the individuals that regressed from obese to overweight offset the reduction achieved in people that started overweight and regressed to normal weight. This effect is clarified by the drop in obesity prevalence.

Figure 2

Costs & DALYs

An overview of economic findings is presented in **table 4**. Overall costs for the modeled disease states could be reduced by 2.26% (95% CI 2.23% — 2.29%) by the year 2035 with an intervention that reduces added sugars intake by 20%. The 50% intervention will reduce overall costs by 6.99% (95% CI: 6.91 — 7.08). DALY burden and averted DALYs are presented in **table 5**. Total amount of DALYs could be reduced by 4.32% (95% CI: 4.27% — 4.38%) or 13.37% (95% CI: 13.24% — 13.51%) respectively. The majority of averted DALYs are due to reduced mortality.

Table 4. Annual costs spent and averted per disease state in 2035

In billions 2015 USD, discounted by 3.0% annually

State	No intervention (CI)	20% reduction (CI)	Difference (CI)	50% reduction (CI)	Difference (CI)
Steatosis	6.48 (6.43-6.53)	6.40 (6.35-6.45)	0.08 (0.080-0.082)	6.23 (6.18-6.28)	0.25 (0.248-0.255)
NASH	5.26 (5.22-5.30)	4.89 (4.85-4.93)	0.37 (0.368-0.375)	4.11 (4.08-4.14)	1.15 (1.139-1.162)
Cirrhosis	7.00 (6.93-7.07)	6.22 (6.16-6.28)	0.78 (0.772-0.791)	4.60 (4.56-4.65)	2.40 (2.371-2.429)
HCC	5.10 (5.04-5.16)	4.55 (4.50-4.60)	0.55 (0.537-0.558)	3.40 (3.36-3.44)	1.70 (1.669-1.721)
CHD	162.2 (160.9-163.6)	160.1 (158.8-161.5)	2.09 (2.06-2.12)	155.7 (154.4-157.0)	6.51 (6.43-6.58)
T2D	200.0 (198.4-201.6)	195.9 (194.3-197.5)	4.07 (4.02-4.12)	187.4 (185.9-188.9)	12.59 (12.46-12.73)
Overweight	16.4 (16.3-16.5)	16.6 (16.5-16.8)	-0.25 (-0.26 - -0.25)	17.2 (17.1-17.3)	-0.79 (-0.81 - -0.78)
Obesity	52.7 (52.3-53.1)	50.1 (49.7-50.5)	2.59 (2.57-2.62)	44.7 (44.3-45.0)	8.03 (7.95-8.12)
Total	**455.1** (451.4-458.9)	**444.9** (441.2-448.5)	**10.3** (10.2-10.4)	**423.3** (419.8-426.8)	**31.8** (31.5-32.2)

NASH: non-alcoholic steatohepatitis; HCC: hepatocellular carcinoma; CHD: coronary heart disease; T2D: type 2 diabetes mellitus; CI: 95% central coverage interval. Numbers might not add up due to rounding.

Table 5. Annual occurring and averted DALYs in 2035

In millions

State	No intervention (CI)	20% reduction (CI)	Difference (CI)	50% reduction (CI)	Difference (CI)
NASH	2.97 (2.955-2.988)	2.76 (2.746-2.777)	0.210 (0.209-0.212)	2.32 (2.309-2.334)	0.650 (0.645-0.655)
Cirrhosis	0.48 (0.475-0.482)	0.42 (0.422-0.428)	0.053 (0.053-0.054)	0.31 (0.312-0.316)	0.164 (0.162-0.165)
HCC	3.06 (3.046-3.084)	2.78 (2.765-2.799)	0.283 (0.279-0.283)	2.19 (2.180-2.206)	0.872 (0.863-0.881)
CHD	2.32 (2.305-2.330)	2.29 (2.276-2.302)	0.028 (0.028-0.029)	2.23 (2.217-2.242)	0.088 (0.086-0.090)
T2D	8.21 (8.180-8.248)	8.06 (8.023-8.089)	0.158 (0.155-0.160)	7.72 (7.690-7.752)	0.492 (0.487-0.498)
Obesity	0.69 (0.689-0.700)	0.66 (0.655-0.666)	0.034 (0.034-0.035)	0.59 (0.584-0.593)	0.106 (0.105-0.107)
Total	**17.74** (17.65-17.83)	**16.97** (16.89-17.06)	**0.767** (0.757-0.777)	**15.37** (15.29-15.44)	**2.372** (2.348-2.396)
From mortality	11.94	11.50	0.439	10.58	1.357
From morbidity	5.80	5.47	0.328	4.78	1.015

NASH: non-alcoholic steatohepatitis; HCC: hepatocellular carcinoma; CHD: coronary heart disease; T2D: type 2 diabetes mellitus; CI: 95% central coverage interval. Numbers might not add up due to rounding.

Sensitivity analyses

We show tornado diagrams for the two most important outcomes: annual costs and DALYs averted by the year 2035 due to an intervention that reduces sugar consumption by 20%. The diagrams show the impact that specific input parameters had on selected results. The ten variables that caused the widest range in results are shown. When varying individual variables, the annual savings by the year 2035 range from 7.9 to 17.1 billion 2015 USD. The tornado diagram (**Figure 3**) shows that the interaction between high added sugars consumption and the progression within the NAFLD and BMI chains had the greatest impact on total costs averted. In the tornado diagram for total annual DALYs averted by the 20% intervention in the year 2035 (**Figure 4**), assigned disability weights had the greatest impact. Total DALYs averted ranged between 0.36 and 1.41 million.

Figure 3 and 4

Discussion

It has been estimated that the cost burden of the diseases of metabolic syndrome are 75% of the total annual health care budget ($3.2 trillion) of the United States. The clinical burden of NAFLD alone is estimated at $103 billion.(153) The proposed model shows clear and significant benefits for interventions that reduce consumption of added sugars. A reduction by 20% will reduce annual direct medical costs for U.S. adults by more than 10 billion USD (2015 dollars) by the year 2035. A 50% reduction will save an additional 21 billion. Together with these economic benefits, population health will significantly improve. A total of 770,000 DALYs could be averted with a 20% reduction in consumption. A 50% reduction in consumption will avert another 1.6 million DALYs. These health and economic benefits are the direct result of lower incidence, prevalence, and mortality of disease in U.S. adults due to lower consumption of added sugars.

Fit with current knowledge

The estimate for health and economic benefit of this model is similar to a number of previously performed economic evaluations. Basu et al. found a reduction in diabetes incidence of 21.7 cases per 100,000 people with a reduction of 20% of added sugars through a cap and trade approach, limiting the amount of sugars in the food supply.(63) We found a reduction of 19.9 cases per 100,000 people, indicating a similar absolute effect size. CHD incidence reduction is estimated to be about 1.5-fold higher than found in a similar study, but we argue that this is mainly because the other study simulated a 20% tax on sugar-sweetened beverages, and therefore the overall added sugars consumption reduction was smaller than the 20% reduction we simulated.(61) In an econometric analysis looking backward in time, Basu et al. found a delay of 3 years between changes in sugar consumption and prevalence of diabetes.(35) Similarly, we found a delay of 3 years going forward in time between reduction of consumption and reduction in prevalence of disease. Prevalence of obesity has been reported to drop by 1.5% — 10% due to a reduction of added sugars by 10% — 20%.(57–59) Our result of 2.1% reduction in obesity prevalence seems to reflect our conservative approach in determining input parameter values.

Costs savings are bigger in our model compared to other models.(58,62,62) This was for three reasons. First, some other models do not use added sugars as a whole but use SSB's, resulting in a smaller effect. Second, our overall prevalence of T2D and CHD is higher than most other models. We have calibrated our model to historic trends reported by the CDC and to future projections of the AHA, ADA and separate studies predicting future prevalence, and therefore argue that our estimate is valid. Third, and perhaps most importantly, no other studies predict future NAFLD prevalence. We present the first model that estimates the effects of sugar interventions on NAFLD prevalence and associated costs and DALYs.

In 2009, the American Heart Association recommended a reduction in added sugar consumption from a median of 90 grams per day to a maximum of 25 grams for women and 37.5 grams for men.(32) In 2016, the USDA and WHO settled on an upper limit of 10% of calories, which approximates 50 grams per day. Given the U.S. current median consumption of 80 grams per day, our microsimulation modeling cutoffs of 20% and 50%, while ambitious, are metabolically rational and in concert with governmental goals.(154)

Our model only allows us to examine the negative side of the balance sheet in terms of cost savings to health care. However, reductions in added sugar consumption have been modeled to provide significant increases to the positive side of the balance sheet in terms of economic productivity. Indeed, a simulation modeling by Morgan Stanley predicted economic growth to decline to zero by the year 2035 using a high-sugar case, whereas stabilization at +2.9% was noted with a low-sugar case.(155)

Strengths and limitations

This study is the first of its kind to model the effect of added sugars on NAFLD as well as on BMI, and therefore it captures a more complete picture of the possible health and economic benefits of interventions that reduce intake of added sugars. Though taxing sugar-sweetened products, mainly beverages, has been widely suggested as a public health strategy, other approaches, e.g. a cap and trade approach, have also been suggested.(56–59,61–63) We have constructed this model to be applicable with each of these interventions, so that it does not rely on any consumption statistics other than added sugars as a whole. A limitation to this approach is that our model does not incorporate a possible change to non-sugared caloric products, containing protein, fat, or other carbohydrates. While it is conceivable that removal of added sugars in the diet could result in subsequent substitution of other foodstuffs to restore an individual's caloric baseline, *ad lib* population studies do not support that such caloric compensation takes place.(156) It is important that effort is put into investigating self- and cross-elasticity of sugar-sweetened products to determine the effect of these caloric replacements. Though this is a limitation, research has clearly shown that the contribution of added sugars in relation to their excessive intake is likely the most important consumption factor for metabolic derangement. Furthermore, added sugars consumption was fixed throughout the simulation for each individual (though specified per sex and ethnic group). We could not find sufficient data on changes in sugar consumption related to incident disease and therefore could not model these changes accurately enough. We argue that keeping the sugar consumption fixed is likely more accurate than modeling changing sugar consumption based solely on age. The main limitation of this model is the uncertainty of input parameters. The

pathophysiology of NAFLD and its associations with other metabolic diseases is still widely under investigation. We have modeled cirrhosis as an irreversible condition, which is not necessarily true in all cases. Furthermore, the input parameters for baseline transition probabilities and interaction (OR) values are still somewhat uncertain. Many studies report associations, but very few studies report plausible quantitative causal relationships. There are several reasons that explain this low number of studies. First, it is hard to accurately determine the individual components in an individual's diet. Second, there is no inexpensive, accurate way to determine the presence of individual NAFLD states. Commonly used ultrasonography possibly underestimates the prevalence of NAFLD and does not differentiate between steatosis and NASH, while up to 79% of patients may have serum alanine aminotransferase (ALT) levels within the normal reference range of < 40 U/mL.(9,157) We have addressed this uncertainty by taking wide ranges in the probabilistic sensitivity analysis, which determines the SD and 95% central coverage interval around the results. Results remain statistically significant, indicating that any minor inaccuracies in input parameter values will not render the effects insignificant. Ultimately, it is desirable to determine incidence of NAFLD states and risk factor relative risks in independent prospective cohort studies, and to assess intervention effectiveness via randomized controlled trials. This model can be refined and updated when new data become available.

It is possible that our results might still underestimate the total effects. We only modeled diagnosed disease, we took a conservative approach when determining input parameter values, and we did not take societal costs into account. Real health, healthcare, and economic benefits are likely larger than estimated. Furthermore, we only modeled the population with an age over 20. Likely, including health effects in children, particularly those with type 2 diabetes, would yield additional benefits.

Implications

This model clarifies the significant health and economic benefits that could be achieved by a public health intervention that reduces consumption of added sugars in U.S. adults. We recommend that health policy makers review options to implement sugar reduction. Important to consider are the barriers to limiting added sugars in the United States. The food industry uses sugar to enhance flavor and as a bulking and browning agent, humectant, and spoilage retardant. Another obstacle is the lowered price for manufacturing, due to government subsidies for corn, cane, and beets. Historically there was another barrier -- lack of consensus on the link between sugar and metabolic disease. However, consensus on causality is now strong. Recently sugar taxation has emerged as a viable strategy, levied in the U.K. and Mexico, as well as several municipalities in the U.S., including San Francisco, Oakland, Berkeley, and Albany, CA, as well as Chicago, IL and Philadelphia, PA.

Future research

Future research should focus on establishing a more precise measurement of NAFLD prevalence, incidence, and risk factors. Furthermore, magnitude and effects of switching to different food groups should be assessed. Finally, changes in added sugars consumption related to ageing and incident disease should be more intensively investigated.

Contributor statement

RAV was involved in conceptualizing the study, reviewing literature, conducting the modelling analysis, analyzing the data and writing the manuscript. AJG was involved in conducting the modelling analysis and in editing the paper. LAR and RHL were involved in conceptualizing the model, providing and structuring data inputs and editing the manuscript. TCP was involved in reviewing and revising the manuscript, checking statistical and mathematical assumptions and establishing overall validity of the model. JGK was involved in conceptualization of the model, input data review, guiding the modelling process and providing a critical review of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare no direct conflicts of interest. However, Dr. Lustig has received author fees from Hudson Street Press regarding his authorship of: "Fat Chance: Beating the Odds Against Sugar, Processed Food, Obesity, and Disease"; "The Fat Chance Cookbook"; and "Sugar has 56 names: A Shopper's Guide". He is also the unpaid chief science officer of the non-profit EatREAL.

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Data sharing statement

An online supplement will be made available containing comprehensive tables of used input data. The modelling code is available through github: https://github.com/alexgoodell/go-mdism or can be accessed via the corresponding author.

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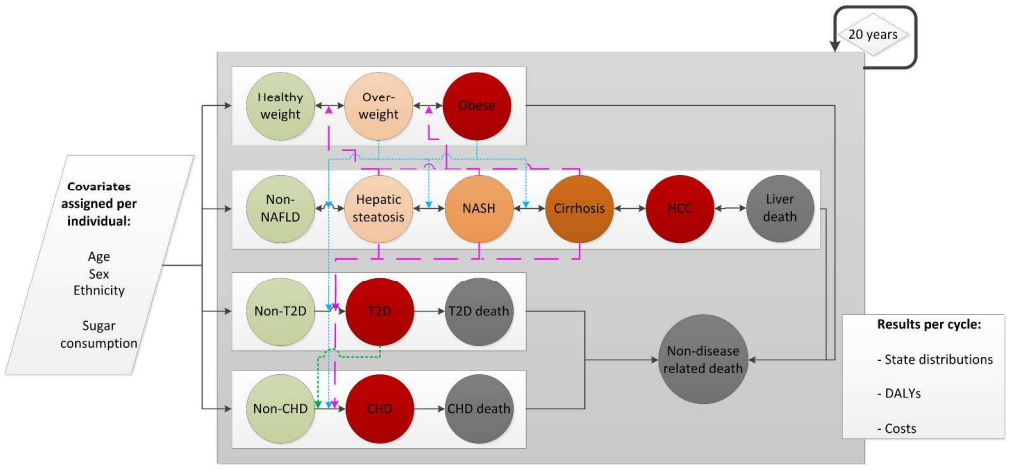

Figure 1. Model state and covariate structure.
Each individual gets assigned a state in each chain at the start of the simulation and their specific covariates (age, sex, ethnicity, high/low sugar consumption). Circles represent disease states. Solid lines indicate a possible transition pathway between states. Coloured lines indicate how being in a state within one chain can affect the value of the transition probability between two states in another chain. These are split into three categories: pink striped lines indicate the effect of NAFLD on progression in the BMI, T2D and CHD chains. Blue dotted lines indicate the effect of overweight and obesity on progression in the NAFLD, T2D and CHD chains. The green dotted line indicates the effect of T2D on progression in the CHD chain. 3 chains contain disease related deaths and the model contains a non-disease related death state for other causes of mortality. The states of individuals are updated every cycle (i.e. annually) for 20 years. Each cycle the state distributions and their related costs and DALYs are generated as output.
NAFLD: non-alcoholic fatty liver disease, T2D: type 2 diabetes, CHD: coronary heart disease, NASH: non-alcoholic steatohepatitis, HCC: hepatocellular carcinoma, DALYs: disability-adjusted life years.

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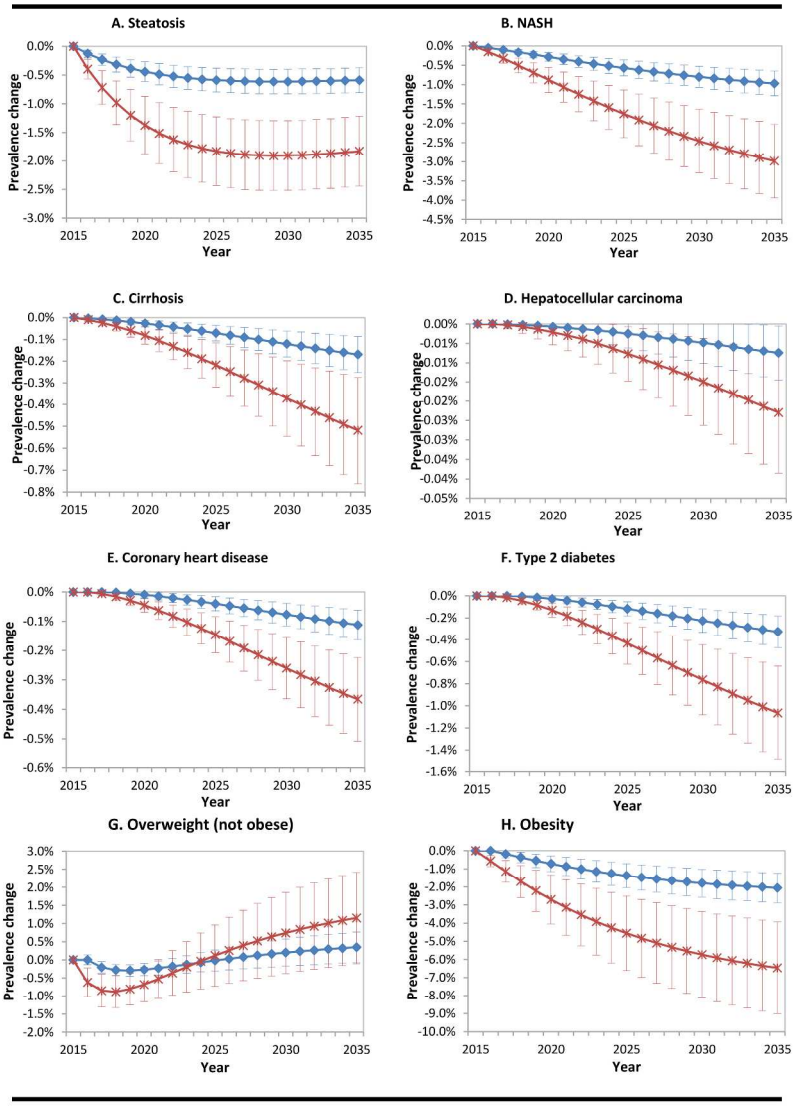

Figure 2, graphs A to H. reduction in population prevalence of disease due to interventions. Lines represent mean values +/- one standard deviation. 0% is the baseline, representing no intervention. The blue lines with diamonds indicate a reduction of added sugar of 20%. The red lines with crosses represent a reduction of 50%. NASH; non-alcoholic steatohepatitis.

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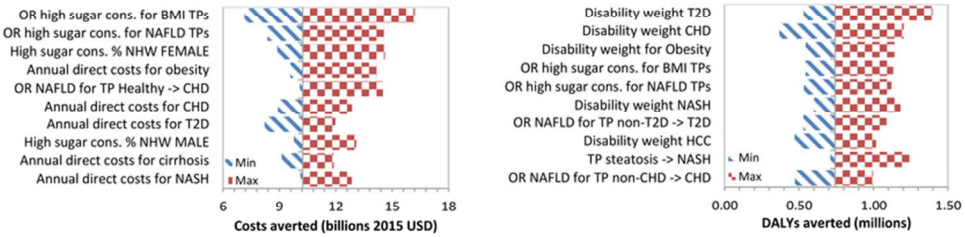

Figure 3. Tornado diagram of the ten most critical variables on total costs averted in the year 2035.
Figure 4. Tornado diagram of the ten most critical variables on total DALYs averted in the year 2035.

73x28mm (300 x 300 DPI)

Online supplement

Non-alcoholic fatty liver disease as a mediator of sugar effects; implications for the health and economic benefits of interventions in the US

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Table 1. Selected model parameter values and ranges.

Parameter					
Initialization	**Distribution**	**Mean**	**Min**	**Max**	**Source**
Age distribution	Fixed	OS2*1	-	-	[1]
Sex distribution	Fixed	OS3*2	-	-	[1]
Ethnicity distribution	Fixed	OS4*3	-	-	[1]
Steatosis prevalence	Beta	27.955%*4	18.637%	41.933%	[2-4]
NASH prevalence	Beta	3.141%*4	2.094%	4.712%	[2-4]
Cirrhosis prevalence	Beta	0.314%*4	0.209%	0.471%	[5-8]
HCC prevalence	Beta	0.025%*4	0.017%	0.038%	[9,10]
CHD prevalence	Fixed	6.544%*5	-	-	[11]
T2D prevalence	Fixed	9.447%*6	-	-	[11]
Overweight prevalence	Fixed	33.473%*7	-	-	[11]
Obesity prevalence	Fixed	37.391%*8	-	-	[11]
High sugar consumption	Beta	57.278%*9	38.186%	85.917%	[12,13]
Baseline transition probabilities	**Distribution**	**Mean chance**	**Min**	**Max**	**Source**
Non-NAFLD -> steatosis	Beta	0.0100	0.006700	0.01500	[14-22]
Non-NAFLD -> NASH	Beta	0.0003	0.000201	0.00045	[14-22]
Steatosis -> non-NAFLD	Beta	0.0200	0.013400	0.03000	[14-22]
Steatosis -> NASH	Beta	0.0060	0.004020	0.00900	[14-22]
Steatosis -> cirrhosis	Beta	0.0002	0.000134	0.00030	[14-22]
NASH -> non-NAFLD	Beta	0.0010	0.000670	0.00150	[14-22]
NASH -> steatosis	Beta	0.0200	0.013400	0.03000	[14-22]
NASH -> cirrhosis	Beta	0.0020	0.001340	0.00300	[14-22]
NASH -> HCC	Beta	0.0001*10	0.000067	0.00015	[14-25]
NASH -> liver death	Beta	0.0038	0.002546	0.00570	[26-29]
Cirrhosis -> HCC	Beta	0.0200*10	0.013400	0.03000	[14-25]
Cirrhosis -> liver death	Beta	0.0340	0.022780	0.05100	[26-29]
HCC -> liver death	Beta	0.5000	0.335000	0.75000	[26-29]
Non-CHD -> CHD	Beta	0.0045*11	0.003015	0.00675	[30,31]
CHD -> CHD death	Beta	0.0100*12	0.006700	0.01500	[30-32]
Non-T2D -> T2D	Beta	0.0045*13	0.003015	0.00675	[33,34]
T2D -> T2D death	Beta	0.0100*14	0.006700	0.01500	[32-34]
Healthy weight -> overweight	Beta	0.0500	0.033500	0.07500	[35-38]
Healthy weight -> obese	Beta	0.0060	0.004020	0.00900	[35-38]
Overweight -> healthy weight	Beta	0.0500	0.033500	0.07500	[35-38]
Overweight -> obese	Beta	0.0180	0.012060	0.02700	[35-38]
Obese-> healthy weight	Beta	0.0060	0.004020	0.00900	[35-38]
Obese -> overweight	Beta	0.0350	0.023450	0.05250	[35-38]
Each alive state -> non-disease related death	Beta	0.0100*15	0.006700	0.01500	[32]
Risk factors	**Distribution**	**Mean value**	**Min**	**Max**	**Source**
NHB ethnicity for progression within NAFLD	Beta	0.93	0.70	1.00	[39]
Hispanic ethnicity for progression within NAFLD	Beta	1.67	1.22	2.22	[39]
Overweight for progression within NAFLD	Beta	2.19	1.60	3.38	[15,40-45]
Obesity for progression within NAFLD	Beta	3.14	2.07	5.28	[15,40-45]
High sugar consumption for progression within NAFLD	Beta	2.00	1.50	3.00	[46,47]
NAFLD for TP non-CHD -> CHD	Beta	2.31	1.66	3.62	[48-52]
Overweight for TP non-CHD -> CHD	Beta	1.22	1.12	1.32	[53-60]
Obesity for TP non-CHD -> CHD	Beta	1.60	1.43	1.79	[53-60]
T2D for TP non-CHD -> CHD	Beta	2.24	1.64	3.06	[61]
NAFLD for TP non-T2D -> T2D	Beta	2.73	1.87	4.46	[62-68]
Overweight for TP non-T2D -> T2D	Beta	2.18	1.59	3.36	[69-75]
Obesity for TP non-T2D -> T2D	Beta	3.36	2.18	5.72	[69-75]
NAFLD for progression within the BMI chain	Beta	2.19	1.60	3.38	[15,40-45]
High sugar consumption for progression within the BMI chain	Beta	2.60	1.20	6.00	[76,77]
Regression rates	**Distribution**	**Mean value**	**Min**	**Max**	**Source**
CHD incidence regression rate/year	Beta	0.985	0.970	1.00	[78-81]
CHD mortality regression rate/year	Beta	0.979	0.958	1.00	[78-81]
Non-disease mortality regression rate/year (20-30)	Beta	1.000	0.990	1.00	[32]
Non-disease mortality regression rate/year (30-55)	Beta	0.980	0.960	1.00	[32]
Non-disease mortality regression rate/year (55+)	Beta	0.970	0.940	1.00	[32]

Table 1. Continued

Costs (annual direct medical, in 2015 USD)	Distribution	Mean value	SD		Source
Steatosis	Gamma	134	50		[82-85]
NASH	Gamma	267	100		[82-85]
Cirrhosis	Gamma	2861	1073		[86]
HCC	Gamma	42644	15992		[87,88]
CHD	Gamma	13233	4962		[89]
T2D	Gamma	8170	3064		[90]
Overweight	Gamma	343	129		[91]
Obesity	Gamma	916	344		[91]
Disability weights	**Distribution**	**Mean value**	**Min**	**Max**	**Source**
NASH	Beta	0.033	0.017	0.066	[3,84]
Cirrhosis	Beta	0.194	0.127	0.273	[92]
HCC	Beta	0.294	0.199	0.411	[92]
CHD	Beta	0.066	0.043	0.095	[92]
T2D	Beta	0.150	0.080	0.220	[92]
Obesity	Beta	0.012	0.001	0.022	[93]

SD: standard deviation, CHD: coronary heart disease, T2D: type 2 diabetes, NAFLD: non-alcoholic fatty liver disease (steatosis, NASH & cirrhosis), NASH: non-alcoholic steatohepatitis, HCC: hepatocellular carcinoma, Hisp: Hispanic, NHW: non-Hispanic white, NHB: non-Hispanic black, TP: transition probability, OR: odds ratio

*1 See online supplement table 2. *2 See online supplement table 3. *3 See online supplement table 4. *4 See online supplement table 5. *5 See online supplement table 6. *6 See online supplement table 7. *7 See online supplement table 8. *8 See online supplement table 9. *9 See online supplement table 10. *10 See online supplement table 11. *11 See online supplement table 12. *12 See online supplement table 13. *13 See online supplement table 14. *14 See online supplement table 15. *15 See online supplement table 16.

Table 2. Age distribution.[1]

Age	Percentage
20	1.9194
21	1.9194
22	1.9194
23	1.9194
24	1.9194
25	1.8701
26	1.8701
27	1.8701
28	1.8701
29	1.8701
30	1.7749
31	1.7749
32	1.7749
33	1.7749
34	1.7749
35	1.7757
36	1.7757
37	1.7757
38	1.7757
39	1.7757
40	1.8487
41	1.8487
42	1.8487
43	1.8487
44	1.8487
45	2.0018
46	2.0018
47	2.0018
48	2.0018
49	2.0018
50	1.9767
51	1.9767
52	1.9767
53	1.9767
54	1.9767
55	1.7505
56	1.7505
57	1.7505
58	1.7505
59	1.7505
60	1.5024
61	1.5024
62	1.5024
63	1.5024
64	1.5024
65	1.1073
66	1.1073
67	1.1073
68	1.1073
69	1.1073
70	0.8256
71	0.8256
72	0.8256
73	0.8256
74	0.8256
75	0.6473
76	0.6473
77	0.6473
78	0.6473
79	0.6473
80	0.5093
81	0.5093
82	0.5093
83	0.5093
84	0.5093
85+	2.4517

Table 3. Sex distribution.[1]

Sex	Percentage
Male	48.4388
Female	51.5612

Table 4. Ethnic distribution.[1]

Age	Percentage
Hispanic	14.0377
Non-hispanic White	74.3771
Non-hispanic Black	11.5852

Table 5. Non-alcoholic fatty liver disease prevalence percentage at start of simulation.[2-10]

Ethnicity	Steatosis	NASH	Cirrhosis	Hepatocellular carcinoma
Hispanic	40.05	4.5	0.45	0.0363
NH-White	26.70	3.0	0.30	0.0242
NH-Black	21.36	2.4	0.24	0.0194

Table 6. Coronary heart disease prevalence percentage at the start of the simulation.[11]

Sex	Ethnicity	Age	Percentage with CHD
Male	Hispanic	20-35	0.00
Male	Hispanic	35-44	1.30
Male	Hispanic	45-54	3.90
Male	Hispanic	55-64	10.60
Male	Hispanic	65-74	19.20
Male	Hispanic	75-84	23.50
Male	Hispanic	85+	23.80
Male	NH-White	20-35	0.00
Male	NH-White	35-44	1.20
Male	NH-White	45-54	6.00
Male	NH-White	55-64	13.80
Male	NH-White	65-74	23.30
Male	NH-White	75-84	31.80
Male	NH-White	85+	38.60
Male	NH-Black	20-35	0.00
Male	NH-Black	35-44	1.70
Male	NH-Black	45-54	7.50
Male	NH-Black	55-64	14.20
Male	NH-Black	65-74	16.90
Male	NH-Black	75-84	22.10
Male	NH-Black	85+	18.80
Female	Hispanic	20-35	0.00
Female	Hispanic	35-44	1.20
Female	Hispanic	45-54	3.00
Female	Hispanic	55-64	6.70
Female	Hispanic	65-74	16.20
Female	Hispanic	75-84	20.30
Female	Hispanic	85+	23.90
Female	NH-White	20-35	0.00
Female	NH-White	35-44	0.90
Female	NH-White	45-54	3.30
Female	NH-White	55-64	6.70
Female	NH-White	65-74	11.20
Female	NH-White	75-84	18.40
Female	NH-White	85+	24.30
Female	NH-Black	20-35	0.00
Female	NH-Black	35-44	1.20
Female	NH-Black	45-54	5.30
Female	NH-Black	55-64	11.20
Female	NH-Black	65-74	17.40
Female	NH-Black	75-84	19.80
Female	NH-Black	85+	21.80

Table 7. Type 2 diabetes prevalence percentage at the start of the simulation.[11]

Sex	Ethnicity	Age	Percentage with T2D
Male	Hispanic	20-24	0.90
Male	Hispanic	25-44	3.50
Male	Hispanic	45-54	14.20
Male	Hispanic	55-64	25.80
Male	Hispanic	65-74	32.80
Male	Hispanic	75-84	31.30
Male	Hispanic	85+	23.80
Male	NH-White	20-24	0.90
Male	NH-White	25-44	2.40
Male	NH-White	45-54	8.20
Male	NH-White	55-64	14.70
Male	NH-White	65-74	20.10
Male	NH-White	75-84	20.50
Male	NH-White	85+	17.90
Male	NH-Black	20-24	1.00
Male	NH-Black	25-44	5.00
Male	NH-Black	45-54	15.00
Male	NH-Black	55-64	24.00
Male	NH-Black	65-74	26.50
Male	NH-Black	75-84	39.00
Male	NH-Black	85+	18.70
Female	Hispanic	20-24	0.90
Female	Hispanic	25-44	3.60
Female	Hispanic	45-54	10.30
Female	Hispanic	55-64	24.00
Female	Hispanic	65-74	34.80
Female	Hispanic	75-84	32.40
Female	Hispanic	85+	22.80
Female	NH-White	20-24	1.20
Female	NH-White	25-44	2.80
Female	NH-White	45-54	7.30
Female	NH-White	55-64	12.10
Female	NH-White	65-74	17.00
Female	NH-White	75-84	17.10
Female	NH-White	85+	12.10
Female	NH-Black	20-24	1.00
Female	NH-Black	25-44	5.20
Female	NH-Black	45-54	10.90
Female	NH-Black	55-64	24.10
Female	NH-Black	65-74	32.60
Female	NH-Black	75-84	31.60
Female	NH-Black	85+	20.20

Table 8. Overweight and obesity prevalence percentages at the start of the simulation.[11]

Sex	Ethnicity	Age	Overweight percentage	Obesity percentage
Male	Hispanic	20-44	39.5	36.8
Male	Hispanic	45-64	43.8	41.0
Male	Hispanic	65+	42.8	44.7
Male	White	20-44	35.7	31.6
Male	White	45-64	40.8	39.0
Male	White	65+	42.5	36.9
Male	Black	20-44	28.7	36.9
Male	Black	45-64	34.3	40.6
Male	Black	65+	37.0	36.7
Female	Hispanic	20-44	33.2	36.8
Female	Hispanic	45-64	32.9	52.9
Female	Hispanic	65+	33.0	49.3
Female	White	20-44	25.3	28.0
Female	White	45-64	32.6	37.4
Female	White	65+	29.5	44.3
Female	Black	20-44	22.3	56.1
Female	Black	45-64	27.1	61.8
Female	Black	65+	25.8	53.7

Table 9. Added sugar consumption distributions.[12,13]

Sex	Ethnicity	Consumption group	% in low vs high risk group
Male	Hispanic	Low sugar consumption	36.40%
Male	Hispanic	High sugar consumption	63.60%
Male	Non-hispanic White	Low sugar consumption	36.40%
Male	Non-hispanic White	High sugar consumption	63.60%
Male	Non-hispanic Black	Low sugar consumption	34.10%
Male	Non-hispanic Black	High sugar consumption	65.90%
Female	Hispanic	Low sugar consumption	52.80%
Female	Hispanic	High sugar consumption	47.20%
Female	Non-hispanic White	Low sugar consumption	49.30%
Female	Non-hispanic White	High sugar consumption	50.70%
Female	Non-hispanic Black	Low sugar consumption	41.70%
Female	Non-hispanic Black	High sugar consumption	58.30%

Table 10. Hepatocellular carcinoma incidence rate from NASH.[14-25]

Age	Incidence rate
40 to 44 years	3.64216E-05
45 to 49 years	4.64842E-05
50 to 54 years	5.93269E-05
55 to 59 years	7.57179E-05
60 to 64 years	9.66373E-05
65 to 69 years	0.000123336
70 to 74 years	0.000157412
75 to 79 years	0.000200902
80 years and over	0.000256408

Table 11. Hepatocellular carcinoma incidence rate from cirrhosis.[14-25]

Age	Incidence rate
40 to 44 years	0.008844339
45 to 49 years	0.011287867
50 to 54 years	0.014406497
55 to 59 years	0.018386746
60 to 64 years	0.023466665
65 to 69 years	0.029950073
70 to 74 years	0.038224725
75 to 79 years	0.048785512
80 years and over	0.062264050

Table 12. Coronary heart disease incidence rate (in %).[30,31]

Year	<35	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
2010	0.0	0.0516	0.0516	0.2007	0.2007	0.3519	0.3519	0.5869	0.5869	1.4447	1.4447	3.0621
2011	0.0	0.0508	0.0508	0.1976	0.1976	0.3466	0.3466	0.5781	0.5781	1.4230	1.4230	3.0162
2012	0.0	0.0501	0.0501	0.1947	0.1947	0.3414	0.3414	0.5694	0.5694	1.4017	1.4017	2.9709
2013	0.0	0.0493	0.0493	0.1918	0.1918	0.3363	0.3363	0.5609	0.5609	1.3806	1.3806	2.9263
2014	0.0	0.0486	0.0486	0.1889	0.1889	0.3312	0.3312	0.5525	0.5525	1.3599	1.3599	2.8825
2015	0.0	0.0478	0.0478	0.1860	0.1860	0.3262	0.3262	0.5442	0.5442	1.3395	1.3395	2.8392
2016	0.0	0.0471	0.0471	0.1833	0.1833	0.3214	0.3214	0.5360	0.5360	1.3194	1.3194	2.7966
2017	0.0	0.0464	0.0464	0.1805	0.1805	0.3165	0.3165	0.5280	0.5280	1.2997	1.2997	2.7547
2018	0.0	0.0457	0.0457	0.1778	0.1778	0.3118	0.3118	0.5201	0.5201	1.2802	1.2802	2.7134
2019	0.0	0.0450	0.0450	0.1751	0.1751	0.3071	0.3071	0.5123	0.5123	1.2610	1.2610	2.6727
2020	0.0	0.0444	0.0444	0.1725	0.1725	0.3025	0.3025	0.5046	0.5046	1.2420	1.2420	2.6326
2021	0.0	0.0437	0.0437	0.1699	0.1699	0.2980	0.2980	0.4970	0.4970	1.2234	1.2234	2.5931
2022	0.0	0.0430	0.0430	0.1674	0.1674	0.2935	0.2935	0.4896	0.4896	1.2051	1.2051	2.5542
2023	0.0	0.0424	0.0424	0.1649	0.1649	0.2891	0.2891	0.4822	0.4822	1.1870	1.1870	2.5159
2024	0.0	0.0418	0.0418	0.1624	0.1624	0.2848	0.2848	0.4750	0.4750	1.1692	1.1692	2.4781
2025	0.0	0.0411	0.0411	0.1600	0.1600	0.2805	0.2805	0.4679	0.4679	1.1516	1.1516	2.4410
2026	0.0	0.0405	0.0405	0.1576	0.1576	0.2763	0.2763	0.4608	0.4608	1.1344	1.1344	2.4043
2027	0.0	0.0399	0.0399	0.1552	0.1552	0.2721	0.2721	0.4539	0.4539	1.1174	1.1174	2.3683
2028	0.0	0.0393	0.0393	0.1529	0.1529	0.2681	0.2681	0.4471	0.4471	1.1006	1.1006	2.3328
2029	0.0	0.0387	0.0387	0.1506	0.1506	0.2640	0.2640	0.4404	0.4404	1.0841	1.0841	2.2978
2030	0.0	0.0381	0.0381	0.1483	0.1483	0.2601	0.2601	0.4338	0.4338	1.0678	1.0678	2.2633
2031	0.0	0.0376	0.0376	0.1461	0.1461	0.2562	0.2562	0.4273	0.4273	1.0518	1.0518	2.2293
2032	0.0	0.0370	0.0370	0.1439	0.1439	0.2523	0.2523	0.4209	0.4209	1.0360	1.0360	2.1959
2033	0.0	0.0364	0.0364	0.1417	0.1417	0.2485	0.2485	0.4146	0.4146	1.0205	1.0205	2.1630
2034	0.0	0.0359	0.0359	0.1396	0.1396	0.2448	0.2448	0.4084	0.4084	1.0052	1.0052	2.1305
2035	0.0	0.0354	0.0354	0.1375	0.1375	0.2411	0.2411	0.4022	0.4022	0.9901	0.9901	2.0986

Table 13. Coronary heart disease mortality rate (in %).[30-32]

Year	<35	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
2010	0.0000	0.5067	0.8506	0.9493	1.3778	1.4767	1.4179	1.1071	2.1109	2.2865	3.9970	9.4859
2011	0.0000	0.4960	0.8327	0.9293	1.3489	1.4457	1.3881	1.0839	2.0665	2.2385	3.9130	9.2867
2012	0.0000	0.4856	0.8152	0.9098	1.3205	1.4153	1.3590	1.0611	2.0231	2.1914	3.8309	9.0917
2013	0.0000	0.4754	0.7981	0.8907	1.2928	1.3856	1.3304	1.0388	1.9807	2.1454	3.7504	8.9007
2014	0.0000	0.4654	0.7813	0.8720	1.2657	1.3565	1.3025	1.0170	1.9391	2.1004	3.6717	8.7138
2015	0.0000	0.4557	0.7649	0.8537	1.2391	1.3280	1.2751	0.9956	1.8983	2.0563	3.5946	8.5308
2016	0.0000	0.4461	0.7489	0.8358	1.2131	1.3002	1.2484	0.9747	1.8585	2.0131	3.5191	8.3517
2017	0.0000	0.4367	0.7331	0.8182	1.1876	1.2728	1.2221	0.9543	1.8195	1.9708	3.4452	8.1763
2018	0.0000	0.4275	0.7177	0.8010	1.1626	1.2461	1.1965	0.9342	1.7812	1.9294	3.3728	8.0046
2019	0.0000	0.4186	0.7027	0.7842	1.1382	1.2199	1.1714	0.9146	1.7438	1.8889	3.3020	7.8365
2020	0.0000	0.4098	0.6879	0.7677	1.1143	1.1943	1.1468	0.8954	1.7072	1.8492	3.2326	7.6719
2021	0.0000	0.4012	0.6735	0.7516	1.0909	1.1692	1.1227	0.8766	1.6714	1.8104	3.1648	7.5108
2022	0.0000	0.3927	0.6593	0.7358	1.0680	1.1447	1.0991	0.8582	1.6363	1.7724	3.0983	7.3531
2023	0.0000	0.3845	0.6455	0.7204	1.0456	1.1207	1.0760	0.8402	1.6019	1.7352	3.0332	7.1987
2024	0.0000	0.3764	0.6319	0.7053	1.0236	1.0971	1.0534	0.8225	1.5683	1.6987	2.9695	7.0475
2025	0.0000	0.3685	0.6187	0.6905	1.0021	1.0741	1.0313	0.8052	1.5353	1.6631	2.9072	6.8995
2026	0.0000	0.3608	0.6057	0.6760	0.9811	1.0515	1.0096	0.7883	1.5031	1.6281	2.8461	6.7546
2027	0.0000	0.3532	0.5929	0.6618	0.9605	1.0294	0.9884	0.7718	1.4715	1.5939	2.7864	6.6128
2028	0.0000	0.3458	0.5805	0.6479	0.9403	1.0078	0.9677	0.7556	1.4406	1.5605	2.7278	6.4739
2029	0.0000	0.3385	0.5683	0.6343	0.9206	0.9867	0.9474	0.7397	1.4104	1.5277	2.6706	6.3380
2030	0.0000	0.3314	0.5564	0.6209	0.9012	0.9659	0.9275	0.7242	1.3808	1.4956	2.6145	6.2049
2031	0.0000	0.3245	0.5447	0.6079	0.8823	0.9457	0.9080	0.7090	1.3518	1.4642	2.5596	6.0746
2032	0.0000	0.3176	0.5332	0.5951	0.8638	0.9258	0.8889	0.6941	1.3234	1.4335	2.5058	5.9470
2033	0.0000	0.3110	0.5220	0.5826	0.8456	0.9064	0.8703	0.6795	1.2956	1.4034	2.4532	5.8221
2034	0.0000	0.3044	0.5111	0.5704	0.8279	0.8873	0.8520	0.6652	1.2684	1.3739	2.4017	5.6998
2035	0.0000	0.2981	0.5004	0.5584	0.8105	0.8687	0.8341	0.6513	1.2417	1.3450	2.3513	5.5801

Table 14. Type 2 diabetes incidence rate.[33,34]

Age	Incidence rate
20-24	0.000447
25-29	0.000762
30-34	0.001090
35-39	0.001625
40-44	0.002880
45-49	0.003575
50-54	0.004957
55-59	0.005071
60-64	0.004662
65-69	0.004450
70-74	0.003925
75-79	0.003609
80+	0.003240

Table 15. Type 2 diabetes mortality rate.[32-34]

Age	Mortality rate
20-24	0.006177
25-29	0.009399
30-34	0.009399
35-39	0.009399
40-44	0.009399
45-49	0.013706
50-54	0.013706
55-59	0.020137
60-64	0.020137
65-69	0.031904
70-74	0.031904
75-79	0.068313
80+	0.068313

Table 16. Non-disease related mortality rate (in %).[32]

Year	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
2010	0.086	0.093	0.105	0.128	0.178	0.275	0.411	0.583	0.822	1.242	1.909	3.038	4.952	11.162
2011	0.086	0.093	0.105	0.125	0.174	0.269	0.403	0.571	0.797	1.205	1.851	2.947	4.804	10.828
2012	0.086	0.093	0.105	0.123	0.171	0.264	0.395	0.560	0.773	1.169	1.796	2.859	4.660	10.503
2013	0.086	0.093	0.105	0.120	0.167	0.259	0.387	0.548	0.750	1.133	1.742	2.773	4.520	10.188
2014	0.086	0.093	0.105	0.118	0.164	0.253	0.379	0.537	0.728	1.099	1.690	2.690	4.384	9.882
2015	0.086	0.093	0.105	0.115	0.161	0.248	0.372	0.527	0.706	1.066	1.639	2.609	4.253	9.586
2016	0.086	0.093	0.105	0.113	0.158	0.243	0.364	0.516	0.685	1.034	1.590	2.531	4.125	9.298
2017	0.086	0.093	0.105	0.111	0.154	0.239	0.357	0.506	0.664	1.003	1.542	2.455	4.002	9.019
2018	0.086	0.093	0.105	0.109	0.151	0.234	0.350	0.496	0.644	0.973	1.496	2.381	3.881	8.749
2019	0.086	0.093	0.105	0.106	0.148	0.229	0.343	0.486	0.625	0.944	1.451	2.310	3.765	8.486
2020	0.086	0.093	0.105	0.104	0.145	0.225	0.336	0.476	0.606	0.916	1.408	2.241	3.652	8.231
2021	0.086	0.093	0.105	0.102	0.142	0.220	0.329	0.467	0.588	0.888	1.365	2.173	3.543	7.985
2022	0.086	0.093	0.105	0.100	0.140	0.216	0.323	0.457	0.570	0.862	1.324	2.108	3.436	7.745
2023	0.086	0.093	0.105	0.098	0.137	0.211	0.316	0.448	0.553	0.836	1.285	2.045	3.333	7.513
2024	0.086	0.093	0.105	0.096	0.134	0.207	0.310	0.439	0.537	0.811	1.246	1.984	3.233	7.287
2025	0.086	0.093	0.105	0.094	0.131	0.203	0.304	0.430	0.521	0.786	1.209	1.924	3.136	7.069
2026	0.086	0.093	0.105	0.092	0.129	0.199	0.298	0.422	0.505	0.763	1.172	1.866	3.042	6.857
2027	0.086	0.093	0.105	0.090	0.126	0.195	0.292	0.413	0.490	0.740	1.137	1.810	2.951	6.651
2028	0.086	0.093	0.105	0.089	0.124	0.191	0.286	0.405	0.475	0.718	1.103	1.756	2.862	6.451
2029	0.086	0.093	0.105	0.087	0.121	0.187	0.280	0.397	0.461	0.696	1.070	1.703	2.776	6.258
2030	0.086	0.093	0.105	0.085	0.119	0.183	0.275	0.389	0.447	0.675	1.038	1.652	2.693	6.070
2031	0.086	0.093	0.105	0.083	0.116	0.180	0.269	0.381	0.434	0.655	1.007	1.603	2.612	5.888
2032	0.086	0.093	0.105	0.082	0.114	0.176	0.264	0.374	0.421	0.635	0.977	1.555	2.534	5.711
2033	0.086	0.093	0.105	0.080	0.112	0.173	0.258	0.366	0.408	0.616	0.947	1.508	2.458	5.540
2034	0.086	0.093	0.105	0.079	0.110	0.169	0.253	0.359	0.396	0.598	0.919	1.463	2.384	5.374
2035	0.086	0.093	0.105	0.077	0.107	0.166	0.248	0.352	0.384	0.580	0.891	1.419	2.313	5.213

Table 17. IHME health-adjusted life expectancy and discounted life expectancy for females. [94,95]

Age of death	WHO HALE	Discounted by 3%
20	51.138	25.981
21	51.138	25.981
22	51.138	25.981
23	51.138	25.981
24	51.138	25.981
25	46.766	24.966
26	46.766	24.966
27	46.766	24.966
28	46.766	24.966
29	46.766	24.966
30	42.466	23.832
31	42.466	23.832
32	42.466	23.832
33	42.466	23.832
34	42.466	23.832
35	38.214	22.560
36	38.214	22.560
37	38.214	22.560
38	38.214	22.560
39	38.214	22.560
40	34.033	21.144
41	34.033	21.144
42	34.033	21.144
43	34.033	21.144
44	34.033	21.144
45	29.960	19.584
46	29.960	19.584
47	29.960	19.584
48	29.960	19.584
49	29.960	19.584
50	26.017	17.884
51	26.017	17.884
52	26.017	17.884
53	26.017	17.884
54	26.017	17.884
55	22.214	16.045
56	22.214	16.045
57	22.214	16.045
58	22.214	16.045
59	22.214	16.045
60	18.574	14.081
61	18.574	14.081
62	18.574	14.081
63	18.574	14.081
64	18.574	14.081
65	15.167	12.042
66	15.167	12.042
67	15.167	12.042
68	15.167	12.042
69	15.167	12.042
70	12.020	9.968
71	12.020	9.968
72	12.020	9.968
73	12.020	9.968
74	12.020	9.968
75	9.169	7.912
76	9.169	7.912
77	9.169	7.912
78	9.169	7.912
79	9.169	7.912
80	6.646	5.942
81	6.646	5.942
82	6.646	5.942
83	6.646	5.942
84	6.646	5.942
85	4.512	4.159
86	4.512	4.159
87	4.512	4.159
88	4.512	4.159
89	4.512	4.159
90	2.915	2.751
91	2.915	2.751
92	2.915	2.751
93	2.915	2.751
94	2.915	2.751
95	1.868	1.789
96	1.868	1.789
97	1.868	1.789
98	1.868	1.789
99	1.868	1.789
100	1.231	1.189
101	1.231	1.189
102	1.231	1.189
103	1.231	1.189
104	1.231	1.189
105	1.000	0.971
106	1.000	0.971
107	1.000	0.971
108	1.000	0.971
109	1.000	0.971
110	1.000	0.971

Table 18. IHME health-adjusted life expectancy and discounted life expectancy for males.[94,95]

Age of death	WHO HALE	Discounted by 3%
20	48.035	25.275
21	48.035	25.275
22	48.035	25.275
23	48.035	25.275
24	48.035	25.275
25	43.802	24.200
26	43.802	24.200
27	43.802	24.200
28	43.802	24.200
29	43.802	24.200
30	39.589	22.989
31	39.589	22.989
32	39.589	22.989
33	39.589	22.989
34	39.589	22.989
35	35.374	21.616
36	35.374	21.616
37	35.374	21.616
38	35.374	21.616
39	35.374	21.616
40	31.217	20.085
41	31.217	20.085
42	31.217	20.085
43	31.217	20.085
44	31.217	20.085
45	27.195	18.412
46	27.195	18.412
47	27.195	18.412
48	27.195	18.412
49	27.195	18.412
50	23.347	16.614
51	23.347	16.614
52	23.347	16.614
53	23.347	16.614
54	23.347	16.614
55	19.705	14.714
56	19.705	14.714
57	19.705	14.714
58	19.705	14.714
59	19.705	14.714
60	16.256	12.716
61	16.256	12.716
62	16.256	12.716
63	16.256	12.716
64	16.256	12.716
65	13.080	10.688
66	13.080	10.688
67	13.080	10.688
68	13.080	10.688
69	13.080	10.688
70	10.208	8.680
71	10.208	8.680
72	10.208	8.680
73	10.208	8.680
74	10.208	8.680
75	7.680	6.767
76	7.680	6.767
77	7.680	6.767
78	7.680	6.767
79	7.680	6.767
80	5.524	5.019
81	5.524	5.019
82	5.524	5.019
83	5.524	5.019
84	5.524	5.019
85	3.723	3.471
86	3.723	3.471
87	3.723	3.471
88	3.723	3.471
89	3.723	3.471
90	2.388	2.269
91	2.388	2.269
92	2.388	2.269
93	2.388	2.269
94	2.388	2.269
95	1.521	1.462
96	1.521	1.462
97	1.521	1.462
98	1.521	1.462
99	1.521	1.462
100	1.000	0.971
101	1.000	0.971
102	1.000	0.971
103	1.000	0.971
104	1.000	0.971
105	1.000	0.971
106	1.000	0.971
107	1.000	0.971
108	1.000	0.971
109	1.000	0.971
110	1.000	0.971

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Additional file 1

EVEREST Statement: Checklist for health economics paper

	Study section	Additional remarks
Study design		
(1) The research question is stated	Introduction	Page 2
(2) The economic importance of the research question is stated	Introduction	Page 2
(3) The viewpoint(s) of the analysis are clearly stated and justified	Introduction, Methods	Page 2 and page 4-5 (interventions)
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Methods	Page 4-5 (interventions)
(5) The alternatives being compared are clearly described	Methods	Page 4-5 (interventions)
(6) The form of economic evaluation used is stated	Methods	Page 3
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Introduction, Methods	Page 3
Data collection		
(8) The source(s) of effectiveness estimates used are stated	Methods; Table 1, Table 2	Page 5 and 6
(9) Details of the design and results of effectiveness study are given (if based on single study)	N/A	Data derived from peer reviewed literature and national health surveys
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	Methods	Page 6
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods	Page 5
(12) Methods to value health states and other benefits are stated	Methods	Page 5; table 1
(13) Details of the subjects from whom valuations were obtained are given	N/A	
(14) Productivity changes (if included) are reported separately	N/A	
(15) The relevance of productivity changes to the study question is discussed	N/A	
(16) Quantities of resources are reported separately from their unit costs	Methods; stated per person; Table 1, Table 2	Page 5 and 6
(17) Methods for the estimation of quantities and unit costs are described	Methods; Table 1, Table 2	Page 5 and 6; Adopted from literature

(18) Currency and price data are recorded	Methods; Table 1, Table 2	Page 5 and 6
(19) Details of currency of price adjustments for inflation or currency conversion are given	Methods	Page 5
(20) Details of any model used are given	Methods	Page 3
(21) The choice of model used and the key parameters on which it is based are justified	Methods	Page 3
Analysis and interpretation of results		
(22) Time horizon of costs and benefits is stated	Methods	Page 5
(23) The discount rate(s) is stated	Methods	Page 5
(24) The choice of rate(s) is justified	Methods	Page 5
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	N/A	
(27) The approach to sensitivity analysis is given	Methods	Page 6
(28) The choice of variables for sensitivity analysis is justified	Methods; Table 1, Table 2	Page 6
(29) The ranges over which the variables are varied are stated	Table 1, Table 2	Page 6
(30) Relevant alternatives are compared	Methods, Results	Page 4 and 5
(31) Incremental analysis is reported	N/A	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	Table 3, 4 and 5	Page 7 and 9
(33) The answer to the study question is given	Discussion, Conclusion	Page 10
(34) Conclusions follow from the data reported	Conclusion	Page 11
(35) Conclusions are accompanied by the appropriate caveats	Discussion, Conclusion	Page 10

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Non-alcoholic fatty liver disease as a mediator of detriments of dietary sugar consumption: implications for the health and economic benefits of interventions in the United States

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Non-alcoholic fatty liver disease as a mediator of detriments of dietary sugar consumption: implications for the health and economic benefits of interventions in the United States

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Abstract

Objectives: Excessive consumption of added sugars in the human diet has been associated with obesity, type 2 diabetes (T2D), coronary heart disease (CHD), and other elements of the metabolic syndrome. Recent studies have shown that non-alcoholic fatty liver disease (NAFLD) is a critical pathway to metabolic syndrome. This model assesses the health and economic benefits of interventions aimed at reducing intake of added sugars.

Methods: Using data from U.S. National Health Surveys and current literature, we simulated an open cohort, for the period 2015 to 2035. We constructed a microsimulation model with Markov chains for NAFLD (including steatosis, non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC)), body mass index (BMI), T2D, and CHD. We assessed reductions in population disease prevalence, disease-attributable disability-adjusted life years (DALYs), and costs, with interventions that reduce added sugars consumption by either 20% or 50%.

Findings: The model estimated that a 20% reduction in added sugars intake will reduce prevalence of hepatic steatosis, NASH, cirrhosis, HCC, obesity, T2D, and CHD. Incidence of T2D and CHD would be expected to decrease by 19.9 (95% CI: 12.8 – 27.0) and 9.4 (95% CI: 3.1 — 15.8) cases per 100,000 people after 20 years, respectively. A 20% reduction in consumption is also projected to annually avert 0.767 million (M) DALYs (95% CI: 0.757M — 0.777M), and a total of 10.3 billion (B) USD (95% CI: 10.2B — 10.4B) in discounted direct medical costs by 2035. These effects increased proportionally when added sugars intake were reduced by 50%.

Conclusions: The decrease in incidence and prevalence of disease is similar to results in other models, but averted costs and DALYs were higher, mainly due to inclusion of NAFLD and CHD. The model suggests that efforts to reduce consumption of added sugars may result in significant public health and economic benefits.

Strengths and limitations of this study

- No previous model has captured the full effects of added sugars through non-alcoholic fatty liver disease, obesity, type 2 diabetes and coronary heart disease.
- This model is applicable to each intervention that is aimed at reducing added sugars.
- The model is based on input parameters from multiple studies who were not always of excellent quality. We have used large intervals around these parameters to ensure reliable results.

Introduction

The social and economic burdens of chronic metabolic disease have been increasing in the United States for the last three decades. Two-thirds of the adult population in the United States is now overweight, and morbid obesity affects 9.9% of all adult women.[1] Prevalence of Type 2 diabetes (T2D) in the U.S. is at 9.3%.[2,3] And the population affected by Coronary heart disease (CHD) increased concurrently from 13 to 15.5 million over the last ten years.[4,5] More than 15% of all deaths are attributable to CHD and more than 3% to diabetes.[6] Costs have simultaneously increased; and costs for CHD are expected to double over the next two decades.[7,8] Though these figures are stunning, they underestimate the magnitude of the problem. Non-alcoholic fatty liver disease (NAFLD) has recently been found to be present in over 45% of Latinos, 33% of Caucasians, and 24% of African-Americans, and is thought to play an important role in metabolic pathophysiology.[9–12] NAFLD is defined by the presence of liver fat in the absence of a primary insult such as alcohol, viral hepatitis, or heavy metal accumulation.[13] NAFLD is further categorized into: a) hepatic steatosis, which is a reversible fat accumulation in the liver defined by an occupation of steatotic hepatocytes of more than 5% of the liver parenchyma; and b) non-alcoholic steatohepatitis (NASH), which is defined as the presence of hepatic steatosis along with lobular and portal inflammation with hepatocyte injury (ballooning). Progressive collagen deposition and vascular remodelling in NASH may lead to cirrhosis, which in turn predisposes one to hepatocellular carcinoma (HCC).[9,13–15] NAFLD is the most common cause of liver disease in the Western world, and NASH is projected to become the leading cause of liver transplantation in the USA by the year 2020.[16,17] Currently 30-40% of NASH-cirrhotic patients succumb to a liver-related death within 10 years.[18,19] Hospitalizations for NAFLD have increased 97% between 2000 and 2012.[20] NAFLD has also been suggested as an important driver of T2D in lean individuals, as liver fat accumulation can cause insulin resistance.[10,21–23] NAFLD can occur as either a cause or consequence of the metabolic syndrome[10], and many now argue that NAFLD is the hepatic manifestation of metabolic syndrome, and should be included in its definition.[24–27] It is important to identify determinants of these metabolic diseases and assess the efficacy of upstream policy interventions to curb the national and the global epidemic of metabolic syndrome.

Added sugars

Added sugars consumption increased in the U.S. over the years 1977-2000, decreased slightly between 2000—2008, and seems to have stabilized in the years thereafter.[28–30] Over 55% of all American adults consumed more than 50 grams of added sugars per day between 2005—2012, which is thought to be the cut-off value for added risk of metabolic derangement, and more than the advised maximum according to the American Heart Association (25 - 37.5 grams).[3,31] The U.S. Department of Agriculture recently established guidance for an upper limit of consumption of added sugars at 10% of total energy intake (amounting to 50 grams per day (200 kcal) for a prototype 2000 kcal/day diet).[32] The European Food and Safety authority does not state an explicit maximum for (added) sugars in their advice, but they do note that a number of authorities have established boundaries of <10% of total energy intake.[33] Furthermore, the American Heart Association recommends that U.S. adolescents restrict their intake of added sugars to less than 25 grams to avoid dyslipidaemia and CVD [34], yet current intake averages 94.0 grams per day in this age group.[35]

The excessive amount of added sugars (glucose + fructose) in the food supply has been associated with NAFLD and with each of the component diseases of the metabolic syndrome.[36–38] Fructose is metabolized by the liver, as it is the only organ with the required Glut5 transporter. Fructose bypasses glycogen, and is metabolized by the glycolytic pathway to acetyl-CoA. From there, excess acetyl-CoA is converted to citrate, diverted from the mitochondria into the cytoplasm via the citrate shuttle, and is then converted into fatty acids through the process of *de novo* lipogenesis(DNL).[39] From there, hepatically-derived excess triglyceride is either packaged with apo-B100 into very-low-density-lipoprotein (VLDL), which is released into the bloodstream and can foment cardiovascular disease; or will precipitate as a lipid droplet, resulting in hepatic steatosis which drives insulin resistance, causing weight gain, and predisposing to T2D. While most early studies of added sugar and chronic disease were correlative and confounded by excess caloric administration, lack of adjustment for total calories, or adiposity, more recent studies demonstrate that the effect is specific for dietary fructose, and independent of calories consumed and BMI.[39–48] For instance, added sugar is directly correlated with risk for metabolic syndrome in adolescents in NHANES even after controlling for total calories and BMI z-score.[35] Added sugar has been associated with elevated uric acid levels and hypertension.[49,50] Two recent studies, both controlled for calories and adiposity and employing a time analysis, support sugar-sweetened beverages as a specific causative agent in the pathogenesis of T2D.[42,51,52] A decade-long global econometric analysis demonstrates that only changes in sugar availability are predictive of changes in diabetes prevalence, unrelated to poverty, urbanization, aging, physical activity, total calories, or obesity.[37] Lastly, in a starch-for-sugar exchange study, our group has documented improvements in metabolic and lipid parameters unrelated to both calories and changes in weight, demonstrating improved metabolic health within 10 days.[40,53] We have demonstrated that the decline in DNL and resultant reduction in liver fat was the primary driver in the metabolic and cardiovascular improvement.[54] By demonstrating that removal of dietary fructose (the macronutrient most closely associated with DNL) commensurately improves liver fat and insulin dynamics irrespective of calories or weight, we are able to infer a causative mechanism of metabolic dysfunction by linking DNL to both liver fat and insulin resistance. We also demonstrated that despite an increase in the glucose (starch) content of the diet, beta-cell insulin secretion reduced, thus protecting against beta-cell exhaustion, thought to be important in the pathogenesis of type 2 diabetes[55]*;* and reducing total body insulin burden, thought to contribute to both obesity and risk for cardiovascular disease.[56,57] Thus, reduction in DNL and liver fat through reduction in consumption of added sugars appears to be a

primary goal of both therapy and prevention of chronic metabolic disease, and forms the rationale for our microsimulation model.

Intervention efficacy

Several studies have modeled the effects of different interventions to reduce added sugars intake. One popular intervention is the implementation of a sugar-sweetened beverage (SSB) tax. Though this does not affect all added sugars in the food supply, SSB's are the main single contributor to overall added sugars intake, and a tax on SSB's is easier to implement than an added sugars tax.[58] A 20% SSB tax is projected to reduce prevalence of obesity anywhere from 1.5 —10%, based on different studies.[59–61] Data from Mexico demonstrate that effects on reduction of consumption are durable, although evidence of mitigation of disease are not yet available.[62] Annual diabetes cases would be expected to decline concurrently between 1.8% and 3.4%, and CHD cases by 0.5 —1.0%.[60,63] Additional research has focused on other strategies to lower added sugars consumption. Banning SSB's from the U.S. Supplemental Nutrition Assistance Program (SNAP) is expected to result in a 0.89% lower obesity prevalence within 10 years, while lowering the amount of sugars in the food supply through a cap and trade approach by 1% annually is expected to lower the prevalence of obesity by 1.7% after 20 years.[64,65]

An important limitation of all these studies is that none of these models incorporate the effects and costs related to sugar-induced NAFLD. Because NAFLD explains a part of the incidence of diabetes in lean individuals and is expected to contribute significantly to overall healthcare burden and costs, it is necessary that models incorporate all of these diseases.

Our goal is to predict the magnitude of the health and economic effects of interventions that are designed to reduce added sugars consumption either by 20% or 50%, respectively. This modelling approach more precisely quantifies the benefits of reducing added sugar consumption. We describe the process of creating, calibrating and validating a microsimulation model. We clarify the relevant interactions that determine progression within this model in Markov chains for NAFLD (including cirrhosis and HCC), obesity, T2D, and CHD, and we describe the creation of a simulated open cohort representative of the US population. We allow the model to run for 20 years into the future to predict effectiveness. We report the outcomes of these simulations in future incidence, prevalence and mortality of disease, and in disability-adjusted life years (DALYs) and costs averted.

Methods

The Methods section is constructed according to the recommendations by the ISPOR taskforce for good modelling practice, and completeness is checked according to the CHEERS statement.[66,67]

Summary

We constructed an individual based model consisting of a base cohort of 22,400 people. New people entered the model each year at age 20, the youngest age group we simulate. Individuals are assigned a state at initialization in each 'chain' of the model. These include age, sex, ethnicity, sugar consumption, NAFLD, BMI, T2D, and CHD. The current health state of each individual at the beginning of a cycle forms a risk profile, and the presence in a risk-inducing state in one of the chains can influence the probability of transitioning between states in a different chain, according to literature-based odds ratios. We simulated 20 annual cycles for each individual, counting events, incurred direct medical costs, and DALYs for each cycle, as well as the overall prevalence for the total cohort. We discounted the costs and DALYs by 3.0% annually, and costs were presented in 2015 USD. Two interventions were simulated: one that reduced each individual's added sugars consumption by 20%, and one that reduced it by 50%. We used identical random numbers for the base case scenario and each of the interventions, to reduce variance. We calibrated the model to other studies reporting historic trends and predicting future prevalence, and validated the model via face validation, cross-validation, and sensitivity analyses. Deterministic sensitivity analysis was used to determine the influence of individual input parameters. Probabilistic sensitivity analysis was used to generate mean results and 95% central coverage intervals.

Model type

An individual-based stochastic Markov model (microsimulation) was used. The model contained a chain for each of four separate diseases. Because each of these diseases has a minimum of 3 states, and the transitions between these states are based on the presence or absence of a set of risk factors, the state-space explosion phenomenon prohibits us from using traditional Markov cohort simulation. An individual-based approach makes it possible to use individual-specific transition rates, capturing the effect of interventions on individual risk factor profiles, thereby avoiding the need to count the number of individuals in all possible states and allowing for complex relationships between several risk factors within a single individual.[68] It also opens up potential for future analyses among subgroups.

Population and setting

The model is based on the adult population (age 20+) of the United States. Outcomes are reported from a healthcare perspective. This includes direct medical costs and DALYs averted. Indirect medical or non-medical costs are excluded. Because this model is meant to assess the benefits of reducing added sugars intake, unrelated to the type of intervention, costs of implementing any specific intervention and possible revenues (e.g. in the case of an excise or general services tax) are also excluded.

Model structure and input parameters

A simplified model transition diagram is presented in **Figure 1.** Model input parameters are presented in **table 1 and 2** and supplementary **table 1**. Individuals will reside in a state within each chain at any given point in time. The probability of staying within a state or moving to another state in each cycle is determined by a set of defined transition probabilities, which are influenced by the risk profile (the current state in the other chains) of the individual. Events in different chains can occur in parallel.

The simulation is initialized by assignment of age (A), sex (S), and ethnicity (E) to each individual. Age states are based on the population distribution that is provided by the Bureau of the Census, and are specified for each age from 20 to 84 and a cumulative age group for anyone above 85. We simulate an open cohort. New individuals with age 20 enter each year.[69] The initial age distribution is specified in supplementary **table 2**. Male and female sex are incorporated with an initial distribution specified in supplementary **table 3**. Ethnicities incorporated into the model are Hispanic, non-Hispanic black, and non-Hispanic-white. Data availability did not allow us to incorporate Asians and Native Americans as separate groups and therefore they were grouped with the non-Hispanic whites. The initial ethnicity distribution is specified in supplementary **table 4**.

When the individual is assigned an age, sex and ethnicity, these determine the state that this individual will be assigned to in each of the chains for NAFLD, BMI, T2D, and CHD at the start of the simulation. Each chain represents a separate disease process, and has its own non-disease state (e.g., non-T2D). This does not mean that this person is actually healthy (e.g. a person can have cirrhosis but not diabetes). The NAFLD chain includes a non-NAFLD state, and states for hepatic steatosis, NASH, cirrhosis, and NASH- or cirrhosis-related HCC. A person is defined as having NAFLD when his or her current state is steatosis, NASH, or cirrhosis. This is different from common terminology, where cirrhosis is excluded. We chose this definition for easy reference, because these three states imply extra risk for progression within other chains. The initial distribution over NAFLD states is specified in supplementary **table 5** and specified per ethnicity group.

It is important to note that modeled cirrhosis and HCC are specifically related to steatosis and NASH, and do not include all cirrhosis and HCC cases within the population, irrespective of cause. Transition directly from the non-NAFLD state to either one is therefore not possible. Baseline transition probabilities are specified in **table 2** and transition rates from NASH and cirrhosis to HCC are specified per age group, as defined in supplementary **table 6 and 7**, starting at age 40. (age groups: 40-44, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79 and 80 years and over), Risk factors for progression are stated in **table 2** and include ethnicity (protective and detrimental factors), being overweight or obese, and high sugar consumption. These risk factors apply for transitions up to the cirrhosis state.

The BMI chain includes states for healthy weight, overweight and obesity. The initial distribution over BMI states is specified in supplementary **table 8,** and specified by sex, ethnicity, and age group (ages 20-35, 35-44, 45-54, 55-64, 65-74, 75-84 and 85+). Baseline transition probabilities are specified in **table 2**. Risk factors for progression are stated in **table 1** and include NAFLD disease states and high sugar consumption.

The T2D chain includes a non-T2D state and a T2D state. The initial distribution over T2D states is specified in supplementary **table 9** and specified by sex, ethnicity, and age group (ages 20-35, 35-44, 45-54, 55-64, 65-74 75-84 and 85+). Average baseline transition probability to T2D is specified in **table 2** and age-specific incidence rates are provided in supplementary **table 10** (age groups: 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79 and 80+). Risk factors for progression to T2D are stated in **table 2** and include NAFLD disease states, overweight, and obesity.

The CHD chain includes a non-CHD state and a CHD state. The distribution over CHD states at simulation start is specified in supplementary **table 11** and specified per sex, ethnicity and age group (ages 20-44, 45-64 and 65+). Average baseline transition probability to CHD is specified in **table 2** and age-specific incidence rates are provided in supplementary **table 12** (age groups: <35, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84 and 85+). Risk factors for progression to CHD are stated in **table 2** and include NAFLD disease states, overweight, obesity, and T2D.

Each individual is assigned a level of consumption of added sugars. There are two states in the sugar chain — high consumption (≥50g of added sugars per day), and low consumption (< 50g of added sugars per day). The distribution of these states among the study population reflects the data of the NHANES 2005-2012, and is specified per sex and ethnicity group, as shown by supplementary **table 13**.[3,35] Dietary intake data in NHANES were collected using two 24-hr dietary recalls, following the United States Department of Agriculture's (USDA) Automated Multiple Pass Method and administered to the adult.[70] The arithmetic mean of added sugar intake in grams per day was obtained by merging individual dietary recalls from NHANES with the USDA Food Patterns Equivalents Database (FPED).[71] Sugar consumption is fixed throughout the simulation for each person.

From each state, individuals can transition to a 'non-disease related death' state. Three disease chains also have a disease-specific death state (i.e.. T2D-death, CHD-death, and liver-related death), allowing calculation of disease-attributable death. Mortality rates from causes outside the model were corrected for the competing risks of modeled causes of mortality to

ensure valid overall mortality. Death in one chain forces an instant transition to the death state in other chains. Average transition probabilities to disease-related death states are specified in **table 2**. Age specific rates for T2D-related death are specified in supplementary **table 14**. Liver death rates are specified in **table 2**. Deaths were attributed to the disease for which the transition to death was established first. To remove confounding because of calculation order, chain calculation order was randomized. This ensures that deaths are attributed to the right disease, e.g. people with T2D and CHD have a chance to die of T2D, CHD or succumb to a non-disease related death.

To determine whether there were temporal trends in incidence or death rates, we plotted the available historic data (1999-2013) and projected this to the future.[5,6,72] These trends were found to be present for the incidence and mortality rate of CHD, and for the non-disease specific mortality rate. We incorporated these regression rates into the model by adjusting the respective baseline transition probabilities before each cycle. Average baseline transition probabilities for CHD and non-disease related deaths are specified in **table 2**. The CHD-specific death rates by year and age are specified in supplementary **table 15** and the non-disease related death rates per year and age are specified in supplementary **table 16**. For DALY calculations, health-adjusted life expectancy for females and males are provided in **supplementary table 17 and 18**.

Final transition probabilities per chain are compared to a pseudo-random number to determine state-transitions each cycle. These final transition probabilities were derived from baseline transition probabilities, adjusting for the relative risk of progression observed for applicable risk factors. The correction formula for the baseline transition probabilities is a multiplicative function of all applicable values (odds ratios) for present risk factors. As an example, imagine a person with high sugar consumption, obesity, and hepatic steatosis, but no T2D or CHD (disregarding age, sex & ethnicity in this example). In the NAFLD chain the transition from steatosis to NASH has a baseline transition probability of 0.0060 (see table 2). This is adjusted to reflect the ORs for applicable risk factors (3.14 for obesity and 2.00 for high sugar consumption), resulting in a revised transition probability of 0.0060 * 3.14 * 2.00 = 0.0377. Similar adjustments are made for transitions to cirrhosis, HCC, death,and non-NAFLD. What remains is the probability of remaining in the steatosis state.

Figure 1

Interventions

Two interventions were simulated: a reduction of 20%, and a reduction of 50% in individual added sugars consumption. A 20% reduction in added sugars was simulated to be consistent with the percentage reduction assessed in several studies.[59–61] In addition, a 50% reduction was simulated because the American Heart Association advises 6-9 teaspoons of added sugar (for females and males respectively) as a maximum per day, which is approximately 50% of the current average consumption.[3,31,35] The individual added sugars consumption distribution was then split into a dichotomous variable; with people consuming less than or equal to 50 grams of added sugars being considered low consumers, and people consuming more than 50 grams per day being considered high consumers. This model did not incorporate substitutions to other food categories, but it did incorporate the overall added sugars reduction, rather than a sole reduction in SSB consumption used in other studies.[60,63] This makes it possible to capture the overall effects of added sugars, contrary to the solitary effect of SSB's. The effects of changes in food consumption to other food groups (e.g. proteins, fat) are not modeled. Detrimental effects of these food categories are less well documented and inferior to the effects of added sugars. NHANES data was used to reduce individual added sugars consumption by the specified amount. From these data, new distributions were calculated to reflect subgroup consumption patterns. These distributions determined the ratio between individuals in the high and the low risk group, and therefore determine progression within disease chains. Identical random numbers were used between interventions to reduce variance, as described by Stout and Goldie.[73]

Time horizon, cycle length

The model had a time horizon of 20 years, modeling the calendar years 2015 to 2035. This duration was chosen to make sure effects within chronic diseases (T2D, CHD) were sufficiently visible. The cycle length was 1 year. Individuals could exit the model through each death state, or live until the end of the simulation.

Outcomes

Outcomes were incidence, prevalence and mortality of disease, and direct medical costs and DALYs averted. Costs were calculated by multiplying prevalence by discounted disease-attributable costs. DALYs were calculated by adding years lived with disability (YLD) and years of life lost (YLL). YLD was calculated as the product of the prevalence of disease times the discounted disability weight. YLL was calculated by multiplying the discounted health-adjusted life expectancy at death by the amount of people that died in that specific year, given a certain age and sex. The discount rate for costs, disability weights, and life expectancy was 3.0% annually. Health-adjusted life expectancy and discounted life expectancy for males and females for the United States were not derived by the model but implemented directly from publications of the Institute for Health Metrics and Evaluation (IHME). They are provided in the online supplement, **table 3 and 4**.

Input parameter determination

The model parameters that determined demographics and the distribution of risk factors and disease at the start of the simulation are mainly derived from NHIS and NHANES data. If data were not sufficient, current literature was consulted. Model input parameters, their distribution ranges, and the sources from which they were acquired are presented in **tables 1 and 2**. Baseline transition probabilities were derived from literature data, and where necessary, via calibration. Also when necessary, we used logistic conversion to adjust transition rates to reflect annual probabilities. Interaction values were derived from literature data. For interactions between chains, we used conservative data when possible, to ensure no overestimation of effect size. We took special care to ensure these odds ratios reflect the case for our model, i.e. reflect decreased risk due to a reduction in overall added sugars intake, not just a reduction in sugar-sweetened beverage intake, which is more commonly investigated. Regression rates were determined by historic and projected trends reported by the CDC and the American Heart Association.[3,5,6] Costs were derived from American population-based studies and, where necessary, were inflated by the inflation calculator of the United States Department of Labor Statistics to 2015 USD.[74] Costs were calculated as specific disease-attributable costs (i.e. costs for CHD due to diabetes were counted as costs due to CHD rather than costs due to diabetes). This was necessary to prevent overlapping costs. Disability weights were adopted from World Health Organizations' burden of disease estimates and current literature. Specific sources are provided in the tables.

Table 1. Model input values and ranges for disease characteristics. Costs are population based, meaning that they include those who do not get care.

	Prevalence at simulation start				Costs (annual)			Disability weights			
Disease state	***Mean***	***Min***	***Max***	**Ref.**	***Mean***	***SD***	***Ref.***	***Mean***	***Min***	***Max***	**Ref.**
Steatosis	27.955%[#]	18.637%	41.933%	[8,16,18]	134	50	[75]	0.000	0.000	0.000	[76–78]
NASH	3.141%[#]	2.094%	4.712%	[8,16,18]	267	100	[75]	0.033	0.017	0.066	[76–78]
Cirrhosis	0.314%[#]	0.209%	0.471%	[79,80]	2,861	1073	[81]	0.194	0.127	0.273	[10,75]
HCC	0.025%[#]	0.017%	0.038%	[82,83]	42,644	15,992	[76,84,85]	0.294	0.199	0.411	[76–78]
CHD	6.544%[#]	-	-	[1,2,6]	13,233	4962	[6,86]	0.066	0.043	0.095	[76]
T2D	9.447%[#]	-	-	[1,2]	8,170	3064	[86–88]	0.150	0.080	0.220	[76,89]
Overweight	33.473%[#]	-	-	[1,2]	343	129	[86,88]	0.000	0.000	0.000	[90]
Obesity	37.391%[#]	-	-	[1,2]	916	344	[86,88]	0.012	0.001	0.022	[90]

SD: standard deviation, NASH: non-alcoholic steatohepatitis, HCC: hepatocellular carcinoma, CHD: coronary heart disease, T2D: type 2 diabetes. CHD, T2D, overweight, and obesity prevalence are not varied in the sensitivity analyses.
Age, sex and/or ethnicity specific values are specified in the online supplement.

Table 2. Selected model input parameter values and ranges.

Parameter				
Initialization	**Mean**	**Min**	**Max**	**Source**
Age distribution	OS1*	-	-	[91]
Sex distribution	OS2**	-	-	[91]
Ethnicity distribution	OS3***	-	-	[91]
High sugar consumption	57.278%[#]	38.186%	85.917%	[3,35,42]
Baseline transition probabilities[##]	**Mean chance**	**Min**	**Max**	**Source**
Non-NAFLD -> steatosis	0.0100	0.006700	0.01500	[92–100]
Non-NAFLD -> NASH	0.0003	0.000201	0.00045	[92–100]
Steatosis -> NASH	0.0060	0.004020	0.00900	[92–100]
Steatosis -> cirrhosis	0.0002	0.000134	0.00030	[92–100]
NASH -> cirrhosis	0.0020	0.001340	0.00300	[92–100]
NASH -> HCC	0.0001[#]	0.000067	0.00015	[92–103]
NASH -> liver death	0.0038	0.002546	0.00570	[104–107]
Cirrhosis -> HCC	0.0200[#]	0.013400	0.03000	[92–103]
Cirrhosis -> liver death	0.0340	0.022780	0.05100	[104–107]
HCC -> liver death	0.5000	0.335000	0.75000	[104–107]
Non-CHD -> CHD	0.0045[#]	0.003015	0.00675	[108,109]
CHD -> CHD death	0.0100[#]	0.006700	0.01500	[5,6,108]
Non-T2D -> T2D	0.0045[#]	0.003015	0.00675	[72,110]
T2D -> T2D death	0.0100[#]	0.006700	0.01500	[6,72,110]

Healthy weight -> overweight	0.0500	0.033500	0.07500	[111–114]
Healthy weight -> o**bese**	0.0060	0.004020	0.00900	[111–114]
Overweight -> obese	0.0180	0.012060	0.02700	[111–114]
Each alive state -> non-disease related death	0.0100[#]	0.006700	0.01500	[6]
Risk factors (odds ratios)	**Mean value**	**Min**	**Max**	**Source**
NHB ethnicity for progression within NAFLD	0.93	0.70	1.00	[115]
Hispanic ethnicity for progression within NAFLD	1.67	1.22	2.22	[115]
Overweight for progression within NAFLD	2.19	1.60	3.38	[93,116–121]
Obesity for progression within NAFLD	3.14	2.07	5.28	[93,116–121]
High sugar consumption for progression within NAFLD	2.00	1.50	3.00	[38,122]
NAFLD for TP non-CHD -> CHD	2.31	1.66	3.62	[123–127]
Overweight for TP non-CHD -> CHD	1.22	1.12	1.32	[128–135]
Obesity for TP non-CHD -> CHD	1.60	1.43	1.79	[128–135]
T2D for TP non-CHD -> CHD	2.24	1.64	3.06	[136]
NAFLD for TP non-T2D -> T2D	2.73	1.87	4.46	[137–143]
Overweight for TP non-T2D -> T2D	2.18	1.59	3.36	[144–150]
Obesity for TP non-T2D -> T2D	3.36	2.18	5.72	[144–150]
NAFLD for progression within the BMI chain	2.19	1.60	3.38	[93,116–121]
High sugar consumption for progression within the BMI chain	2.60	1.20	6.00	[149,150]

SD: standard deviation, NAFLD: non-alcoholic fatty liver disease (steatosis, NASH & cirrhosis), NASH: non-alcoholic steatohepatitis, HCC: hepatocellular carcinoma, CHD: coronary heart disease, T2D: type 2 diabetes, NHB: non-Hispanic black.
* See online supplement table 1. ** See online supplement table 2. *** See online supplement table 3.
# Age, sex and/or ethnicity specific values are specified in the online supplement.
Transition probabilities for regression to less severe disease are specified in the online supplement.

Calibration

Incidence, prevalence, mortality and costs of overweight and obesity, T2D, and CHD were calibrated to reflect historic data from the CDC and projections from the American Heart Association (AHA) and several individual studies predicting future disease.[6,7,151–155] NASH- and cirrhosis-related HCC incidence and mortality was calibrated to historic trends reported by the CDC, and future predictions reported by the American Cancer Association.[6,156]

Validation

Validation of the model occurred via face validation, cross-validation, and sensitivity analyses. Face validation was performed manually by the authors. Each chain was checked separately for functionality before merging them. Cross-validation was performed by comparing epidemiological outcomes and predictions from our model with reported results from different studies on each subject, as presented in the Discussion.

Uncertainty was assessed using deterministic and probabilistic sensitivity analysis (DSA & PSA). DSA was conducted using a five-point analysis, with the minima and maxima specified in **tables 1 and 2**. If a mean and standard deviation (SD) are specified, we used a range of mean ± 1.96*SD. DSA results are only presented for the two main outcomes: total costs and DALYs averted in the year 2035. PSA was conducted using the distributions defined in **tables 1 and 2**, to produce a mean and 95% central coverage interval for all outcome values by running the simulation 10,000 times (each of which including the base case and two interventions).

Cohort simulation

To produce stable results, limit computational requirements, and have a cohort that remained representative of the U.S. population, we simulated a base cohort of 22,400 people, with new entry of 416 people each year, reflecting CDC population prospects.[69] Because of computational requirements, the model was built in Golang programming language (Google Inc, Mountain View, CA). Model code is publicly available via https://github.com/alexgoodell/go-mdism or can be acquired through the corresponding author. Sensitivity analyses were conducted using a 20-machine cluster (Amazon Web Services, Seattle, WA). Outcome analysis was completed in Excel 2010 (Microsoft, Redmond, WA).

Results

Incidence and mortality

The incidence of T2D, CHD, and HCC and the corresponding death rates in the year 2035 are stated in **table 3**. Diabetes incidence is expected to rise over the next 20 years, resulting in an incidence rate of 1035 cases per 100,000 people. The interventions are expected to reduce this by 19.9 and 83.5 respectively. CHD incidence is expected to rise to 665 cases per 100,000 people by 2035. This can be reduced by 9.4 and 39 cases by the 20% and the 50% intervention respectively. NASH- or cirrhosis-related HCC incidence will rise to 4.4 cases per 100,000 people. Interventions could reduce this amount by 0.3 and 1.3 respectively. Liver death can be due to HCC, or it can be related to NASH or cirrhosis in the absence of HCC. Liver-

related deaths will rise substantially, to 19.8 deaths per 100,000 people by 2035. This can be reduced by 1.4 or 5.8 deaths per 100,000 people by the 20% and 50% intervention, respectively.

Table 3. Annual occurring and averted events in 2035

Per 100,000 people

Events	No intervention (CI)	20% red. (CI)	Difference (CI)	50% red. (CI)	Difference (CI)
T2D cases	1034.6 (1031.0-1038.2)	1014.7 (1011.3-1018.2)	19.9 (12.8-27.0)	951.2 (947.9-954.4)	83.5 (76.7-90.3)
T2D deaths	576.6 (574.2-578.9)	569.3 (567.0-571.6)	7.2 (2.7-11.8)	546.4 (544.2-548.6)	30.2 (25.7-34.6)
CHD cases	665.1 (661.9-668.2)	655.6 (652.5-658.8)	9.4 (3.1-15.8)	626.1 (623.1-629.1)	39.0 (32.8-45.2)
CHD deaths	203.6 (202.2-205.0)	201.9 (200.5-203.3)	1.6 (-1.2-4.4)	197.2 (195.9-198.6)	6.3 (3.6-9.1)
HCC cases	4.4 (4.32-4.41)	4.0 (3.95-4.05)	0.3 (0.24-0.39)	3.1 (3.02-3.18)	1.3 (1.24-1.38)
Liver deaths	19.8 (19.65-20.02)	18.5 (18.29-18.63)	1.4 (1.02-1.73)	14.1 (13.94-14.21)	5.8 (5.44-6.08)

NASH: non-alcoholic steatohepatitis; HCC: hepatocellular carcinoma; CHD: coronary heart disease; T2D: type 2 diabetes mellitus; CI: 95% central coverage interval. Numbers might not add up due to rounding.

Prevalence

Figure 2, graphs A-H show the reduction in prevalence of disease due to the two intervention strategies. A 20% reduction in added sugars consumption is expected to decrease prevalence of each disease state significantly after 20 years, except for overweight prevalence, which does not change significantly. A 50% reduction in added sugars consumption will proportionally affect prevalence. Effects on T2D and CHD prevalences start to accumulate after an initial 3-year lag period. Graph G shows that overweight prevalence is not reduced. This is because the individuals that regressed from obese to overweight offset the reduction achieved in people that started overweight and regressed to normal weight. This effect is clarified by the drop in obesity prevalence.

Figure 2

Costs & DALYs

An overview of economic findings is presented in **table 4**. Overall costs for the modeled disease states could be reduced by 2.26% (95% CI 2.23% — 2.29%) by the year 2035 with an intervention that reduces added sugars intake by 20%. The 50% intervention will reduce overall costs by 6.99% (95% CI: 6.91 — 7.08). DALY burden and averted DALYs are presented in **table 5**. Total amount of DALYs could be reduced by 4.32% (95% CI: 4.27% — 4.38%) or 13.37% (95% CI: 13.24% — 13.51%) respectively. The majority of averted DALYs are due to reduced mortality.

Table 4. Annual costs spent and averted per disease state in 2035

In billions 2015 USD, discounted by 3.0% annually

State	No intervention (CI)	20% reduction (CI)	Difference (CI)	50% reduction (CI)	Difference (CI)
Steatosis	6.48 (6.43-6.53)	6.40 (6.35-6.45)	0.08 (0.080-0.082)	6.23 (6.18-6.28)	0.25 (0.248-0.255)
NASH	5.26 (5.22-5.30)	4.89 (4.85-4.93)	0.37 (0.368-0.375)	4.11 (4.08-4.14)	1.15 (1.139-1.162)
Cirrhosis	7.00 (6.93-7.07)	6.22 (6.16-6.28)	0.78 (0.772-0.791)	4.60 (4.56-4.65)	2.40 (2.371-2.429)
HCC	5.10 (5.04-5.16)	4.55 (4.50-4.60)	0.55 (0.537-0.558)	3.40 (3.36-3.44)	1.70 (1.669-1.721)
CHD	162.2 (160.9-163.6)	160.1 (158.8-161.5)	2.09 (2.06-2.12)	155.7 (154.4-157.0)	6.51 (6.43-6.58)
T2D	200.0 (198.4-201.6)	195.9 (194.3-197.5)	4.07 (4.02-4.12)	187.4 (185.9-188.9)	12.59 (12.46-12.73)
Overweight	16.4 (16.3-16.5)	16.6 (16.5-16.8)	-0.25 (-0.26 - -0.25)	17.2 (17.1-17.3)	-0.79 (-0.81 - -0.78)
Obesity	52.7 (52.3-53.1)	50.1 (49.7-50.5)	2.59 (2.57-2.62)	44.7 (44.3-45.0)	8.03 (7.95-8.12)
Total	**455.1** (451.4-458.9)	**444.9** (441.2-448.5)	**10.3** (10.2-10.4)	**423.3** (419.8-426.8)	**31.8** (31.5-32.2)

NASH: non-alcoholic steatohepatitis; HCC: hepatocellular carcinoma; CHD: coronary heart disease; T2D: type 2 diabetes mellitus; CI: 95% central coverage interval. Numbers might not add up due to rounding.

Table 5. Annual occurring and averted DALYs in 2035

In millions

State	No intervention (CI)	20% reduction (CI)	Difference (CI)	50% reduction (CI)	Difference (CI)
NASH	2.97 (2.955-2.988)	2.76 (2.746-2.777)	0.210 (0.209-0.212)	2.32 (2.309-2.334)	0.650 (0.645-0.655)
Cirrhosis	0.48 (0.475-0.482)	0.42 (0.422-0.428)	0.053 (0.053-0.054)	0.31 (0.312-0.316)	0.164 (0.162-0.165)
HCC	3.06 (3.046-3.084)	2.78 (2.765-2.799)	0.283 (0.279-0.283)	2.19 (2.180-2.206)	0.872 (0.863-0.881)
CHD	2.32 (2.305-2.330)	2.29 (2.276-2.302)	0.028 (0.028-0.029)	2.23 (2.217-2.242)	0.088 (0.086-0.090)
T2D	8.21 (8.180-8.248)	8.06 (8.023-8.089)	0.158 (0.155-0.160)	7.72 (7.690-7.752)	0.492 (0.487-0.498)

Obesity	0.69 (0.689-0.700)	0.66 (0.655-0.666)	0.034 (0.034-0.035)	0.59 (0.584-0.593)	0.106 (0.105-0.107)
Total	**17.74** (17.65-17.83)	**16.97** (16.89-17.06)	**0.767** (0.757-0.777)	**15.37** (15.29-15.44)	**2.372** (2.348-2.396)
From mortality	11.94	11.50	0.439	10.58	1.357
From morbidity	5.80	5.47	0.328	4.78	1.015

NASH: non-alcoholic steatohepatitis; HCC: hepatocellular carcinoma; CHD: coronary heart disease; T2D: type 2 diabetes mellitus; CI: 95% central coverage interval. Numbers might not add up due to rounding.

Sensitivity analyses

We show tornado diagrams for the two most important outcomes: annual costs and DALYs averted by the year 2035 due to an intervention that reduces sugar consumption by 20%. The diagrams show the impact that specific input parameters had on selected results. The ten variables that caused the widest range in results are shown. When varying individual variables, the annual savings by the year 2035 range from 7.9 to 17.1 billion 2015 USD. The tornado diagram (**Figure 3**) shows that the interaction between high added sugars consumption and the progression within the NAFLD and BMI chains had the greatest impact on total costs averted. In the tornado diagram for total annual DALYs averted by the 20% intervention in the year 2035 (**Figure 4**), assigned disability weights had the greatest impact. Total DALYs averted ranged between 0.36 and 1.41 million.

Figure 3&4

Discussion

It has been estimated that the cost burden of the diseases of metabolic syndrome are 75% of the total annual health care budget ($3.2 trillion) of the United States. The clinical burden of NAFLD alone is estimated at $103 billion**.**[157] The proposed model shows clear and significant benefits for interventions that reduce consumption of added sugars. A reduction by 20% will reduce annual direct medical costs for U.S. adults by more than 10 billion USD (2015 dollars) by the year 2035. A 50% reduction will save an additional 21 billion. Together with these economic benefits, population health will significantly improve. A total of 770,000 DALYs could be averted with a 20% reduction in consumption. A 50% reduction in consumption will avert another 1.6 million DALYs. These health and economic benefits are the direct result of lower incidence, prevalence, and mortality of disease in U.S. adults due to lower consumption of added sugars. Averted costs are achieved primarily through reduced costs for CHD, T2D, overweight, and obesity. This is mainly because costs for the most prevalent NAFLD states, namely steatosis and NASH, are fairly low, whereas costs for other illnesses are much higher (Table 1). In averted DALYs, we find that the combination of disability weight and prevalence changes are predictors of DALY reductions. E.g. NASH has a lower disability weight but higher prevalence reductions and therefore we find almost equal DALY reductions compared to HCC or CHD. T2D has the highest reduction in DALY burden because it has relatively large values for both prevalence reduction and disability weight.

Fit with current knowledge

The estimate for health and economic benefit of this model is similar to a number of previously performed economic evaluations. Basu et al. found a reduction in diabetes incidence of 21.7 cases per 100,000 people with a reduction of 20% of added sugars through a cap and trade approach, limiting the amount of sugars in the food supply.[65] We found a reduction of 19.9 cases per 100,000 people, indicating a similar absolute effect size. CHD incidence reduction is estimated to be about 1.5-fold higher than found in a similar study, but we argue that this is mainly because the other study simulated a 20% tax on sugar-sweetened beverages, and therefore the overall added sugars consumption reduction was smaller than the 20% reduction we simulated.[63] In an econometric analysis looking backward in time, Basu et al. found a delay of 3 years between changes in sugar consumption and prevalence of diabetes.[37] Similarly, we found a delay of 3 years going forward in time between reduction of consumption and reduction in prevalence of disease. Prevalence of obesity has been reported to drop by 1.5% — 10% due to a reduction of added sugars by 10% — 20%.[59–61] Our result of 2.1% reduction in obesity prevalence seems to reflect our conservative approach in determining input parameter values.

Costs savings are bigger in our model compared to other models.[60,64,64] This was for three reasons. First, some other models do not use added sugars as a whole but use SSB's, resulting in a smaller effect. Second, our overall prevalence of T2D and CHD is higher than most other models. We have calibrated our model to historic trends reported by the CDC and to future projections of the AHA, ADA and separate studies predicting future prevalence, and therefore argue that our estimate is valid. Third, and perhaps most importantly, no other studies predict future NAFLD prevalence. We present the first model that estimates the effects of sugar interventions on NAFLD prevalence and associated costs and DALYs.

In 2009, the American Heart Association recommended a reduction in added sugar consumption from a median of 90 grams per day to a maximum of 25 grams for women and 37.5 grams for men.[31] In 2016, the USDA and WHO settled on an upper limit of 10% of calories, which approximates 50 grams per day. Given the U.S. current median consumption of 80 grams per day, our microsimulation modeling cutoffs of 20% and 50%, while ambitious, are metabolically rational and in

concert with governmental goals.[158]

Our model only allows us to examine the negative side of the balance sheet in terms of cost savings to health care. However, reductions in added sugar consumption have been modeled to provide significant increases to the positive side of the balance sheet in terms of economic productivity. Indeed, a simulation modeling by Morgan Stanley predicted economic growth to decline to zero by the year 2035 using a high-sugar case, whereas stabilization at +2.9% was noted with a low-sugar case.[159]

Strengths and limitations

This study is the first of its kind to model the effect of added sugars on NAFLD as well as on BMI, and therefore it captures a more complete picture of the possible health and economic benefits of interventions that reduce intake of added sugars. Though taxing sugar-sweetened products, mainly beverages, has been widely suggested as a public health strategy, other approaches, e.g. a cap and trade approach, have also been suggested.[58–61,63–65] We have constructed this model to be applicable with each of these interventions, so that it does not rely on any consumption statistics other than added sugars as a whole. A limitation to this approach is that our model does not incorporate a possible change to non-sugared caloric products, containing protein, fat, or other carbohydrates. While it is conceivable that removal of added sugars in the diet could result in subsequent substitution of other foodstuffs to restore an individual's caloric baseline, *ad lib* population studies do not support that such caloric compensation takes place.[160] It is important that effort is put into investigating self- and cross-elasticity of sugar-sweetened products to determine the effect of these caloric replacements. Though this is a limitation, research has clearly shown that the contribution of added sugars in relation to their excessive intake is likely the most important consumption factor for metabolic derangement. Furthermore, added sugars consumption was fixed throughout the simulation for each individual (though specified per sex and ethnic group). We could not find sufficient data on changes in sugar consumption related to incident disease and therefore could not model these changes accurately enough. We argue that keeping the sugar consumption fixed is likely more accurate than modeling changing sugar consumption based solely on age. The main limitation of this model is the uncertainty of input parameters. The pathophysiology of NAFLD and its associations with other metabolic diseases is still widely under investigation. We have modeled cirrhosis as an irreversible condition, which is not necessarily true in all cases. Furthermore, the input parameters for baseline transition probabilities and interaction (OR) values are still somewhat uncertain. Many studies report associations, but very few studies report plausible quantitative causal relationships. There are several reasons that explain this low number of studies. First, it is hard to accurately determine the individual components in an individual's diet. Second, there is no inexpensive, accurate way to determine the presence of individual NAFLD states. Commonly used ultrasonography possibly underestimates the prevalence of NAFLD and does not differentiate between steatosis and NASH, while up to 79% of patients may have serum alanine aminotransferase (ALT) levels within the normal reference range of < 40 U/mL.[9,161] Additionally, the studies that we included to define our input parameters are generally not a perfect reflection of the population that we modeled, which may lead to imperfect estimates of values. We have addressed these uncertainties in inputs by taking wide ranges in the probabilistic sensitivity analysis, which determines the SD and 95% central coverage interval around the results. Results remain statistically significant, indicating that any minor inaccuracies in input parameter values will not render the effects insignificant. Ultimately, it is desirable to determine incidence of NAFLD states and risk factor relative risks in independent prospective cohort studies, and to assess intervention effectiveness via randomized controlled trials. This model can be refined and updated when new data become available.

It is possible that our results might still underestimate the total effects. We only modeled diagnosed disease, we took a conservative approach when determining input parameter values, and we did not take societal costs into account. Real health, healthcare, and economic benefits are likely larger than estimated. Furthermore, we only modeled the population with an age over 20. Likely, including health effects in children, particularly those with type 2 diabetes, would yield additional benefits.

Implications

This model clarifies the significant health and economic benefits that could be achieved by a public health intervention that reduces consumption of added sugars in U.S. adults. We recommend that health policy makers review options to implement sugar reduction. Important to consider are the barriers to limiting added sugars in the United States. The food industry uses sugar to enhance flavor and as a bulking and browning agent, humectant, and spoilage retardant. Another obstacle is the lowered price for manufacturing, due to government subsidies for corn, cane, and beets. Historically there was another barrier -- lack of consensus on the link between sugar and metabolic disease. However, consensus on causality is now strong.[162] Recently sugar taxation has emerged as a viable strategy, levied in the U.K. and Mexico, as well as several municipalities in the U.S., including San Francisco, Oakland, Berkeley, and Albany, CA, as well as Chicago, IL and Philadelphia, PA.

Future research

Future research should focus on establishing a more precise measurement of NAFLD prevalence, incidence, and risk factors. Furthermore, magnitude and effects of switching to different food groups should be assessed. Finally, changes in added sugars consumption related to ageing and incident disease should be more intensively investigated.

Contributor statement
RAV was involved in conceptualizing the study, reviewing literature, conducting the modelling analysis, analyzing the data and writing the manuscript. AJG was involved in conducting the modelling analysis and in editing the paper. LAR and RHL were involved in conceptualizing the model, providing and structuring data inputs and editing the manuscript. TCP was involved in reviewing and revising the manuscript, checking statistical and mathematical assumptions and establishing overall validity of the model. JGK was involved in conceptualization of the model, input data review, guiding the modelling process and providing a critical review of the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare no direct conflicts of interest. However, Dr. Lustig has received author fees from Hudson Street Press regarding his authorship of: "Fat Chance: Beating the Odds Against Sugar, Processed Food, Obesity, and Disease"; "The Fat Chance Cookbook"; and "Sugar has 56 names: A Shopper's Guide". He is also the unpaid chief science officer of the non-profit EatREAL.

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Data sharing statement
An online supplement will be made available containing comprehensive tables of used input data. The modelling code is available through github: https://github.com/alexgoodell/go-mdism or can be accessed via the corresponding author.

Figure legends
Figure 1. Model state and covariate structure.
Each individual gets assigned a state in each chain at the start of the simulation and their specific covariates (age, sex, ethnicity, high/low sugar consumption). Circles represent disease states. Solid lines indicate a possible transition pathway between states. Coloured lines indicate how being in a state within one chain can affect the value of the transition probability between two states in another chain. These are split into three categories: pink striped lines indicate the effect of NAFLD on progression in the BMI, T2D and CHD chains. Blue dotted lines indicate the effect of overweight and obesity on progression in the NAFLD, T2D and CHD chains. The green dotted line indicates the effect of T2D on progression in the CHD chain. 3 chains contain disease related deaths and the model contains a non-disease related death state for other causes of mortality. The states of individuals are updated every cycle (i.e. annually) for 20 years. Each cycle the state distributions and their related costs and DALYs are generated as output.
NAFLD: non-alcoholic fatty liver disease, T2D: type 2 diabetes, CHD: coronary heart disease, NASH: non-alcoholic steatohepatitis, HCC: hepatocellular carcinoma, DALYs: disability-adjusted life years.

Figure 2, graphs A to H.
Reduction in population prevalence of disease due to interventions. Lines represent mean values +/- one standard deviation. 0% is the baseline, representing no intervention. The blue lines with diamonds indicate a reduction of added sugar of 20%. The red lines with crosses represent a reduction of 50%. NASH; non-alcoholic steatohepatitis.

Figure 3. Tornado diagram of the ten most critical variables on total costs averted in the year 2035.
Figure 4. Tornado diagram of the ten most critical variables on total DALYs averted in the year 2035.

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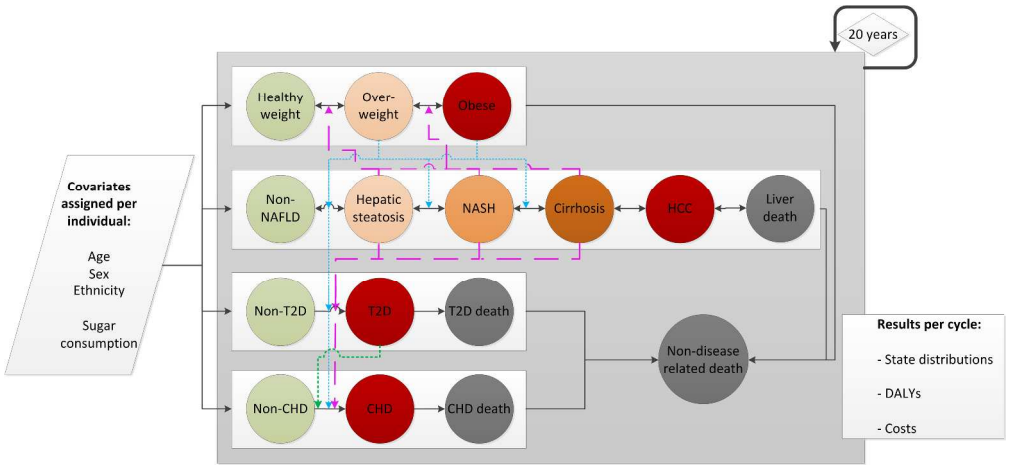

Figure 1. Model state and covariate structure.
Each individual gets assigned a state in each chain at the start of the simulation and their specific covariates (age, sex, ethnicity, high/low sugar consumption). Circles represent disease states. Solid lines indicate a possible transition pathway between states. Coloured lines indicate how being in a state within one chain can affect the value of the transition probability between two states in another chain. These are split into three categories: pink striped lines indicate the effect of NAFLD on progression in the BMI, T2D and CHD chains. Blue dotted lines indicate the effect of overweight and obesity on progression in the NAFLD, T2D and CHD chains. The green dotted line indicates the effect of T2D on progression in the CHD chain. 3 chains contain disease related deaths and the model contains a non-disease related death state for other causes of mortality. The states of individuals are updated every cycle (i.e. annually) for 20 years. Each cycle the state distributions and their related costs and DALYs are generated as output.
NAFLD: non-alcoholic fatty liver disease, T2D: type 2 diabetes, CHD: coronary heart disease, NASH: non-alcoholic steatohepatitis, HCC: hepatocellular carcinoma, DALYs: disability-adjusted life years.

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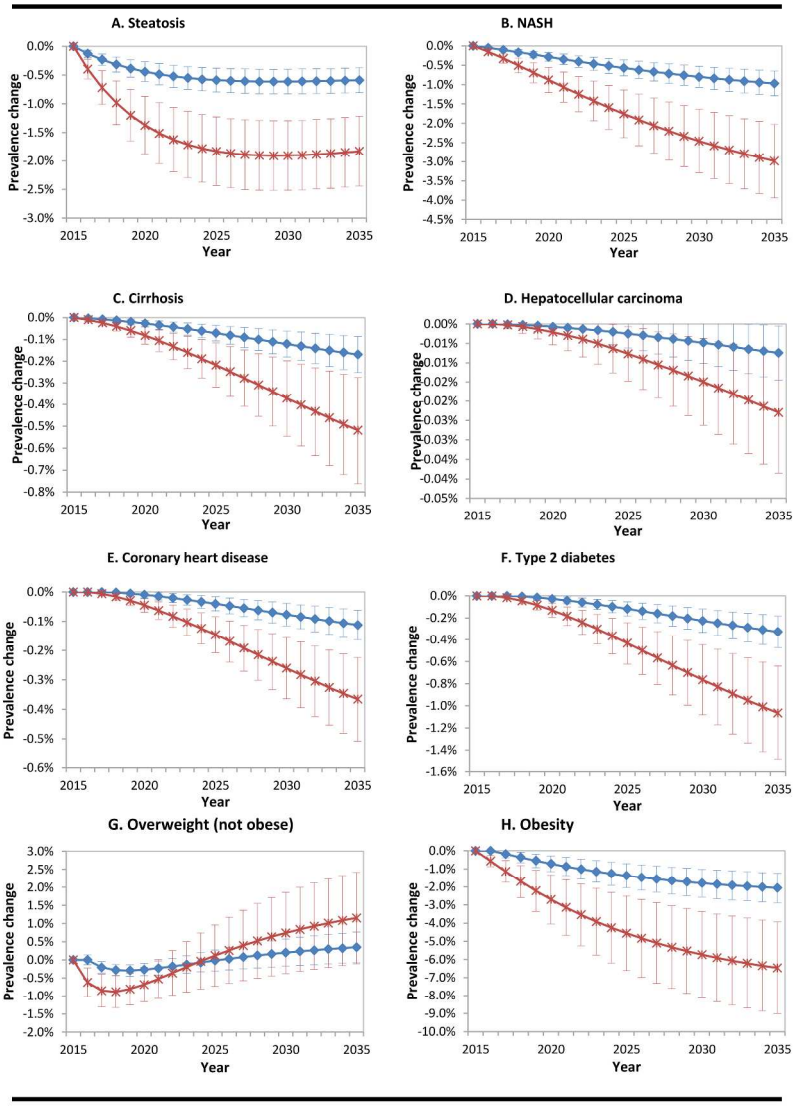

Figure 2, graphs A to H. reduction in population prevalence of disease due to interventions. Lines represent mean values +/- one standard deviation. 0% is the baseline, representing no intervention. The blue lines with diamonds indicate a reduction of added sugar of 20%. The red lines with crosses represent a reduction of 50%. NASH; non-alcoholic steatohepatitis.

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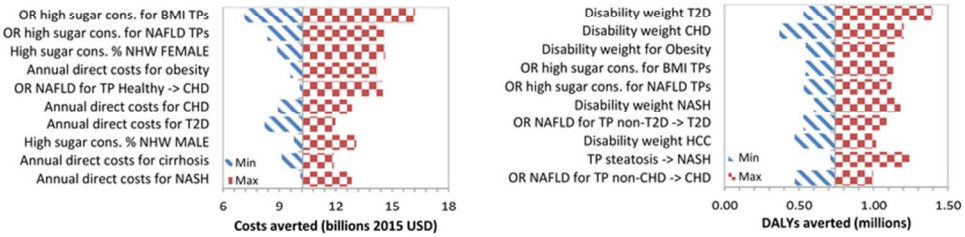

Figure 3. Tornado diagram of the ten most critical variables on total costs averted in the year 2035.
Figure 4. Tornado diagram of the ten most critical variables on total DALYs averted in the year 2035.

73x28mm (300 x 300 DPI)

Online supplement

Non-alcoholic fatty liver disease as a mediator of sugar effects; implications for the health and economic benefits of interventions in the US

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Table 1. Selected model parameter values and ranges.

Parameter					
Initialization	**Distribution**	**Mean**	**Min**	**Max**	**Source**
Age distribution	Fixed	OS2*1	-	-	[1]
Sex distribution	Fixed	OS3*2	-	-	[1]
Ethnicity distribution	Fixed	OS4*3	-	-	[1]
Steatosis prevalence	Beta	27.955%*4	18.637%	41.933%	[2-4]
NASH prevalence	Beta	3.141%*4	2.094%	4.712%	[2-4]
Cirrhosis prevalence	Beta	0.314%*4	0.209%	0.471%	[5-8]
HCC prevalence	Beta	0.025%*4	0.017%	0.038%	[9,10]
CHD prevalence	Fixed	6.544%*5	-	-	[11]
T2D prevalence	Fixed	9.447%*6	-	-	[11]
Overweight prevalence	Fixed	33.473%*7	-	-	[11]
Obesity prevalence	Fixed	37.391%*8	-	-	[11]
High sugar consumption	Beta	57.278%*9	38.186%	85.917%	[12,13]
Baseline transition probabilities	**Distribution**	**Mean chance**	**Min**	**Max**	**Source**
Non-NAFLD -> steatosis	Beta	0.0100	0.006700	0.01500	[14-22]
Non-NAFLD -> NASH	Beta	0.0003	0.000201	0.00045	[14-22]
Steatosis -> non-NAFLD	Beta	0.0200	0.013400	0.03000	[14-22]
Steatosis -> NASH	Beta	0.0060	0.004020	0.00900	[14-22]
Steatosis -> cirrhosis	Beta	0.0002	0.000134	0.00030	[14-22]
NASH -> non-NAFLD	Beta	0.0010	0.000670	0.00150	[14-22]
NASH -> steatosis	Beta	0.0200	0.013400	0.03000	[14-22]
NASH -> cirrhosis	Beta	0.0020	0.001340	0.00300	[14-22]
NASH -> HCC	Beta	0.0001*10	0.000067	0.00015	[14-25]
NASH -> liver death	Beta	0.0038	0.002546	0.00570	[26-29]
Cirrhosis -> HCC	Beta	0.0200*10	0.013400	0.03000	[14-25]
Cirrhosis -> liver death	Beta	0.0340	0.022780	0.05100	[26-29]
HCC -> liver death	Beta	0.5000	0.335000	0.75000	[26-29]
Non-CHD -> CHD	Beta	0.0045*11	0.003015	0.00675	[30,31]
CHD -> CHD death	Beta	0.0100*12	0.006700	0.01500	[30-32]
Non-T2D -> T2D	Beta	0.0045*13	0.003015	0.00675	[33,34]
T2D -> T2D death	Beta	0.0100*14	0.006700	0.01500	[32-34]
Healthy weight -> overweight	Beta	0.0500	0.033500	0.07500	[35-38]
Healthy weight -> obese	Beta	0.0060	0.004020	0.00900	[35-38]
Overweight -> healthy weight	Beta	0.0500	0.033500	0.07500	[35-38]
Overweight -> obese	Beta	0.0180	0.012060	0.02700	[35-38]
Obese-> healthy weight	Beta	0.0060	0.004020	0.00900	[35-38]
Obese -> overweight	Beta	0.0350	0.023450	0.05250	[35-38]
Each alive state -> non-disease related death	Beta	0.0100*15	0.006700	0.01500	[32]
Risk factors	**Distribution**	**Mean value**	**Min**	**Max**	**Source**
NHB ethnicity for progression within NAFLD	Beta	0.93	0.70	1.00	[39]
Hispanic ethnicity for progression within NAFLD	Beta	1.67	1.22	2.22	[39]
Overweight for progression within NAFLD	Beta	2.19	1.60	3.38	[15,40-45]
Obesity for progression within NAFLD	Beta	3.14	2.07	5.28	[15,40-45]
High sugar consumption for progression within NAFLD	Beta	2.00	1.50	3.00	[46,47]
NAFLD for TP non-CHD -> CHD	Beta	2.31	1.66	3.62	[48-52]
Overweight for TP non-CHD -> CHD	Beta	1.22	1.12	1.32	[53-60]
Obesity for TP non-CHD -> CHD	Beta	1.60	1.43	1.79	[53-60]
T2D for TP non-CHD -> CHD	Beta	2.24	1.64	3.06	[61]
NAFLD for TP non-T2D -> T2D	Beta	2.73	1.87	4.46	[62-68]
Overweight for TP non-T2D -> T2D	Beta	2.18	1.59	3.36	[69-75]
Obesity for TP non-T2D -> T2D	Beta	3.36	2.18	5.72	[69-75]
NAFLD for progression within the BMI chain	Beta	2.19	1.60	3.38	[15,40-45]
High sugar consumption for progression within the BMI chain	Beta	2.60	1.20	6.00	[76,77]
Regression rates	**Distribution**	**Mean value**	**Min**	**Max**	**Source**
CHD incidence regression rate/year	Beta	0.985	0.970	1.00	[78-81]
CHD mortality regression rate/year	Beta	0.979	0.958	1.00	[78-81]
Non-disease mortality regression rate/year (20-30)	Beta	1.000	0.990	1.00	[32]
Non-disease mortality regression rate/year (30-55)	Beta	0.980	0.960	1.00	[32]
Non-disease mortality regression rate/year (55+)	Beta	0.970	0.940	1.00	[32]

Table 1. Continued					
Costs (annual direct medical, in 2015 USD)	**Distribution**	**Mean value**	**SD**		**Source**
Steatosis	Gamma	134	50		[82-85]
NASH	Gamma	267	100		[82-85]
Cirrhosis	Gamma	2861	1073		[86]
HCC	Gamma	42644	15992		[87,88]
CHD	Gamma	13233	4962		[89]
T2D	Gamma	8170	3064		[90]
Overweight	Gamma	343	129		[91]
Obesity	Gamma	916	344		[91]
Disability weights	**Distribution**	**Mean value**	**Min**	**Max**	**Source**
NASH	Beta	0.033	0.017	0.066	[3,84]
Cirrhosis	Beta	0.194	0.127	0.273	[92]
HCC	Beta	0.294	0.199	0.411	[92]
CHD	Beta	0.066	0.043	0.095	[92]
T2D	Beta	0.150	0.080	0.220	[92]
Obesity	Beta	0.012	0.001	0.022	[93]

SD: standard deviation, CHD: coronary heart disease, T2D: type 2 diabetes, NAFLD: non-alcoholic fatty liver disease (steatosis, NASH & cirrhosis), NASH: non-alcoholic steatohepatitis, HCC: hepatocellular carcinoma, Hisp: Hispanic, NHW: non-Hispanic white, NHB: non-Hispanic black, TP: transition probability, OR: odds ratio

*1 See online supplement table 2. *2 See online supplement table 3. *3 See online supplement table 4. *4 See online supplement table 5. *5 See online supplement table 6. *6 See online supplement table 7. *7 See online supplement table 8. *8 See online supplement table 9. *9 See online supplement table 10. *10 See online supplement table 11. *11 See online supplement table 12. *12 See online supplement table 13. *13 See online supplement table 14. *14 See online supplement table 15. *15 See online supplement table 16.

Table 2. Age distribution.[1]

Age	Percentage
20	1.9194
21	1.9194
22	1.9194
23	1.9194
24	1.9194
25	1.8701
26	1.8701
27	1.8701
28	1.8701
29	1.8701
30	1.7749
31	1.7749
32	1.7749
33	1.7749
34	1.7749
35	1.7757
36	1.7757
37	1.7757
38	1.7757
39	1.7757
40	1.8487
41	1.8487
42	1.8487
43	1.8487
44	1.8487
45	2.0018
46	2.0018
47	2.0018
48	2.0018
49	2.0018
50	1.9767
51	1.9767
52	1.9767
53	1.9767
54	1.9767
55	1.7505
56	1.7505
57	1.7505
58	1.7505
59	1.7505
60	1.5024
61	1.5024
62	1.5024
63	1.5024
64	1.5024
65	1.1073
66	1.1073
67	1.1073
68	1.1073
69	1.1073
70	0.8256
71	0.8256
72	0.8256
73	0.8256
74	0.8256
75	0.6473
76	0.6473
77	0.6473
78	0.6473
79	0.6473
80	0.5093
81	0.5093
82	0.5093
83	0.5093
84	0.5093
85+	2.4517

Table 3. Sex distribution.[1]

Sex	Percentage
Male	48.4388
Female	51.5612

Table 4. Ethnic distribution.[1]

Age	Percentage
Hispanic	14.0377
Non-hispanic White	74.3771
Non-hispanic Black	11.5852

Table 5. Non-alcoholic fatty liver disease prevalence percentage at start of simulation.[2-10]

Ethnicity	Steatosis	NASH	Cirrhosis	Hepatocellular carcinoma
Hispanic	40.05	4.5	0.45	0.0363
NH-White	26.70	3.0	0.30	0.0242
NH-Black	21.36	2.4	0.24	0.0194

Table 6. Hepatocellular carcinoma incidence rate from NASH.[14-25]

Age	Incidence rate
40 to 44 years	3.64216E-05
45 to 49 years	4.64842E-05
50 to 54 years	5.93269E-05
55 to 59 years	7.57179E-05
60 to 64 years	9.66373E-05
65 to 69 years	0.000123336
70 to 74 years	0.000157412
75 to 79 years	0.000200902
80 years and over	0.000256408

Table 7. Hepatocellular carcinoma incidence rate from cirrhosis.[14-25]

Age	Incidence rate
40 to 44 years	0.008844339
45 to 49 years	0.011287867
50 to 54 years	0.014406497
55 to 59 years	0.018386746
60 to 64 years	0.023466665
65 to 69 years	0.029950073
70 to 74 years	0.038224725
75 to 79 years	0.048785512
80 years and over	0.062264050

Table 8. Overweight and obesity prevalence percentages at the start of the simulation.[11]

Sex	Ethnicity	Age	Overweight percentage	Obesity percentage
Male	Hispanic	20-44	39.5	36.8
Male	Hispanic	45-64	43.8	41.0
Male	Hispanic	65+	42.8	44.7
Male	White	20-44	35.7	31.6
Male	White	45-64	40.8	39.0
Male	White	65+	42.5	36.9
Male	Black	20-44	28.7	36.9
Male	Black	45-64	34.3	40.6
Male	Black	65+	37.0	36.7
Female	Hispanic	20-44	33.2	36.8
Female	Hispanic	45-64	32.9	52.9
Female	Hispanic	65+	33.0	49.3
Female	White	20-44	25.3	28.0
Female	White	45-64	32.6	37.4
Female	White	65+	29.5	44.3
Female	Black	20-44	22.3	56.1
Female	Black	45-64	27.1	61.8
Female	Black	65+	25.8	53.7

Table 9. Type 2 diabetes prevalence percentage at the start of the simulation.[11]

Sex	Ethnicity	Age	Percentage with T2D
Male	Hispanic	20-24	0.90
Male	Hispanic	25-44	3.50
Male	Hispanic	45-54	14.20
Male	Hispanic	55-64	25.80
Male	Hispanic	65-74	32.80
Male	Hispanic	75-84	31.30
Male	Hispanic	85+	23.80
Male	NH-White	20-24	0.90
Male	NH-White	25-44	2.40
Male	NH-White	45-54	8.20
Male	NH-White	55-64	14.70
Male	NH-White	65-74	20.10
Male	NH-White	75-84	20.50
Male	NH-White	85+	17.90
Male	NH-Black	20-24	1.00
Male	NH-Black	25-44	5.00
Male	NH-Black	45-54	15.00
Male	NH-Black	55-64	24.00
Male	NH-Black	65-74	26.50
Male	NH-Black	75-84	39.00
Male	NH-Black	85+	18.70
Female	Hispanic	20-24	0.90
Female	Hispanic	25-44	3.60
Female	Hispanic	45-54	10.30
Female	Hispanic	55-64	24.00
Female	Hispanic	65-74	34.80
Female	Hispanic	75-84	32.40
Female	Hispanic	85+	22.80
Female	NH-White	20-24	1.20
Female	NH-White	25-44	2.80
Female	NH-White	45-54	7.30
Female	NH-White	55-64	12.10
Female	NH-White	65-74	17.00
Female	NH-White	75-84	17.10
Female	NH-White	85+	12.10
Female	NH-Black	20-24	1.00
Female	NH-Black	25-44	5.20
Female	NH-Black	45-54	10.90
Female	NH-Black	55-64	24.10
Female	NH-Black	65-74	32.60
Female	NH-Black	75-84	31.60
Female	NH-Black	85+	20.20

Table 10. Type 2 diabetes incidence rate.[33,34]

Age	Incidence rate
20-24	0.000447
25-29	0.000762
30-34	0.001090
35-39	0.001625
40-44	0.002880
45-49	0.003575
50-54	0.004957
55-59	0.005071
60-64	0.004662
65-69	0.004450
70-74	0.003925
75-79	0.003609
80+	0.003240

Table 11. Coronary heart disease prevalence percentage at the start of the simulation.[11]

Sex	Ethnicity	Age	Percentage with CHD
Male	Hispanic	20-35	0.00
Male	Hispanic	35-44	1.30
Male	Hispanic	45-54	3.90
Male	Hispanic	55-64	10.60
Male	Hispanic	65-74	19.20
Male	Hispanic	75-84	23.50
Male	Hispanic	85+	23.80
Male	NH-White	20-35	0.00
Male	NH-White	35-44	1.20
Male	NH-White	45-54	6.00
Male	NH-White	55-64	13.80
Male	NH-White	65-74	23.30
Male	NH-White	75-84	31.80
Male	NH-White	85+	38.60
Male	NH-Black	20-35	0.00
Male	NH-Black	35-44	1.70
Male	NH-Black	45-54	7.50
Male	NH-Black	55-64	14.20
Male	NH-Black	65-74	16.90
Male	NH-Black	75-84	22.10
Male	NH-Black	85+	18.80
Female	Hispanic	20-35	0.00
Female	Hispanic	35-44	1.20
Female	Hispanic	45-54	3.00
Female	Hispanic	55-64	6.70
Female	Hispanic	65-74	16.20
Female	Hispanic	75-84	20.30
Female	Hispanic	85+	23.90
Female	NH-White	20-35	0.00
Female	NH-White	35-44	0.90
Female	NH-White	45-54	3.30
Female	NH-White	55-64	6.70
Female	NH-White	65-74	11.20
Female	NH-White	75-84	18.40
Female	NH-White	85+	24.30
Female	NH-Black	20-35	0.00
Female	NH-Black	35-44	1.20
Female	NH-Black	45-54	5.30
Female	NH-Black	55-64	11.20
Female	NH-Black	65-74	17.40
Female	NH-Black	75-84	19.80
Female	NH-Black	85+	21.80

Table 12. Coronary heart disease incidence rate (in %).[30,31]

Year	<35	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
2010	0.0	0.0516	0.0516	0.2007	0.2007	0.3519	0.3519	0.5869	0.5869	1.4447	1.4447	3.0621
2011	0.0	0.0508	0.0508	0.1976	0.1976	0.3466	0.3466	0.5781	0.5781	1.4230	1.4230	3.0162
2012	0.0	0.0501	0.0501	0.1947	0.1947	0.3414	0.3414	0.5694	0.5694	1.4017	1.4017	2.9709
2013	0.0	0.0493	0.0493	0.1918	0.1918	0.3363	0.3363	0.5609	0.5609	1.3806	1.3806	2.9263
2014	0.0	0.0486	0.0486	0.1889	0.1889	0.3312	0.3312	0.5525	0.5525	1.3599	1.3599	2.8825
2015	0.0	0.0478	0.0478	0.1860	0.1860	0.3262	0.3262	0.5442	0.5442	1.3395	1.3395	2.8392
2016	0.0	0.0471	0.0471	0.1833	0.1833	0.3214	0.3214	0.5360	0.5360	1.3194	1.3194	2.7966
2017	0.0	0.0464	0.0464	0.1805	0.1805	0.3165	0.3165	0.5280	0.5280	1.2997	1.2997	2.7547
2018	0.0	0.0457	0.0457	0.1778	0.1778	0.3118	0.3118	0.5201	0.5201	1.2802	1.2802	2.7134
2019	0.0	0.0450	0.0450	0.1751	0.1751	0.3071	0.3071	0.5123	0.5123	1.2610	1.2610	2.6727
2020	0.0	0.0444	0.0444	0.1725	0.1725	0.3025	0.3025	0.5046	0.5046	1.2420	1.2420	2.6326
2021	0.0	0.0437	0.0437	0.1699	0.1699	0.2980	0.2980	0.4970	0.4970	1.2234	1.2234	2.5931
2022	0.0	0.0430	0.0430	0.1674	0.1674	0.2935	0.2935	0.4896	0.4896	1.2051	1.2051	2.5542
2023	0.0	0.0424	0.0424	0.1649	0.1649	0.2891	0.2891	0.4822	0.4822	1.1870	1.1870	2.5159
2024	0.0	0.0418	0.0418	0.1624	0.1624	0.2848	0.2848	0.4750	0.4750	1.1692	1.1692	2.4781
2025	0.0	0.0411	0.0411	0.1600	0.1600	0.2805	0.2805	0.4679	0.4679	1.1516	1.1516	2.4410
2026	0.0	0.0405	0.0405	0.1576	0.1576	0.2763	0.2763	0.4608	0.4608	1.1344	1.1344	2.4043
2027	0.0	0.0399	0.0399	0.1552	0.1552	0.2721	0.2721	0.4539	0.4539	1.1174	1.1174	2.3683
2028	0.0	0.0393	0.0393	0.1529	0.1529	0.2681	0.2681	0.4471	0.4471	1.1006	1.1006	2.3328
2029	0.0	0.0387	0.0387	0.1506	0.1506	0.2640	0.2640	0.4404	0.4404	1.0841	1.0841	2.2978
2030	0.0	0.0381	0.0381	0.1483	0.1483	0.2601	0.2601	0.4338	0.4338	1.0678	1.0678	2.2633
2031	0.0	0.0376	0.0376	0.1461	0.1461	0.2562	0.2562	0.4273	0.4273	1.0518	1.0518	2.2293
2032	0.0	0.0370	0.0370	0.1439	0.1439	0.2523	0.2523	0.4209	0.4209	1.0360	1.0360	2.1959
2033	0.0	0.0364	0.0364	0.1417	0.1417	0.2485	0.2485	0.4146	0.4146	1.0205	1.0205	2.1630
2034	0.0	0.0359	0.0359	0.1396	0.1396	0.2448	0.2448	0.4084	0.4084	1.0052	1.0052	2.1305
2035	0.0	0.0354	0.0354	0.1375	0.1375	0.2411	0.2411	0.4022	0.4022	0.9901	0.9901	2.0986

Table 13. Added sugar consumption distributions.[12,13]

Sex	Ethnicity	Consumption group	% in low vs high risk group
Male	Hispanic	Low sugar consumption	36.40%
Male	Hispanic	High sugar consumption	63.60%
Male	Non-hispanic White	Low sugar consumption	36.40%
Male	Non-hispanic White	High sugar consumption	63.60%
Male	Non-hispanic Black	Low sugar consumption	34.10%
Male	Non-hispanic Black	High sugar consumption	65.90%
Female	Hispanic	Low sugar consumption	52.80%
Female	Hispanic	High sugar consumption	47.20%
Female	Non-hispanic White	Low sugar consumption	49.30%
Female	Non-hispanic White	High sugar consumption	50.70%
Female	Non-hispanic Black	Low sugar consumption	41.70%
Female	Non-hispanic Black	High sugar consumption	58.30%

Table 14. Type 2 diabetes mortality rate.[32-34]

Age	Mortality rate
20-24	0.006177
25-29	0.009399
30-34	0.009399
35-39	0.009399
40-44	0.009399
45-49	0.013706
50-54	0.013706
55-59	0.020137
60-64	0.020137
65-69	0.031904
70-74	0.031904
75-79	0.068313
80+	0.068313

Table 15. Coronary heart disease mortality rate (in %).[30-32]

Year	<35	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
2010	0.0000	0.5067	0.8506	0.9493	1.3778	1.4767	1.4179	1.1071	2.1109	2.2865	3.9970	9.4859
2011	0.0000	0.4960	0.8327	0.9293	1.3489	1.4457	1.3881	1.0839	2.0665	2.2385	3.9130	9.2867
2012	0.0000	0.4856	0.8152	0.9098	1.3205	1.4153	1.3590	1.0611	2.0231	2.1914	3.8309	9.0917
2013	0.0000	0.4754	0.7981	0.8907	1.2928	1.3856	1.3304	1.0388	1.9807	2.1454	3.7504	8.9007
2014	0.0000	0.4654	0.7813	0.8720	1.2657	1.3565	1.3025	1.0170	1.9391	2.1004	3.6717	8.7138
2015	0.0000	0.4557	0.7649	0.8537	1.2391	1.3280	1.2751	0.9956	1.8983	2.0563	3.5946	8.5308
2016	0.0000	0.4461	0.7489	0.8358	1.2131	1.3002	1.2484	0.9747	1.8585	2.0131	3.5191	8.3517
2017	0.0000	0.4367	0.7331	0.8182	1.1876	1.2728	1.2221	0.9543	1.8195	1.9708	3.4452	8.1763
2018	0.0000	0.4275	0.7177	0.8010	1.1626	1.2461	1.1965	0.9342	1.7812	1.9294	3.3728	8.0046
2019	0.0000	0.4186	0.7027	0.7842	1.1382	1.2199	1.1714	0.9146	1.7438	1.8889	3.3020	7.8365
2020	0.0000	0.4098	0.6879	0.7677	1.1143	1.1943	1.1468	0.8954	1.7072	1.8492	3.2326	7.6719
2021	0.0000	0.4012	0.6735	0.7516	1.0909	1.1692	1.1227	0.8766	1.6714	1.8104	3.1648	7.5108
2022	0.0000	0.3927	0.6593	0.7358	1.0680	1.1447	1.0991	0.8582	1.6363	1.7724	3.0983	7.3531
2023	0.0000	0.3845	0.6455	0.7204	1.0456	1.1207	1.0760	0.8402	1.6019	1.7352	3.0332	7.1987
2024	0.0000	0.3764	0.6319	0.7053	1.0236	1.0971	1.0534	0.8225	1.5683	1.6987	2.9695	7.0475
2025	0.0000	0.3685	0.6187	0.6905	1.0021	1.0741	1.0313	0.8052	1.5353	1.6631	2.9072	6.8995
2026	0.0000	0.3608	0.6057	0.6760	0.9811	1.0515	1.0096	0.7883	1.5031	1.6281	2.8461	6.7546
2027	0.0000	0.3532	0.5929	0.6618	0.9605	1.0294	0.9884	0.7718	1.4715	1.5939	2.7864	6.6128
2028	0.0000	0.3458	0.5805	0.6479	0.9403	1.0078	0.9677	0.7556	1.4406	1.5605	2.7278	6.4739
2029	0.0000	0.3385	0.5683	0.6343	0.9206	0.9867	0.9474	0.7397	1.4104	1.5277	2.6706	6.3380
2030	0.0000	0.3314	0.5564	0.6209	0.9012	0.9659	0.9275	0.7242	1.3808	1.4956	2.6145	6.2049
2031	0.0000	0.3245	0.5447	0.6079	0.8823	0.9457	0.9080	0.7090	1.3518	1.4642	2.5596	6.0746
2032	0.0000	0.3176	0.5332	0.5951	0.8638	0.9258	0.8889	0.6941	1.3234	1.4335	2.5058	5.9470
2033	0.0000	0.3110	0.5220	0.5826	0.8456	0.9064	0.8703	0.6795	1.2956	1.4034	2.4532	5.8221
2034	0.0000	0.3044	0.5111	0.5704	0.8279	0.8873	0.8520	0.6652	1.2684	1.3739	2.4017	5.6998
2035	0.0000	0.2981	0.5004	0.5584	0.8105	0.8687	0.8341	0.6513	1.2417	1.3450	2.3513	5.5801

Table 16. Non-disease related mortality rate (in %).[32]

Year	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
2010	0.086	0.093	0.105	0.128	0.178	0.275	0.411	0.583	0.822	1.242	1.909	3.038	4.952	11.162
2011	0.086	0.093	0.105	0.125	0.174	0.269	0.403	0.571	0.797	1.205	1.851	2.947	4.804	10.828
2012	0.086	0.093	0.105	0.123	0.171	0.264	0.395	0.560	0.773	1.169	1.796	2.859	4.660	10.503
2013	0.086	0.093	0.105	0.120	0.167	0.259	0.387	0.548	0.750	1.133	1.742	2.773	4.520	10.188
2014	0.086	0.093	0.105	0.118	0.164	0.253	0.379	0.537	0.728	1.099	1.690	2.690	4.384	9.882
2015	0.086	0.093	0.105	0.115	0.161	0.248	0.372	0.527	0.706	1.066	1.639	2.609	4.253	9.586
2016	0.086	0.093	0.105	0.113	0.158	0.243	0.364	0.516	0.685	1.034	1.590	2.531	4.125	9.298
2017	0.086	0.093	0.105	0.111	0.154	0.239	0.357	0.506	0.664	1.003	1.542	2.455	4.002	9.019
2018	0.086	0.093	0.105	0.109	0.151	0.234	0.350	0.496	0.644	0.973	1.496	2.381	3.881	8.749
2019	0.086	0.093	0.105	0.106	0.148	0.229	0.343	0.486	0.625	0.944	1.451	2.310	3.765	8.486
2020	0.086	0.093	0.105	0.104	0.145	0.225	0.336	0.476	0.606	0.916	1.408	2.241	3.652	8.231
2021	0.086	0.093	0.105	0.102	0.142	0.220	0.329	0.467	0.588	0.888	1.365	2.173	3.543	7.985
2022	0.086	0.093	0.105	0.100	0.140	0.216	0.323	0.457	0.570	0.862	1.324	2.108	3.436	7.745
2023	0.086	0.093	0.105	0.098	0.137	0.211	0.316	0.448	0.553	0.836	1.285	2.045	3.333	7.513
2024	0.086	0.093	0.105	0.096	0.134	0.207	0.310	0.439	0.537	0.811	1.246	1.984	3.233	7.287
2025	0.086	0.093	0.105	0.094	0.131	0.203	0.304	0.430	0.521	0.786	1.209	1.924	3.136	7.069
2026	0.086	0.093	0.105	0.092	0.129	0.199	0.298	0.422	0.505	0.763	1.172	1.866	3.042	6.857
2027	0.086	0.093	0.105	0.090	0.126	0.195	0.292	0.413	0.490	0.740	1.137	1.810	2.951	6.651
2028	0.086	0.093	0.105	0.089	0.124	0.191	0.286	0.405	0.475	0.718	1.103	1.756	2.862	6.451
2029	0.086	0.093	0.105	0.087	0.121	0.187	0.280	0.397	0.461	0.696	1.070	1.703	2.776	6.258
2030	0.086	0.093	0.105	0.085	0.119	0.183	0.275	0.389	0.447	0.675	1.038	1.652	2.693	6.070
2031	0.086	0.093	0.105	0.083	0.116	0.180	0.269	0.381	0.434	0.655	1.007	1.603	2.612	5.888
2032	0.086	0.093	0.105	0.082	0.114	0.176	0.264	0.374	0.421	0.635	0.977	1.555	2.534	5.711
2033	0.086	0.093	0.105	0.080	0.112	0.173	0.258	0.366	0.408	0.616	0.947	1.508	2.458	5.540
2034	0.086	0.093	0.105	0.079	0.110	0.169	0.253	0.359	0.396	0.598	0.919	1.463	2.384	5.374
2035	0.086	0.093	0.105	0.077	0.107	0.166	0.248	0.352	0.384	0.580	0.891	1.419	2.313	5.213

Table 17. IHME health-adjusted life expectancy and discounted life expectancy for females. [94,95]

Age of death	WHO HALE	Discounted by 3%
20	51.138	25.981
21	51.138	25.981
22	51.138	25.981
23	51.138	25.981
24	51.138	25.981
25	46.766	24.966
26	46.766	24.966
27	46.766	24.966
28	46.766	24.966
29	46.766	24.966
30	42.466	23.832
31	42.466	23.832
32	42.466	23.832
33	42.466	23.832
34	42.466	23.832
35	38.214	22.560
36	38.214	22.560
37	38.214	22.560
38	38.214	22.560
39	38.214	22.560
40	34.033	21.144
41	34.033	21.144
42	34.033	21.144
43	34.033	21.144
44	34.033	21.144
45	29.960	19.584
46	29.960	19.584
47	29.960	19.584
48	29.960	19.584
49	29.960	19.584
50	26.017	17.884
51	26.017	17.884
52	26.017	17.884
53	26.017	17.884
54	26.017	17.884
55	22.214	16.045
56	22.214	16.045
57	22.214	16.045
58	22.214	16.045
59	22.214	16.045
60	18.574	14.081
61	18.574	14.081
62	18.574	14.081
63	18.574	14.081
64	18.574	14.081
65	15.167	12.042
66	15.167	12.042
67	15.167	12.042
68	15.167	12.042
69	15.167	12.042
70	12.020	9.968
71	12.020	9.968
72	12.020	9.968
73	12.020	9.968
74	12.020	9.968
75	9.169	7.912
76	9.169	7.912
77	9.169	7.912
78	9.169	7.912
79	9.169	7.912
80	6.646	5.942
81	6.646	5.942
82	6.646	5.942
83	6.646	5.942
84	6.646	5.942
85	4.512	4.159
86	4.512	4.159
87	4.512	4.159
88	4.512	4.159
89	4.512	4.159
90	2.915	2.751
91	2.915	2.751
92	2.915	2.751
93	2.915	2.751
94	2.915	2.751
95	1.868	1.789
96	1.868	1.789
97	1.868	1.789
98	1.868	1.789
99	1.868	1.789
100	1.231	1.189
101	1.231	1.189
102	1.231	1.189
103	1.231	1.189
104	1.231	1.189
105	1.000	0.971
106	1.000	0.971
107	1.000	0.971
108	1.000	0.971
109	1.000	0.971
110	1.000	0.971

Table 18. IHME health-adjusted life expectancy and discounted life expectancy for males.[94,95]

Age of death	WHO HALE	Discounted by 3%
20	48.035	25.275
21	48.035	25.275
22	48.035	25.275
23	48.035	25.275
24	48.035	25.275
25	43.802	24.200
26	43.802	24.200
27	43.802	24.200
28	43.802	24.200
29	43.802	24.200
30	39.589	22.989
31	39.589	22.989
32	39.589	22.989
33	39.589	22.989
34	39.589	22.989
35	35.374	21.616
36	35.374	21.616
37	35.374	21.616
38	35.374	21.616
39	35.374	21.616
40	31.217	20.085
41	31.217	20.085
42	31.217	20.085
43	31.217	20.085
44	31.217	20.085
45	27.195	18.412
46	27.195	18.412
47	27.195	18.412
48	27.195	18.412
49	27.195	18.412
50	23.347	16.614
51	23.347	16.614
52	23.347	16.614
53	23.347	16.614
54	23.347	16.614
55	19.705	14.714
56	19.705	14.714
57	19.705	14.714
58	19.705	14.714
59	19.705	14.714
60	16.256	12.716
61	16.256	12.716
62	16.256	12.716
63	16.256	12.716
64	16.256	12.716
65	13.080	10.688
66	13.080	10.688
67	13.080	10.688
68	13.080	10.688
69	13.080	10.688
70	10.208	8.680
71	10.208	8.680
72	10.208	8.680
73	10.208	8.680
74	10.208	8.680
75	7.680	6.767
76	7.680	6.767
77	7.680	6.767
78	7.680	6.767
79	7.680	6.767
80	5.524	5.019
81	5.524	5.019
82	5.524	5.019
83	5.524	5.019
84	5.524	5.019
85	3.723	3.471
86	3.723	3.471
87	3.723	3.471
88	3.723	3.471
89	3.723	3.471
90	2.388	2.269
91	2.388	2.269
92	2.388	2.269
93	2.388	2.269
94	2.388	2.269
95	1.521	1.462
96	1.521	1.462
97	1.521	1.462
98	1.521	1.462
99	1.521	1.462
100	1.000	0.971
101	1.000	0.971
102	1.000	0.971
103	1.000	0.971
104	1.000	0.971
105	1.000	0.971
106	1.000	0.971
107	1.000	0.971
108	1.000	0.971
109	1.000	0.971
110	1.000	0.971

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Additional file 1

EVEREST Statement: Checklist for health economics paper

	Study section	Additional remarks
Study design		
(1) The research question is stated	Introduction	Page 2
(2) The economic importance of the research question is stated	Introduction	Page 2
(3) The viewpoint(s) of the analysis are clearly stated and justified	Introduction, Methods	Page 2 and page 4-5 (interventions)
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Methods	Page 4-5 (interventions)
(5) The alternatives being compared are clearly described	Methods	Page 4-5 (interventions)
(6) The form of economic evaluation used is stated	Methods	Page 3
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Introduction, Methods	Page 3
Data collection		
(8) The source(s) of effectiveness estimates used are stated	Methods; Table 1, Table 2	Page 5 and 6
(9) Details of the design and results of effectiveness study are given (if based on single study)	N/A	Data derived from peer reviewed literature and national health surveys
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	Methods	Page 6
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods	Page 5
(12) Methods to value health states and other benefits are stated	Methods	Page 5; table 1
(13) Details of the subjects from whom valuations were obtained are given	N/A	
(14) Productivity changes (if included) are reported separately	N/A	
(15) The relevance of productivity changes to the study question is discussed	N/A	
(16) Quantities of resources are reported separately from their unit costs	Methods; stated per person; Table 1, Table 2	Page 5 and 6
(17) Methods for the estimation of quantities and unit costs are described	Methods; Table 1, Table 2	Page 5 and 6; Adopted from literature

(18) Currency and price data are recorded	Methods; Table 1, Table 2	Page 5 and 6
(19) Details of currency of price adjustments for inflation or currency conversion are given	Methods	Page 5
(20) Details of any model used are given	Methods	Page 3
(21) The choice of model used and the key parameters on which it is based are justified	Methods	Page 3
Analysis and interpretation of results		
(22) Time horizon of costs and benefits is stated	Methods	Page 5
(23) The discount rate(s) is stated	Methods	Page 5
(24) The choice of rate(s) is justified	Methods	Page 5
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	N/A	
(27) The approach to sensitivity analysis is given	Methods	Page 6
(28) The choice of variables for sensitivity analysis is justified	Methods; Table 1, Table 2	Page 6
(29) The ranges over which the variables are varied are stated	Table 1, Table 2	Page 6
(30) Relevant alternatives are compared	Methods, Results	Page 4 and 5
(31) Incremental analysis is reported	N/A	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	Table 3, 4 and 5	Page 7 and 9
(33) The answer to the study question is given	Discussion, Conclusion	Page 10
(34) Conclusions follow from the data reported	Conclusion	Page 11
(35) Conclusions are accompanied by the appropriate caveats	Discussion, Conclusion	Page 10

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Health and economic benefits of reducing sugar intake in the United States, including effects via non-alcoholic fatty liver disease: A microsimulation model

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Health and economic benefits of reducing sugar intake in the United States, including effects via non-alcoholic fatty liver disease: A microsimulation model

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Abstract

Objectives: Excessive consumption of added sugars in the human diet has been associated with obesity, type 2 diabetes (T2D), coronary heart disease (CHD), and other elements of the metabolic syndrome. Recent studies have shown that non-alcoholic fatty liver disease (NAFLD) is a critical pathway to metabolic syndrome. This model assesses the health and economic benefits of interventions aimed at reducing intake of added sugars.

Methods: Using data from U.S. National Health Surveys and current literature, we simulated an open cohort, for the period 2015 to 2035. We constructed a microsimulation model with Markov chains for NAFLD (including steatosis, non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma (HCC)), body mass index (BMI), T2D, and CHD. We assessed reductions in population disease prevalence, disease-attributable disability-adjusted life years (DALYs), and costs, with interventions that reduce added sugars consumption by either 20% or 50%.

Findings: The model estimated that a 20% reduction in added sugars intake will reduce prevalence of hepatic steatosis, NASH, cirrhosis, HCC, obesity, T2D, and CHD. Incidence of T2D and CHD would be expected to decrease by 19.9 (95% CI: 12.8 – 27.0) and 9.4 (95% CI: 3.1 — 15.8) cases per 100,000 people after 20 years, respectively. A 20% reduction in consumption is also projected to annually avert 0.767 million (M) DALYs (95% CI: 0.757M — 0.777M), and a total of 10.3 billion (B) USD (95% CI: 10.2B — 10.4B) in discounted direct medical costs by 2035. These effects increased proportionally when added sugars intake were reduced by 50%.

Conclusions: The decrease in incidence and prevalence of disease is similar to results in other models, but averted costs and DALYs were higher, mainly due to inclusion of NAFLD and CHD. The model suggests that efforts to reduce consumption of added sugars may result in significant public health and economic benefits.

Strengths and limitations of this study

- This model captures the full effects of dietary sugar acting on non-alcoholic fatty liver disease, as well as obesity, type 2 diabetes and coronary heart disease.
- The model is based on input parameters from multiple studies which were of mixed quality and alignment with the modelled population. We examined large uncertainty intervals to assess robustness of results.
- The model does not consider a shift to non-sugared caloric foods.

Introduction

The social and economic burdens of chronic metabolic disease have been increasing in the United States for the last three decades. Two-thirds of the adult population in the United States is now overweight, and morbid obesity affects 9.9% of all adult women.[1] Prevalence of Type 2 diabetes (T2D) in the U.S. is at 9.3%.[2,3] And the population affected by Coronary heart disease (CHD) increased concurrently from 13 to 15.5 million over the last ten years.[4,5] More than 15% of all deaths are attributable to CHD and more than 3% to diabetes.[6] Costs have simultaneously increased; and costs for CHD are expected to double over the next two decades.[7,8] Though these figures are stunning, they underestimate the magnitude of the problem. Non-alcoholic fatty liver disease (NAFLD) has recently been found to be present in over 45% of Latinos, 33% of Caucasians, and 24% of African-Americans, and is thought to play an important role in metabolic pathophysiology.[9–12] NAFLD is defined by the presence of liver fat in the absence of a primary insult such as alcohol, viral hepatitis, or heavy metal accumulation.[13] NAFLD is further categorized into: a) hepatic steatosis, which is a reversible fat accumulation in the liver defined by an occupation of steatotic hepatocytes of more than 5% of the liver parenchyma; and b) non-alcoholic steatohepatitis (NASH), which is defined as the presence of hepatic steatosis along with lobular and portal inflammation with hepatocyte injury (ballooning). Progressive collagen deposition and vascular remodelling in NASH may lead to cirrhosis, which in turn predisposes one to hepatocellular carcinoma (HCC).[9,13–15] NAFLD is the most common cause of liver disease in the Western world, and NASH is projected to become the leading cause of liver transplantation in the USA by the year 2020.[16,17] Currently 30-40% of NASH-cirrhotic patients succumb to a liver-related death within 10 years.[18,19] Hospitalizations for NAFLD have increased 97% between 2000 and 2012.[20] NAFLD has also been suggested as an important driver of T2D in lean individuals, as liver fat accumulation can cause insulin resistance.[10,21–23] NAFLD can occur as either a cause or consequence of the metabolic syndrome[10], and many now argue that NAFLD is the hepatic manifestation of metabolic syndrome, and should be included in its definition.[24–27] It is important to identify determinants of these metabolic diseases and assess the efficacy of upstream policy interventions to curb the national and the global epidemic of metabolic syndrome.

Added sugars

Added sugars consumption increased in the U.S. over the years 1977-2000, decreased slightly between 2000—2008, and seems to have stabilized in the years thereafter.[28–30] Over 55% of all American adults consumed more than 50 grams of added sugars per day between 2005—2012, which is thought to be the cut-off value for added risk of metabolic derangement, and more than the advised maximum according to the American Heart Association (25 - 37.5 grams).[3,31] The U.S. Department of Agriculture recently established guidance for an upper limit of consumption of added sugars at 10% of total energy intake (amounting to 50 grams per day (200 kcal) for a prototype 2000 kcal/day diet).[32] The European Food and Safety authority does not state an explicit maximum for (added) sugars in their advice, but they do note that a number of authorities have established boundaries of <10% of total energy intake.[33] Furthermore, the American Heart Association recommends that U.S. adolescents restrict their intake of added sugars to less than 25 grams to avoid dyslipidaemia and CVD [34], yet current intake averages 94.0 grams per day in this age group.[35]

The excessive amount of added sugars (glucose + fructose) in the food supply has been associated with NAFLD and with each of the component diseases of the metabolic syndrome.[36–38] Fructose is metabolized by the liver, as it is the only organ with the required Glut5 transporter. Fructose bypasses glycogen, and is metabolized by the glycolytic pathway to acetyl-CoA. From there, excess acetyl-CoA is converted to citrate, diverted from the mitochondria into the cytoplasm via the citrate shuttle, and is then converted into fatty acids through the process of *de novo* lipogenesis(DNL).[39] From there, hepatically-derived excess triglyceride is either packaged with apo-B100 into very-low-density-lipoprotein (VLDL), which is released into the bloodstream and can foment cardiovascular disease; or will precipitate as a lipid droplet, resulting in hepatic steatosis which drives insulin resistance, causing weight gain, and predisposing to T2D. While most early studies of added sugar and chronic disease were correlative and confounded by excess caloric administration, lack of adjustment for total calories, or adiposity, more recent studies demonstrate that the effect is specific for dietary fructose, and independent of calories consumed and BMI.[39–48] For instance, added sugar is directly correlated with risk for metabolic syndrome in adolescents in NHANES even after controlling for total calories and BMI z-score.[35] Added sugar has been associated with elevated uric acid levels and hypertension.[49,50] Two recent studies, both controlled for calories and adiposity and employing a time analysis, support sugar-sweetened beverages as a specific causative agent in the pathogenesis of T2D.[42,51,52] A decade-long global econometric analysis demonstrates that only changes in sugar availability are predictive of changes in diabetes prevalence, unrelated to poverty, urbanization, aging, physical activity, total calories, or obesity.[37] Lastly, in a starch-for-sugar exchange study, our group has documented improvements in metabolic and lipid parameters unrelated to both calories and changes in weight, demonstrating improved metabolic health within 10 days.[40,53] We have demonstrated that the decline in DNL and resultant reduction in liver fat was the primary driver in the metabolic and cardiovascular improvement.[54] By demonstrating that removal of dietary fructose (the macronutrient most closely associated with DNL) commensurately improves liver fat and insulin dynamics irrespective of calories or weight, we are able to infer a causative mechanism of metabolic dysfunction by linking DNL to both liver fat and insulin resistance. We also demonstrated that despite an increase in the glucose (starch) content of the diet, beta-cell insulin secretion reduced, thus protecting against beta-cell exhaustion, thought to be important in the pathogenesis of type 2 diabetes[55]; and reducing total body insulin burden, thought to contribute to both obesity and risk for cardiovascular disease.[56,57] Thus, reduction in DNL and liver fat through reduction in consumption of added sugars appears to be a

primary goal of both therapy and prevention of chronic metabolic disease, and forms the rationale for our microsimulation model.

Intervention efficacy

Several studies have modeled the effects of different interventions to reduce added sugars intake. One popular intervention is the implementation of a sugar-sweetened beverage (SSB) tax. Though this does not affect all added sugars in the food supply, SSB's are the main single contributor to overall added sugars intake, and a tax on SSB's is easier to implement than an added sugars tax.[58] A 20% SSB tax is projected to reduce prevalence of obesity anywhere from 1.5 —10%, based on different studies.[59–61] Data from Mexico demonstrate that effects on reduction of consumption are durable, although evidence of mitigation of disease are not yet available.[62] Annual diabetes cases would be expected to decline concurrently between 1.8% and 3.4%, and CHD cases by 0.5 —1.0%.[60,63] Additional research has focused on other strategies to lower added sugars consumption. Banning SSB's from the U.S. Supplemental Nutrition Assistance Program (SNAP) is expected to result in a 0.89% lower obesity prevalence within 10 years, while lowering the amount of sugars in the food supply through a cap and trade approach by 1% annually is expected to lower the prevalence of obesity by 1.7% after 20 years.[64,65]

An important limitation of all these studies is that none of these models incorporate the effects and costs related to sugar-induced NAFLD. Because NAFLD explains a part of the incidence of diabetes in lean individuals and is expected to contribute significantly to overall healthcare burden and costs, it is necessary that models incorporate all of these diseases.

Our goal is to predict the magnitude of the health and economic effects of interventions that are designed to reduce added sugars consumption either by 20% or 50%, respectively. This modelling approach more precisely quantifies the benefits of reducing added sugar consumption. We describe the process of creating, calibrating and validating a microsimulation model. We clarify the relevant interactions that determine progression within this model in Markov chains for NAFLD (including cirrhosis and HCC), obesity, T2D, and CHD, and we describe the creation of a simulated open cohort representative of the US population. We allow the model to run for 20 years into the future to predict effectiveness. We report the outcomes of these simulations in future incidence, prevalence and mortality of disease, and in disability-adjusted life years (DALYs) and costs averted.

Methods

The Methods section is constructed according to the recommendations by the ISPOR taskforce for good modelling practice, and completeness is checked according to the CHEERS statement.[66,67]

Summary

We constructed an individual based model consisting of a base cohort of 22,400 people. New people entered the model each year at age 20, the youngest age group we simulate. Individuals are assigned a state at initialization in each 'chain' of the model. These include age, sex, ethnicity, sugar consumption, NAFLD, BMI, T2D, and CHD. The current health state of each individual at the beginning of a cycle forms a risk profile, and the presence in a risk-inducing state in one of the chains can influence the probability of transitioning between states in a different chain, according to literature-based odds ratios. We simulated 20 annual cycles for each individual, counting events, incurred direct medical costs, and DALYs for each cycle, as well as the overall prevalence for the total cohort. We discounted the costs and DALYs by 3.0% annually, and costs were presented in 2015 USD. Two interventions were simulated: one that reduced each individual's added sugars consumption by 20%, and one that reduced it by 50%. We used identical random numbers for the base case scenario and each of the interventions, to reduce variance. We calibrated the model to other studies reporting historic trends and predicting future prevalence, and validated the model via face validation, cross-validation, and sensitivity analyses. Deterministic sensitivity analysis was used to determine the influence of individual input parameters. Probabilistic sensitivity analysis was used to generate mean results and 95% central coverage intervals.

Model type

An individual-based stochastic Markov model (microsimulation) was used. The model contained a chain for each of four separate diseases. Because each of these diseases has a minimum of 3 states, and the transitions between these states are based on the presence or absence of a set of risk factors, the state-space explosion phenomenon prohibits us from using traditional Markov cohort simulation. An individual-based approach makes it possible to use individual-specific transition rates, capturing the effect of interventions on individual risk factor profiles, thereby avoiding the need to count the number of individuals in all possible states and allowing for complex relationships between several risk factors within a single individual.[68] It also opens up potential for future analyses among subgroups.

Population and setting

The model is based on the adult population (age 20+) of the United States. Outcomes are reported from a healthcare perspective. This includes direct medical costs and DALYs averted. Indirect medical or non-medical costs are excluded. Because this model is meant to assess the benefits of reducing added sugars intake, unrelated to the type of intervention, costs of implementing any specific intervention and possible revenues (e.g. in the case of an excise or general services tax) are also excluded.

Model structure and input parameters

A simplified model transition diagram is presented in **Figure 1.** Model input parameters are presented in **table 1 and 2** and supplementary **table 1**. Individuals will reside in a state within each chain at any given point in time. The probability of staying within a state or moving to another state in each cycle is determined by a set of defined transition probabilities, which are influenced by the risk profile (the current state in the other chains) of the individual. Events in different chains can occur in parallel.

The simulation is initialized by assignment of age (A), sex (S), and ethnicity (E) to each individual. Age states are based on the population distribution that is provided by the Bureau of the Census, and are specified for each age from 20 to 84 and a cumulative age group for anyone above 85. We simulate an open cohort. New individuals with age 20 enter each year.[69] The initial age distribution is specified in supplementary **table 2**. Male and female sex are incorporated with an initial distribution specified in supplementary **table 3**. Ethnicities incorporated into the model are Hispanic, non-Hispanic black, and non-Hispanic-white. Data availability did not allow us to incorporate Asians and Native Americans as separate groups and therefore they were grouped with the non-Hispanic whites. The initial ethnicity distribution is specified in supplementary **table 4**.

When the individual is assigned an age, sex and ethnicity, these determine the state that this individual will be assigned to in each of the chains for NAFLD, BMI, T2D, and CHD at the start of the simulation. Each chain represents a separate disease process, and has its own non-disease state (e.g., non-T2D). This does not mean that this person is actually healthy (e.g. a person can have cirrhosis but not diabetes). The NAFLD chain includes a non-NAFLD state, and states for hepatic steatosis, NASH, cirrhosis, and NASH- or cirrhosis-related HCC. A person is defined as having NAFLD when his or her current state is steatosis, NASH, or cirrhosis. This is different from common terminology, where cirrhosis is excluded. We chose this definition for easy reference, because these three states imply extra risk for progression within other chains. The initial distribution over NAFLD states is specified in supplementary **table 5** and specified per ethnicity group.

It is important to note that modeled cirrhosis and HCC are specifically related to steatosis and NASH, and do not include all cirrhosis and HCC cases within the population, irrespective of cause. Transition directly from the non-NAFLD state to either one is therefore not possible. Baseline transition probabilities are specified in **table 2** and transition rates from NASH and cirrhosis to HCC are specified per age group, as defined in supplementary **table 6 and 7**, starting at age 40. (age groups: 40-44, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79 and 80 years and over), Risk factors for progression are stated in **table 2** and include ethnicity (protective and detrimental factors), being overweight or obese, and high sugar consumption. These risk factors apply for transitions up to the cirrhosis state.

The BMI chain includes states for healthy weight, overweight and obesity. The initial distribution over BMI states is specified in supplementary **table 8,** and specified by sex, ethnicity, and age group (ages 20-35, 35-44, 45-54, 55-64, 65-74, 75-84 and 85+). Baseline transition probabilities are specified in **table 2**. Risk factors for progression are stated in **table 1** and include NAFLD disease states and high sugar consumption.

The T2D chain includes a non-T2D state and a T2D state. The initial distribution over T2D states is specified in supplementary **table 9** and specified by sex, ethnicity, and age group (ages 20-35, 35-44, 45-54, 55-64, 65-74 75-84 and 85+). Average baseline transition probability to T2D is specified in **table 2** and age-specific incidence rates are provided in supplementary **table 10** (age groups: 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79 and 80+). Risk factors for progression to T2D are stated in **table 2** and include NAFLD disease states, overweight, and obesity.

The CHD chain includes a non-CHD state and a CHD state. The distribution over CHD states at simulation start is specified in supplementary **table 11** and specified per sex, ethnicity and age group (ages 20-44, 45-64 and 65+). Average baseline transition probability to CHD is specified in **table 2** and age-specific incidence rates are provided in supplementary **table 12** (age groups: <35, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84 and 85+). Risk factors for progression to CHD are stated in **table 2** and include NAFLD disease states, overweight, obesity, and T2D.

Each individual is assigned a level of consumption of added sugars. There are two states in the sugar chain — high consumption (≥50g of added sugars per day), and low consumption (< 50g of added sugars per day). The distribution of these states among the study population reflects the data of the NHANES 2005-2012, and is specified per sex and ethnicity group, as shown by supplementary **table 13**.[3,35] Dietary intake data in NHANES were collected using two 24-hr dietary recalls, following the United States Department of Agriculture's (USDA) Automated Multiple Pass Method and administered to the adult.[70] The arithmetic mean of added sugar intake in grams per day was obtained by merging individual dietary recalls from NHANES with the USDA Food Patterns Equivalents Database (FPED).[71] Sugar consumption is fixed throughout the simulation for each person.

From each state, individuals can transition to a 'non-disease related death' state. Three disease chains also have a disease-specific death state (i.e.. T2D-death, CHD-death, and liver-related death), allowing calculation of disease-attributable death. Mortality rates from causes outside the model were corrected for the competing risks of modeled causes of mortality to

ensure valid overall mortality. Death in one chain forces an instant transition to the death state in other chains. Average transition probabilities to disease-related death states are specified in **table 2**. Age specific rates for T2D-related death are specified in supplementary **table 14**. Liver death rates are specified in **table 2**. Deaths were attributed to the disease for which the transition to death was established first. To remove confounding because of calculation order, chain calculation order was randomized. This ensures that deaths are attributed to the right disease, e.g. people with T2D and CHD have a chance to die of T2D, CHD or succumb to a non-disease related death.

To determine whether there were temporal trends in incidence or death rates, we plotted the available historic data (1999-2013) and projected this to the future.[5,6,72] These trends were found to be present for the incidence and mortality rate of CHD, and for the non-disease specific mortality rate. We incorporated these regression rates into the model by adjusting the respective baseline transition probabilities before each cycle. Average baseline transition probabilities for CHD and non-disease related deaths are specified in **table 2**. The CHD-specific death rates by year and age are specified in supplementary **table 15** and the non-disease related death rates per year and age are specified in supplementary **table 16**. For DALY calculations, health-adjusted life expectancy for females and males are provided in **supplementary table 17 and 18**.

Final transition probabilities per chain are compared to a pseudo-random number to determine state-transitions each cycle. These final transition probabilities were derived from baseline transition probabilities, adjusting for the relative risk of progression observed for applicable risk factors. The correction formula for the baseline transition probabilities is a multiplicative function of all applicable values (odds ratios) for present risk factors. As an example, imagine a person with high sugar consumption, obesity, and hepatic steatosis, but no T2D or CHD (disregarding age, sex & ethnicity in this example). In the NAFLD chain the transition from steatosis to NASH has a baseline transition probability of 0.0060 (see table 2). This is adjusted to reflect the ORs for applicable risk factors (3.14 for obesity and 2.00 for high sugar consumption), resulting in a revised transition probability of 0.0060 * 3.14 * 2.00 = 0.0377. Similar adjustments are made for transitions to cirrhosis, HCC, death,and non-NAFLD. What remains is the probability of remaining in the steatosis state.

Figure 1

Interventions

Two interventions were simulated: a reduction of 20%, and a reduction of 50% in individual added sugars consumption. A 20% reduction in added sugars was simulated to be consistent with the percentage reduction assessed in several studies.[59–61] In addition, a 50% reduction was simulated because the American Heart Association advises 6-9 teaspoons of added sugar (for females and males respectively) as a maximum per day, which is approximately 50% of the current average consumption.[3,31,35] The individual added sugars consumption distribution was then split into a dichotomous variable; with people consuming less than or equal to 50 grams of added sugars being considered low consumers, and people consuming more than 50 grams per day being considered high consumers. This model did not incorporate substitutions to other food categories, but it did incorporate the overall added sugars reduction, rather than a sole reduction in SSB consumption used in other studies.[60,63] This makes it possible to capture the overall effects of added sugars, contrary to the solitary effect of SSB's. The effects of changes in food consumption to other food groups (e.g. proteins, fat) are not modeled. Detrimental effects of these food categories are less well documented and inferior to the effects of added sugars. NHANES data was used to reduce individual added sugars consumption by the specified amount. From these data, new distributions were calculated to reflect subgroup consumption patterns. These distributions determined the ratio between individuals in the high and the low risk group, and therefore determine progression within disease chains. Identical random numbers were used between interventions to reduce variance, as described by Stout and Goldie.[73]

Time horizon, cycle length

The model had a time horizon of 20 years, modeling the calendar years 2015 to 2035. This duration was chosen to make sure effects within chronic diseases (T2D, CHD) were sufficiently visible. The cycle length was 1 year. Individuals could exit the model through each death state, or live until the end of the simulation.

Outcomes

Outcomes were incidence, prevalence and mortality of disease, and direct medical costs and DALYs averted. Costs were calculated by multiplying prevalence by discounted disease-attributable costs. DALYs were calculated by adding years lived with disability (YLD) and years of life lost (YLL). YLD was calculated as the product of the prevalence of disease times the discounted disability weight. YLL was calculated by multiplying the discounted health-adjusted life expectancy at death by the amount of people that died in that specific year, given a certain age and sex. The discount rate for costs, disability weights, and life expectancy was 3.0% annually. Health-adjusted life expectancy and discounted life expectancy for males and females for the United States were not derived by the model but implemented directly from publications of the Institute for Health Metrics and Evaluation (IHME). They are provided in the online supplement, **table 3 and 4**.

Input parameter determination

The model parameters that determined demographics and the distribution of risk factors and disease at the start of the simulation are mainly derived from NHIS and NHANES data. If data were not sufficient, current literature was consulted. Model input parameters, their distribution ranges, and the sources from which they were acquired are presented in **tables 1 and 2**. Baseline transition probabilities were derived from literature data, and where necessary, via calibration. Also when necessary, we used logistic conversion to adjust transition rates to reflect annual probabilities. Interaction values were derived from literature data. For interactions between chains, we used conservative data when possible, to ensure no overestimation of effect size. We took special care to ensure these odds ratios reflect the case for our model, i.e. reflect decreased risk due to a reduction in overall added sugars intake, not just a reduction in sugar-sweetened beverage intake, which is more commonly investigated. Regression rates were determined by historic and projected trends reported by the CDC and the American Heart Association.[3,5,6] Costs were derived from American population-based studies and, where necessary, were inflated by the inflation calculator of the United States Department of Labor Statistics to 2015 USD.[74] Costs were calculated as specific disease-attributable costs (i.e. costs for CHD due to diabetes were counted as costs due to CHD rather than costs due to diabetes). This was necessary to prevent overlapping costs. Disability weights were adopted from World Health Organizations' burden of disease estimates and current literature. Specific sources are provided in the tables.

Table 1. Model input values and ranges for disease characteristics. Costs are population based, meaning that they include those who do not get care.

	Prevalence at simulation start				Costs (annual)			Disability weights			
Disease state	***Mean***	***Min***	***Max***	**Ref.**	***Mean***	***SD***	***Ref.***	***Mean***	***Min***	***Max***	**Ref.**
Steatosis	27.955%[#]	18.637%	41.933%	[8,16,18]	134	50	[75]	0.000	0.000	0.000	[76–78]
NASH	3.141%[#]	2.094%	4.712%	[8,16,18]	267	100	[75]	0.033	0.017	0.066	[76–78]
Cirrhosis	0.314%[#]	0.209%	0.471%	[79,80]	2,861	1073	[81]	0.194	0.127	0.273	[10,75]
HCC	0.025%[#]	0.017%	0.038%	[82,83]	42,644	15,992	[76,84,85]	0.294	0.199	0.411	[76–78]
CHD	6.544%[#]	-	-	[1,2,6]	13,233	4962	[6,86]	0.066	0.043	0.095	[76]
T2D	9.447%[#]	-	-	[1,2]	8,170	3064	[86–88]	0.150	0.080	0.220	[76,89]
Overweight	33.473%[#]	-	-	[1,2]	343	129	[86,88]	0.000	0.000	0.000	[90]
Obesity	37.391%[#]	-	-	[1,2]	916	344	[86,88]	0.012	0.001	0.022	[90]

SD: standard deviation, NASH: non-alcoholic steatohepatitis, HCC: hepatocellular carcinoma, CHD: coronary heart disease, T2D: type 2 diabetes. CHD, T2D, overweight, and obesity prevalence are not varied in the sensitivity analyses.
Age, sex and/or ethnicity specific values are specified in the online supplement.

Table 2. Selected model input parameter values and ranges.

Parameter				
Initialization	**Mean**	**Min**	**Max**	**Source**
Age distribution	OS1*	-	-	[91]
Sex distribution	OS2**	-	-	[91]
Ethnicity distribution	OS3***	-	-	[91]
High sugar consumption	57.278%[#]	38.186%	85.917%	[3,35,42]
Baseline transition probabilities[##]	**Mean chance**	**Min**	**Max**	**Source**
Non-NAFLD -> steatosis	0.0100	0.006700	0.01500	[92–100]
Non-NAFLD -> NASH	0.0003	0.000201	0.00045	[92–100]
Steatosis -> NASH	0.0060	0.004020	0.00900	[92–100]
Steatosis -> cirrhosis	0.0002	0.000134	0.00030	[92–100]
NASH -> cirrhosis	0.0020	0.001340	0.00300	[92–100]
NASH -> HCC	0.0001[#]	0.000067	0.00015	[92–103]
NASH -> liver death	0.0038	0.002546	0.00570	[104–107]
Cirrhosis -> HCC	0.0200[#]	0.013400	0.03000	[92–103]
Cirrhosis -> liver death	0.0340	0.022780	0.05100	[104–107]
HCC -> liver death	0.5000	0.335000	0.75000	[104–107]
Non-CHD -> CHD	0.0045[#]	0.003015	0.00675	[108,109]
CHD -> CHD death	0.0100[#]	0.006700	0.01500	[5,6,108]
Non-T2D -> T2D	0.0045[#]	0.003015	0.00675	[72,110]
T2D -> T2D death	0.0100[#]	0.006700	0.01500	[6,72,110]

Healthy weight -> overweight	0.0500	0.033500	0.07500	[111–114]
Healthy weight -> o**bese**	0.0060	0.004020	0.00900	[111–114]
Overweight -> obese	0.0180	0.012060	0.02700	[111–114]
Each alive state -> non-disease related death	0.0100[#]	0.006700	0.01500	[6]
Risk factors (odds ratios)	**Mean value**	**Min**	**Max**	**Source**
NHB ethnicity for progression within NAFLD	0.93	0.70	1.00	[115]
Hispanic ethnicity for progression within NAFLD	1.67	1.22	2.22	[115]
Overweight for progression within NAFLD	2.19	1.60	3.38	[93,116–121]
Obesity for progression within NAFLD	3.14	2.07	5.28	[93,116–121]
High sugar consumption for progression within NAFLD	2.00	1.50	3.00	[38,122]
NAFLD for TP non-CHD -> CHD	2.31	1.66	3.62	[123–127]
Overweight for TP non-CHD -> CHD	1.22	1.12	1.32	[128–135]
Obesity for TP non-CHD -> CHD	1.60	1.43	1.79	[128–135]
T2D for TP non-CHD -> CHD	2.24	1.64	3.06	[136]
NAFLD for TP non-T2D -> T2D	2.73	1.87	4.46	[137–143]
Overweight for TP non-T2D -> T2D	2.18	1.59	3.36	[144–150]
Obesity for TP non-T2D -> T2D	3.36	2.18	5.72	[144–150]
NAFLD for progression within the BMI chain	2.19	1.60	3.38	[93,116–121]
High sugar consumption for progression within the BMI chain	2.60	1.20	6.00	[149,150]

SD: standard deviation, NAFLD: non-alcoholic fatty liver disease (steatosis, NASH & cirrhosis), NASH: non-alcoholic steatohepatitis, HCC: hepatocellular carcinoma, CHD: coronary heart disease, T2D: type 2 diabetes, NHB: non-Hispanic black.
* See online supplement table 1. ** See online supplement table 2. *** See online supplement table 3.
# Age, sex and/or ethnicity specific values are specified in the online supplement.
Transition probabilities for regression to less severe disease are specified in the online supplement.

Calibration

Incidence, prevalence, mortality and costs of overweight and obesity, T2D, and CHD were calibrated to reflect historic data from the CDC and projections from the American Heart Association (AHA) and several individual studies predicting future disease.[6,7,151–155] NASH- and cirrhosis-related HCC incidence and mortality was calibrated to historic trends reported by the CDC, and future predictions reported by the American Cancer Association.[6,156]

Validation

Validation of the model occurred via face validation, cross-validation, and sensitivity analyses. Face validation was performed manually by the authors. Each chain was checked separately for functionality before merging them. Cross-validation was performed by comparing epidemiological outcomes and predictions from our model with reported results from different studies on each subject, as presented in the Discussion.

Uncertainty was assessed using deterministic and probabilistic sensitivity analysis (DSA & PSA). DSA was conducted using a five-point analysis, with the minima and maxima specified in **tables 1 and 2**. If a mean and standard deviation (SD) are specified, we used a range of mean ± 1.96*SD. DSA results are only presented for the two main outcomes: total costs and DALYs averted in the year 2035. PSA was conducted using the distributions defined in **tables 1 and 2**, to produce a mean and 95% central coverage interval for all outcome values by running the simulation 10,000 times (each of which including the base case and two interventions).

Cohort simulation

To produce stable results, limit computational requirements, and have a cohort that remained representative of the U.S. population, we simulated a base cohort of 22,400 people, with new entry of 416 people each year, reflecting CDC population prospects.[69] Because of computational requirements, the model was built in Golang programming language (Google Inc, Mountain View, CA). Model code is publicly available via https://github.com/alexgoodell/go-mdism or can be acquired through the corresponding author. Sensitivity analyses were conducted using a 20-machine cluster (Amazon Web Services, Seattle, WA). Outcome analysis was completed in Excel 2010 (Microsoft, Redmond, WA).

Results

Incidence and mortality

The incidence of T2D, CHD, and HCC and the corresponding death rates in the year 2035 are stated in **table 3**. Diabetes incidence is expected to rise over the next 20 years, resulting in an incidence rate of 1035 cases per 100,000 people. The interventions are expected to reduce this by 19.9 and 83.5 respectively. CHD incidence is expected to rise to 665 cases per 100,000 people by 2035. This can be reduced by 9.4 and 39 cases by the 20% and the 50% intervention respectively. NASH- or cirrhosis-related HCC incidence will rise to 4.4 cases per 100,000 people. Interventions could reduce this amount by 0.3 and 1.3 respectively. Liver death can be due to HCC, or it can be related to NASH or cirrhosis in the absence of HCC. Liver-

related deaths will rise substantially, to 19.8 deaths per 100,000 people by 2035. This can be reduced by 1.4 or 5.8 deaths per 100,000 people by the 20% and 50% intervention, respectively.

Table 3. Annual occurring and averted events in 2035

Per 100,000 people

Events	No intervention (CI)	20% red. (CI)	Difference (CI)	50% red. (CI)	Difference (CI)
T2D cases	1034.6 (1031.0-1038.2)	1014.7 (1011.3-1018.2)	19.9 (12.8-27.0)	951.2 (947.9-954.4)	83.5 (76.7-90.3)
T2D deaths	576.6 (574.2-578.9)	569.3 (567.0-571.6)	7.2 (2.7-11.8)	546.4 (544.2-548.6)	30.2 (25.7-34.6)
CHD cases	665.1 (661.9-668.2)	655.6 (652.5-658.8)	9.4 (3.1-15.8)	626.1 (623.1-629.1)	39.0 (32.8-45.2)
CHD deaths	203.6 (202.2-205.0)	201.9 (200.5-203.3)	1.6 (-1.2-4.4)	197.2 (195.9-198.6)	6.3 (3.6-9.1)
HCC cases	4.4 (4.32-4.41)	4.0 (3.95-4.05)	0.3 (0.24-0.39)	3.1 (3.02-3.18)	1.3 (1.24-1.38)
Liver deaths	19.8 (19.65-20.02)	18.5 (18.29-18.63)	1.4 (1.02-1.73)	14.1 (13.94-14.21)	5.8 (5.44-6.08)

NASH: non-alcoholic steatohepatitis; HCC: hepatocellular carcinoma; CHD: coronary heart disease; T2D: type 2 diabetes mellitus; CI: 95% central coverage interval. Numbers might not add up due to rounding.

Prevalence

Figure 2, graphs A-H show the reduction in prevalence of disease due to the two intervention strategies. A 20% reduction in added sugars consumption is expected to decrease prevalence of each disease state significantly after 20 years, except for overweight prevalence, which does not change significantly. A 50% reduction in added sugars consumption will proportionally affect prevalence. Effects on T2D and CHD prevalences start to accumulate after an initial 3-year lag period. Graph G shows that overweight prevalence is not reduced. This is because the individuals that regressed from obese to overweight offset the reduction achieved in people that started overweight and regressed to normal weight. This effect is clarified by the drop in obesity prevalence.

Figure 2

Costs & DALYs

An overview of economic findings is presented in **table 4**. Overall costs for the modeled disease states could be reduced by 2.26% (95% CI 2.23% — 2.29%) by the year 2035 with an intervention that reduces added sugars intake by 20%. The 50% intervention will reduce overall costs by 6.99% (95% CI: 6.91 — 7.08). DALY burden and averted DALYs are presented in **table 5**. Total amount of DALYs could be reduced by 4.32% (95% CI: 4.27% — 4.38%) or 13.37% (95% CI: 13.24% — 13.51%) respectively. The majority of averted DALYs are due to reduced mortality.

Table 4. Annual costs spent and averted per disease state in 2035

In billions 2015 USD, discounted by 3.0% annually

State	No intervention (CI)	20% reduction (CI)	Difference (CI)	50% reduction (CI)	Difference (CI)
Steatosis	6.48 (6.43-6.53)	6.40 (6.35-6.45)	0.08 (0.080-0.082)	6.23 (6.18-6.28)	0.25 (0.248-0.255)
NASH	5.26 (5.22-5.30)	4.89 (4.85-4.93)	0.37 (0.368-0.375)	4.11 (4.08-4.14)	1.15 (1.139-1.162)
Cirrhosis	7.00 (6.93-7.07)	6.22 (6.16-6.28)	0.78 (0.772-0.791)	4.60 (4.56-4.65)	2.40 (2.371-2.429)
HCC	5.10 (5.04-5.16)	4.55 (4.50-4.60)	0.55 (0.537-0.558)	3.40 (3.36-3.44)	1.70 (1.669-1.721)
CHD	162.2 (160.9-163.6)	160.1 (158.8-161.5)	2.09 (2.06-2.12)	155.7 (154.4-157.0)	6.51 (6.43-6.58)
T2D	200.0 (198.4-201.6)	195.9 (194.3-197.5)	4.07 (4.02-4.12)	187.4 (185.9-188.9)	12.59 (12.46-12.73)
Overweight	16.4 (16.3-16.5)	16.6 (16.5-16.8)	-0.25 (-0.26 - -0.25)	17.2 (17.1-17.3)	-0.79 (-0.81 - -0.78)
Obesity	52.7 (52.3-53.1)	50.1 (49.7-50.5)	2.59 (2.57-2.62)	44.7 (44.3-45.0)	8.03 (7.95-8.12)
Total	**455.1** (451.4-458.9)	**444.9** (441.2-448.5)	**10.3** (10.2-10.4)	**423.3** (419.8-426.8)	**31.8** (31.5-32.2)

NASH: non-alcoholic steatohepatitis; HCC: hepatocellular carcinoma; CHD: coronary heart disease; T2D: type 2 diabetes mellitus; CI: 95% central coverage interval. Numbers might not add up due to rounding.

Table 5. Annual occurring and averted DALYs in 2035

In millions

State	No intervention (CI)	20% reduction (CI)	Difference (CI)	50% reduction (CI)	Difference (CI)
NASH	2.97 (2.955-2.988)	2.76 (2.746-2.777)	0.210 (0.209-0.212)	2.32 (2.309-2.334)	0.650 (0.645-0.655)
Cirrhosis	0.48 (0.475-0.482)	0.42 (0.422-0.428)	0.053 (0.053-0.054)	0.31 (0.312-0.316)	0.164 (0.162-0.165)
HCC	3.06 (3.046-3.084)	2.78 (2.765-2.799)	0.283 (0.279-0.283)	2.19 (2.180-2.206)	0.872 (0.863-0.881)
CHD	2.32 (2.305-2.330)	2.29 (2.276-2.302)	0.028 (0.028-0.029)	2.23 (2.217-2.242)	0.088 (0.086-0.090)
T2D	8.21 (8.180-8.248)	8.06 (8.023-8.089)	0.158 (0.155-0.160)	7.72 (7.690-7.752)	0.492 (0.487-0.498)

Obesity	0.69 (0.689-0.700)	0.66 (0.655-0.666)	0.034 (0.034-0.035)	0.59 (0.584-0.593)	0.106 (0.105-0.107)
Total	**17.74** (17.65-17.83)	**16.97** (16.89-17.06)	**0.767** (0.757-0.777)	**15.37** (15.29-15.44)	**2.372** (2.348-2.396)
From mortality	11.94	11.50	0.439	10.58	1.357
From morbidity	5.80	5.47	0.328	4.78	1.015

NASH: non-alcoholic steatohepatitis; HCC: hepatocellular carcinoma; CHD: coronary heart disease; T2D: type 2 diabetes mellitus; CI: 95% central coverage interval. Numbers might not add up due to rounding.

Sensitivity analyses

We show tornado diagrams for the two most important outcomes: annual costs and DALYs averted by the year 2035 due to an intervention that reduces sugar consumption by 20%. The diagrams show the impact that specific input parameters had on selected results. The ten variables that caused the widest range in results are shown. When varying individual variables, the annual savings by the year 2035 range from 7.9 to 17.1 billion 2015 USD. The tornado diagram (**Figure 3**) shows that the interaction between high added sugars consumption and the progression within the NAFLD and BMI chains had the greatest impact on total costs averted. In the tornado diagram for total annual DALYs averted by the 20% intervention in the year 2035 (**Figure 4**), assigned disability weights had the greatest impact. Total DALYs averted ranged between 0.36 and 1.41 million.

Figure 3&4

Discussion

It has been estimated that the cost burden of the diseases of metabolic syndrome are 75% of the total annual health care budget ($3.2 trillion) of the United States. The clinical burden of NAFLD alone is estimated at $103 billion**.**[157] The proposed model shows clear and significant benefits for interventions that reduce consumption of added sugars. A reduction by 20% will reduce annual direct medical costs for U.S. adults by more than 10 billion USD (2015 dollars) by the year 2035. A 50% reduction will save an additional 21 billion. Together with these economic benefits, population health will significantly improve. A total of 770,000 DALYs could be averted with a 20% reduction in consumption. A 50% reduction in consumption will avert another 1.6 million DALYs. These health and economic benefits are the direct result of lower incidence, prevalence, and mortality of disease in U.S. adults due to lower consumption of added sugars. Averted costs are achieved primarily through reduced costs for CHD, T2D, overweight, and obesity. This is mainly because costs for the most prevalent NAFLD states, namely steatosis and NASH, are fairly low, whereas costs for other illnesses are much higher (Table 1). In averted DALYs, we find that the combination of disability weight and prevalence changes are predictors of DALY reductions. E.g. NASH has a lower disability weight but higher prevalence reductions and therefore we find almost equal DALY reductions compared to HCC or CHD. T2D has the highest reduction in DALY burden because it has relatively large values for both prevalence reduction and disability weight.

Fit with current knowledge

The estimate for health and economic benefit of this model is similar to a number of previously performed economic evaluations. Basu et al. found a reduction in diabetes incidence of 21.7 cases per 100,000 people with a reduction of 20% of added sugars through a cap and trade approach, limiting the amount of sugars in the food supply.[65] We found a reduction of 19.9 cases per 100,000 people, indicating a similar absolute effect size. CHD incidence reduction is estimated to be about 1.5-fold higher than found in a similar study, but we argue that this is mainly because the other study simulated a 20% tax on sugar-sweetened beverages, and therefore the overall added sugars consumption reduction was smaller than the 20% reduction we simulated.[63] In an econometric analysis looking backward in time, Basu et al. found a delay of 3 years between changes in sugar consumption and prevalence of diabetes.[37] Similarly, we found a delay of 3 years going forward in time between reduction of consumption and reduction in prevalence of disease. Prevalence of obesity has been reported to drop by 1.5% — 10% due to a reduction of added sugars by 10% — 20%.[59–61] Our result of 2.1% reduction in obesity prevalence seems to reflect our conservative approach in determining input parameter values.

Costs savings are bigger in our model compared to other models.[60,64,64] This was for three reasons. First, some other models do not use added sugars as a whole but use SSB's, resulting in a smaller effect. Second, our overall prevalence of T2D and CHD is higher than most other models. We have calibrated our model to historic trends reported by the CDC and to future projections of the AHA, ADA and separate studies predicting future prevalence, and therefore argue that our estimate is valid. Third, and perhaps most importantly, no other studies predict future NAFLD prevalence. We present the first model that estimates the effects of sugar interventions on NAFLD prevalence and associated costs and DALYs.

In 2009, the American Heart Association recommended a reduction in added sugar consumption from a median of 90 grams per day to a maximum of 25 grams for women and 37.5 grams for men.[31] In 2016, the USDA and WHO settled on an upper limit of 10% of calories, which approximates 50 grams per day. Given the U.S. current median consumption of 80 grams per day, our microsimulation modeling cutoffs of 20% and 50%, while ambitious, are metabolically rational and in

concert with governmental goals.[158]

Our model only allows us to examine the negative side of the balance sheet in terms of cost savings to health care. However, reductions in added sugar consumption have been modeled to provide significant increases to the positive side of the balance sheet in terms of economic productivity. Indeed, a simulation modeling by Morgan Stanley predicted economic growth to decline to zero by the year 2035 using a high-sugar case, whereas stabilization at +2.9% was noted with a low-sugar case.[159]

Strengths and limitations

This study is the first of its kind to model the effect of added sugars on NAFLD as well as on BMI, and therefore it captures a more complete picture of the possible health and economic benefits of interventions that reduce intake of added sugars. Though taxing sugar-sweetened products, mainly beverages, has been widely suggested as a public health strategy, other approaches, e.g. a cap and trade approach, have also been suggested.[58–61,63–65] We have constructed this model to be applicable with each of these interventions, so that it does not rely on any consumption statistics other than added sugars as a whole. A limitation to this approach is that our model does not incorporate a possible change to non-sugared caloric products, containing protein, fat, or other carbohydrates. While it is conceivable that removal of added sugars in the diet could result in subsequent substitution of other foodstuffs to restore an individual's caloric baseline, *ad lib* population studies do not support that such caloric compensation takes place.[160] It is important that effort is put into investigating self- and cross-elasticity of sugar-sweetened products to determine the effect of these caloric replacements. Though this is a limitation, research has clearly shown that the contribution of added sugars in relation to their excessive intake is likely the most important consumption factor for metabolic derangement. Furthermore, added sugars consumption was fixed throughout the simulation for each individual (though specified per sex and ethnic group). We could not find sufficient data on changes in sugar consumption related to incident disease and therefore could not model these changes accurately enough. We argue that keeping the sugar consumption fixed is likely more accurate than modeling changing sugar consumption based solely on age. The main limitation of this model is the uncertainty of input parameters. The pathophysiology of NAFLD and its associations with other metabolic diseases is still widely under investigation. We have modeled cirrhosis as an irreversible condition, which is not necessarily true in all cases. Furthermore, the input parameters for baseline transition probabilities and interaction (OR) values are still somewhat uncertain. Many studies report associations, but very few studies report plausible quantitative causal relationships. There are several reasons that explain this low number of studies. First, it is hard to accurately determine the individual components in an individual's diet. Second, there is no inexpensive, accurate way to determine the presence of individual NAFLD states. Commonly used ultrasonography possibly underestimates the prevalence of NAFLD and does not differentiate between steatosis and NASH, while up to 79% of patients may have serum alanine aminotransferase (ALT) levels within the normal reference range of < 40 U/mL.[9,161] Additionally, the studies that we included to define our input parameters are generally not a perfect reflection of the population that we modeled, which may lead to imperfect estimates of values. We have addressed these uncertainties in inputs by taking wide ranges in the probabilistic sensitivity analysis, which determines the SD and 95% central coverage interval around the results. Results remain statistically significant, indicating that any minor inaccuracies in input parameter values will not render the effects insignificant. Ultimately, it is desirable to determine incidence of NAFLD states and risk factor relative risks in independent prospective cohort studies, and to assess intervention effectiveness via randomized controlled trials. This model can be refined and updated when new data become available.

It is possible that our results might still underestimate the total effects. We only modeled diagnosed disease, we took a conservative approach when determining input parameter values, and we did not take societal costs into account. Real health, healthcare, and economic benefits are likely larger than estimated. Furthermore, we only modeled the population with an age over 20. Likely, including health effects in children, particularly those with type 2 diabetes, would yield additional benefits.

Implications

This model clarifies the significant health and economic benefits that could be achieved by a public health intervention that reduces consumption of added sugars in U.S. adults. We recommend that health policy makers review options to implement sugar reduction. Important to consider are the barriers to limiting added sugars in the United States. The food industry uses sugar to enhance flavor and as a bulking and browning agent, humectant, and spoilage retardant. Another obstacle is the lowered price for manufacturing, due to government subsidies for corn, cane, and beets. Historically there was another barrier -- lack of consensus on the link between sugar and metabolic disease. However, consensus on causality is now strong.[162] Recently sugar taxation has emerged as a viable strategy, levied in the U.K. and Mexico, as well as several municipalities in the U.S., including San Francisco, Oakland, Berkeley, and Albany, CA, as well as Chicago, IL and Philadelphia, PA.

Future research

Future research should focus on establishing a more precise measurement of NAFLD prevalence, incidence, and risk factors. Furthermore, magnitude and effects of switching to different food groups should be assessed. Finally, changes in added sugars consumption related to ageing and incident disease should be more intensively investigated.

Contributor statement
RAV was involved in conceptualizing the study, reviewing literature, conducting the modelling analysis, analyzing the data and writing the manuscript. AJG was involved in conducting the modelling analysis and in editing the paper. LAR and RHL were involved in conceptualizing the model, providing and structuring data inputs and editing the manuscript. TCP was involved in reviewing and revising the manuscript, checking statistical and mathematical assumptions and establishing overall validity of the model. JGK was involved in conceptualization of the model, input data review, guiding the modelling process and providing a critical review of the manuscript. All authors read and approved the final manuscript.

Competing interests
The authors declare no direct conflicts of interest. However, Dr. Lustig has received author fees from Hudson Street Press regarding his authorship of: "Fat Chance: Beating the Odds Against Sugar, Processed Food, Obesity, and Disease"; "The Fat Chance Cookbook"; and "Sugar has 56 names: A Shopper's Guide". He is also the unpaid chief science officer of the non-profit EatREAL.

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Data sharing statement
An online supplement will be made available containing comprehensive tables of used input data. The modelling code is available through github: https://github.com/alexgoodell/go-mdism or can be accessed via the corresponding author.

Figure legends
Figure 1. Model state and covariate structure.
Each individual gets assigned a state in each chain at the start of the simulation and their specific covariates (age, sex, ethnicity, high/low sugar consumption). Circles represent disease states. Solid lines indicate a possible transition pathway between states. Coloured lines indicate how being in a state within one chain can affect the value of the transition probability between two states in another chain. These are split into three categories: pink striped lines indicate the effect of NAFLD on progression in the BMI, T2D and CHD chains. Blue dotted lines indicate the effect of overweight and obesity on progression in the NAFLD, T2D and CHD chains. The green dotted line indicates the effect of T2D on progression in the CHD chain. 3 chains contain disease related deaths and the model contains a non-disease related death state for other causes of mortality. The states of individuals are updated every cycle (i.e. annually) for 20 years. Each cycle the state distributions and their related costs and DALYs are generated as output.
NAFLD: non-alcoholic fatty liver disease, T2D: type 2 diabetes, CHD: coronary heart disease, NASH: non-alcoholic steatohepatitis, HCC: hepatocellular carcinoma, DALYs: disability-adjusted life years.

Figure 2, graphs A to H.
Reduction in population prevalence of disease due to interventions. Lines represent mean values +/- one standard deviation. 0% is the baseline, representing no intervention. The blue lines with diamonds indicate a reduction of added sugar of 20%. The red lines with crosses represent a reduction of 50%. NASH; non-alcoholic steatohepatitis.

Figure 3. Tornado diagram of the ten most critical variables on total costs averted in the year 2035.
Figure 4. Tornado diagram of the ten most critical variables on total DALYs averted in the year 2035.

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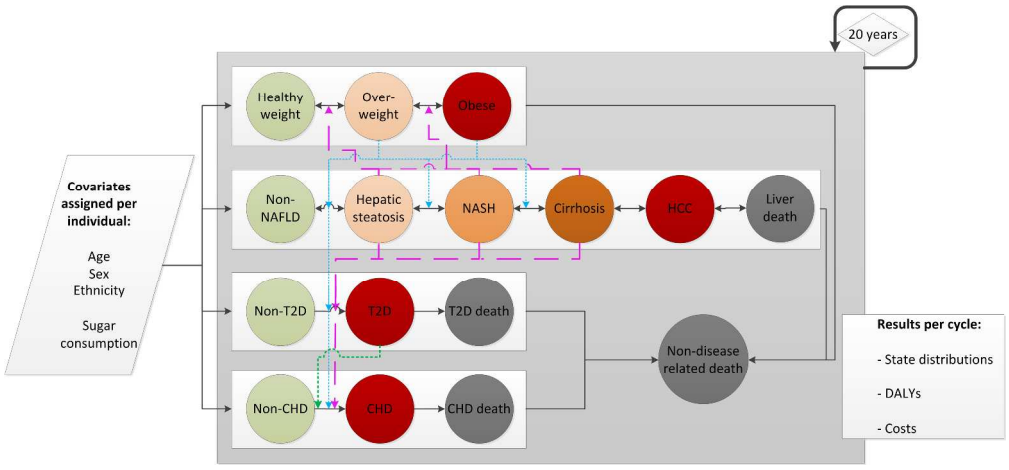

Figure 1. Model state and covariate structure.
Each individual gets assigned a state in each chain at the start of the simulation and their specific covariates (age, sex, ethnicity, high/low sugar consumption). Circles represent disease states. Solid lines indicate a possible transition pathway between states. Coloured lines indicate how being in a state within one chain can affect the value of the transition probability between two states in another chain. These are split into three categories: pink striped lines indicate the effect of NAFLD on progression in the BMI, T2D and CHD chains. Blue dotted lines indicate the effect of overweight and obesity on progression in the NAFLD, T2D and CHD chains. The green dotted line indicates the effect of T2D on progression in the CHD chain. 3 chains contain disease related deaths and the model contains a non-disease related death state for other causes of mortality. The states of individuals are updated every cycle (i.e. annually) for 20 years. Each cycle the state distributions and their related costs and DALYs are generated as output.
NAFLD: non-alcoholic fatty liver disease, T2D: type 2 diabetes, CHD: coronary heart disease, NASH: non-alcoholic steatohepatitis, HCC: hepatocellular carcinoma, DALYs: disability-adjusted life years.

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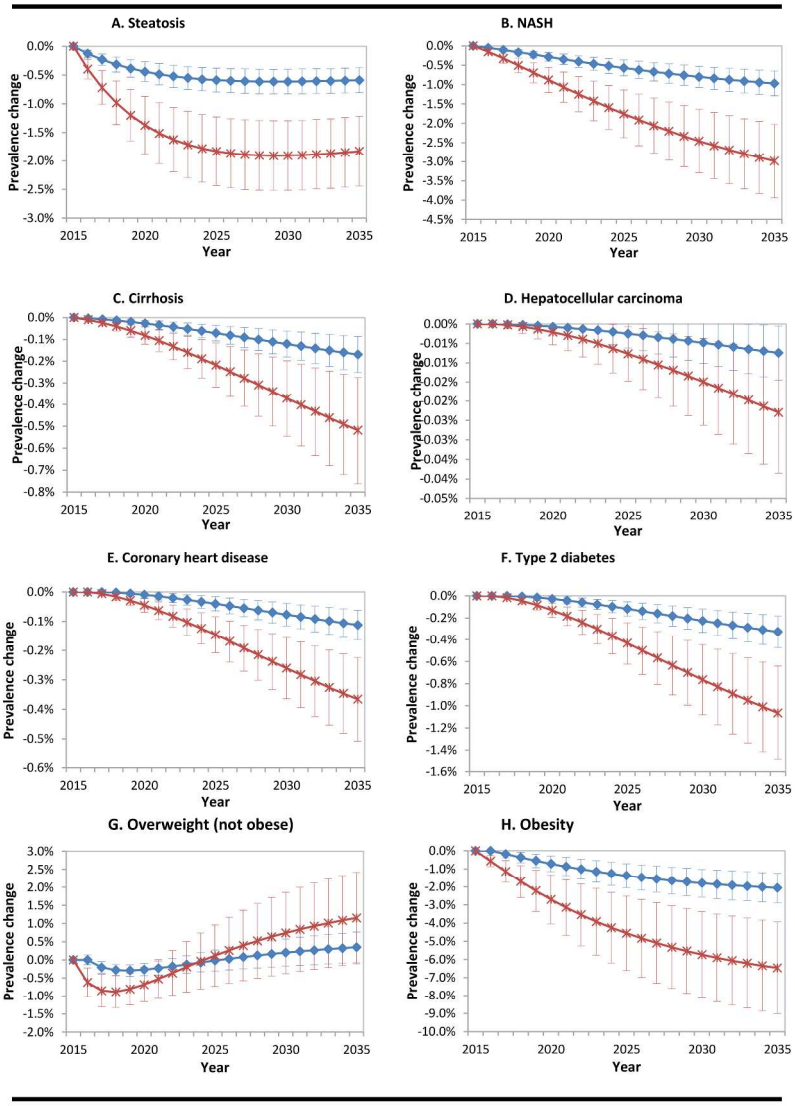

Figure 2, graphs A to H. reduction in population prevalence of disease due to interventions. Lines represent mean values +/- one standard deviation. 0% is the baseline, representing no intervention. The blue lines with diamonds indicate a reduction of added sugar of 20%. The red lines with crosses represent a reduction of 50%. NASH; non-alcoholic steatohepatitis.

249x346mm (300 x 300 DPI)

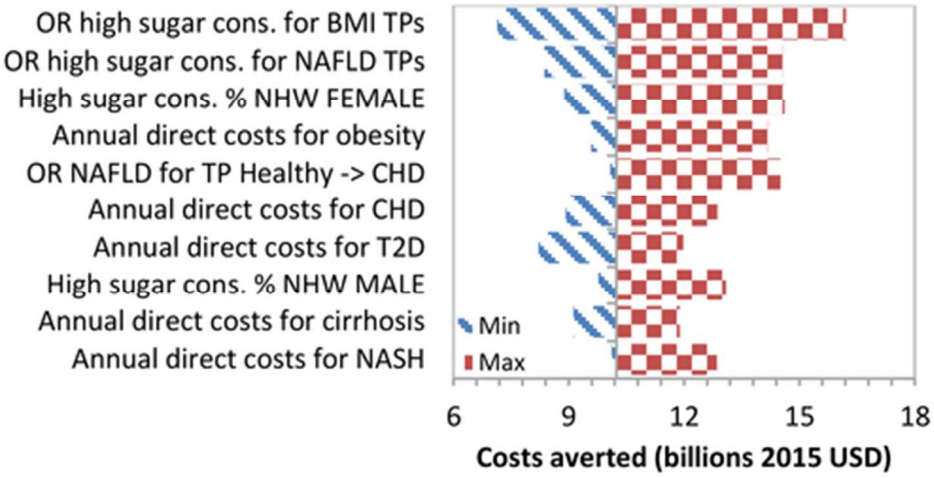

Figure 3. Tornado diagram of the ten most critical variables on total costs averted in the year 2035.

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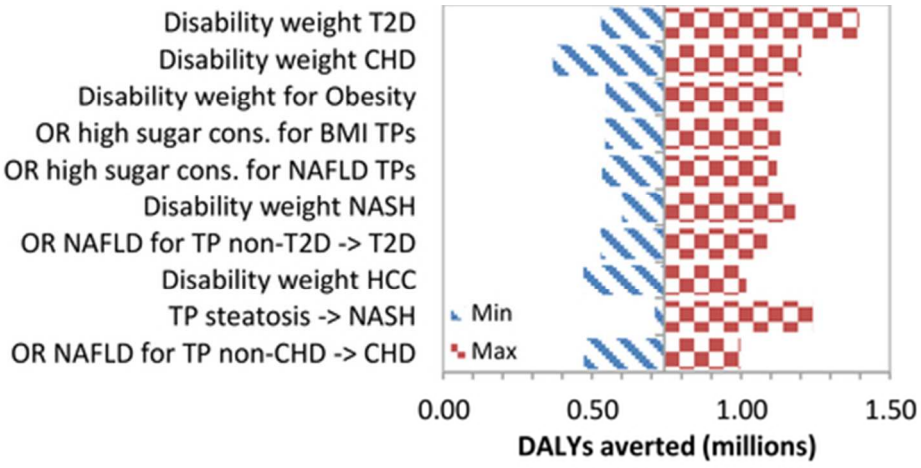

Figure 4. Tornado diagram of the ten most critical variables on total DALYs averted in the year 2035.

45x21mm (300 x 300 DPI)

Online supplement

Non-alcoholic fatty liver disease as a mediator of sugar effects; implications for the health and economic benefits of interventions in the US

Rick A Vreman, Alex J Goodell, Luis A Rodriguez, Travis C Porco, Robert H Lustig, James G Kahn

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Table 1. Selected model parameter values and ranges.

Parameter					
Initialization	**Distribution**	**Mean**	**Min**	**Max**	**Source**
Age distribution	Fixed	OS2*1	-	-	[1]
Sex distribution	Fixed	OS3*2	-	-	[1]
Ethnicity distribution	Fixed	OS4*3	-	-	[1]
Steatosis prevalence	Beta	27.955%*4	18.637%	41.933%	[2-4]
NASH prevalence	Beta	3.141%*4	2.094%	4.712%	[2-4]
Cirrhosis prevalence	Beta	0.314%*4	0.209%	0.471%	[5-8]
HCC prevalence	Beta	0.025%*4	0.017%	0.038%	[9,10]
CHD prevalence	Fixed	6.544%*5	-	-	[11]
T2D prevalence	Fixed	9.447%*6	-	-	[11]
Overweight prevalence	Fixed	33.473%*7	-	-	[11]
Obesity prevalence	Fixed	37.391%*8	-	-	[11]
High sugar consumption	Beta	57.278%*9	38.186%	85.917%	[12,13]
Baseline transition probabilities	**Distribution**	**Mean chance**	**Min**	**Max**	**Source**
Non-NAFLD -> steatosis	Beta	0.0100	0.006700	0.01500	[14-22]
Non-NAFLD -> NASH	Beta	0.0003	0.000201	0.00045	[14-22]
Steatosis -> non-NAFLD	Beta	0.0200	0.013400	0.03000	[14-22]
Steatosis -> NASH	Beta	0.0060	0.004020	0.00900	[14-22]
Steatosis -> cirrhosis	Beta	0.0002	0.000134	0.00030	[14-22]
NASH -> non-NAFLD	Beta	0.0010	0.000670	0.00150	[14-22]
NASH -> steatosis	Beta	0.0200	0.013400	0.03000	[14-22]
NASH -> cirrhosis	Beta	0.0020	0.001340	0.00300	[14-22]
NASH -> HCC	Beta	0.0001*10	0.000067	0.00015	[14-25]
NASH -> liver death	Beta	0.0038	0.002546	0.00570	[26-29]
Cirrhosis -> HCC	Beta	0.0200*10	0.013400	0.03000	[14-25]
Cirrhosis -> liver death	Beta	0.0340	0.022780	0.05100	[26-29]
HCC -> liver death	Beta	0.5000	0.335000	0.75000	[26-29]
Non-CHD -> CHD	Beta	0.0045*11	0.003015	0.00675	[30,31]
CHD -> CHD death	Beta	0.0100*12	0.006700	0.01500	[30-32]
Non-T2D -> T2D	Beta	0.0045*13	0.003015	0.00675	[33,34]
T2D -> T2D death	Beta	0.0100*14	0.006700	0.01500	[32-34]
Healthy weight -> overweight	Beta	0.0500	0.033500	0.07500	[35-38]
Healthy weight -> obese	Beta	0.0060	0.004020	0.00900	[35-38]
Overweight -> healthy weight	Beta	0.0500	0.033500	0.07500	[35-38]
Overweight -> obese	Beta	0.0180	0.012060	0.02700	[35-38]
Obese-> healthy weight	Beta	0.0060	0.004020	0.00900	[35-38]
Obese -> overweight	Beta	0.0350	0.023450	0.05250	[35-38]
Each alive state -> non-disease related death	Beta	0.0100*15	0.006700	0.01500	[32]
Risk factors	**Distribution**	**Mean value**	**Min**	**Max**	**Source**
NHB ethnicity for progression within NAFLD	Beta	0.93	0.70	1.00	[39]
Hispanic ethnicity for progression within NAFLD	Beta	1.67	1.22	2.22	[39]
Overweight for progression within NAFLD	Beta	2.19	1.60	3.38	[15,40-45]
Obesity for progression within NAFLD	Beta	3.14	2.07	5.28	[15,40-45]
High sugar consumption for progression within NAFLD	Beta	2.00	1.50	3.00	[46,47]
NAFLD for TP non-CHD -> CHD	Beta	2.31	1.66	3.62	[48-52]
Overweight for TP non-CHD -> CHD	Beta	1.22	1.12	1.32	[53-60]
Obesity for TP non-CHD -> CHD	Beta	1.60	1.43	1.79	[53-60]
T2D for TP non-CHD -> CHD	Beta	2.24	1.64	3.06	[61]
NAFLD for TP non-T2D -> T2D	Beta	2.73	1.87	4.46	[62-68]
Overweight for TP non-T2D -> T2D	Beta	2.18	1.59	3.36	[69-75]
Obesity for TP non-T2D -> T2D	Beta	3.36	2.18	5.72	[69-75]
NAFLD for progression within the BMI chain	Beta	2.19	1.60	3.38	[15,40-45]
High sugar consumption for progression within the BMI chain	Beta	2.60	1.20	6.00	[76,77]
Regression rates	**Distribution**	**Mean value**	**Min**	**Max**	**Source**
CHD incidence regression rate/year	Beta	0.985	0.970	1.00	[78-81]
CHD mortality regression rate/year	Beta	0.979	0.958	1.00	[78-81]
Non-disease mortality regression rate/year (20-30)	Beta	1.000	0.990	1.00	[32]
Non-disease mortality regression rate/year (30-55)	Beta	0.980	0.960	1.00	[32]
Non-disease mortality regression rate/year (55+)	Beta	0.970	0.940	1.00	[32]

Table 1. Continued

Costs (annual direct medical, in 2015 USD)	Distribution	Mean value	SD		Source
Steatosis	Gamma	134	50		[82-85]
NASH	Gamma	267	100		[82-85]
Cirrhosis	Gamma	2861	1073		[86]
HCC	Gamma	42644	15992		[87,88]
CHD	Gamma	13233	4962		[89]
T2D	Gamma	8170	3064		[90]
Overweight	Gamma	343	129		[91]
Obesity	Gamma	916	344		[91]
Disability weights	**Distribution**	**Mean value**	**Min**	**Max**	**Source**
NASH	Beta	0.033	0.017	0.066	[3,84]
Cirrhosis	Beta	0.194	0.127	0.273	[92]
HCC	Beta	0.294	0.199	0.411	[92]
CHD	Beta	0.066	0.043	0.095	[92]
T2D	Beta	0.150	0.080	0.220	[92]
Obesity	Beta	0.012	0.001	0.022	[93]

SD: standard deviation, CHD: coronary heart disease, T2D: type 2 diabetes, NAFLD: non-alcoholic fatty liver disease (steatosis, NASH & cirrhosis), NASH: non-alcoholic steatohepatitis, HCC: hepatocellular carcinoma, Hisp: Hispanic, NHW: non-Hispanic white, NHB: non-Hispanic black, TP: transition probability, OR: odds ratio

*1 See online supplement table 2. *2 See online supplement table 3. *3 See online supplement table 4. *4 See online supplement table 5. *5 See online supplement table 6. *6 See online supplement table 7. *7 See online supplement table 8. *8 See online supplement table 9. *9 See online supplement table 10. *10 See online supplement table 11. *11 See online supplement table 12. *12 See online supplement table 13. *13 See online supplement table 14. *14 See online supplement table 15. *15 See online supplement table 16.

Table 2. Age distribution.[1]

Age	Percentage
20	1.9194
21	1.9194
22	1.9194
23	1.9194
24	1.9194
25	1.8701
26	1.8701
27	1.8701
28	1.8701
29	1.8701
30	1.7749
31	1.7749
32	1.7749
33	1.7749
34	1.7749
35	1.7757
36	1.7757
37	1.7757
38	1.7757
39	1.7757
40	1.8487
41	1.8487
42	1.8487
43	1.8487
44	1.8487
45	2.0018
46	2.0018
47	2.0018
48	2.0018
49	2.0018
50	1.9767
51	1.9767
52	1.9767
53	1.9767
54	1.9767
55	1.7505
56	1.7505
57	1.7505
58	1.7505
59	1.7505
60	1.5024
61	1.5024
62	1.5024
63	1.5024
64	1.5024
65	1.1073
66	1.1073
67	1.1073
68	1.1073
69	1.1073
70	0.8256
71	0.8256
72	0.8256
73	0.8256
74	0.8256
75	0.6473
76	0.6473
77	0.6473
78	0.6473
79	0.6473
80	0.5093
81	0.5093
82	0.5093
83	0.5093
84	0.5093
85+	2.4517

Table 3. Sex distribution.[1]

Sex	Percentage
Male	48.4388
Female	51.5612

Table 4. Ethnic distribution.[1]

Age	Percentage
Hispanic	14.0377
Non-hispanic White	74.3771
Non-hispanic Black	11.5852

Table 5. Non-alcoholic fatty liver disease prevalence percentage at start of simulation.[2-10]

Ethnicity	Steatosis	NASH	Cirrhosis	Hepatocellular carcinoma
Hispanic	40.05	4.5	0.45	0.0363
NH-White	26.70	3.0	0.30	0.0242
NH-Black	21.36	2.4	0.24	0.0194

Table 6. Hepatocellular carcinoma incidence rate from NASH.[14-25]

Age	Incidence rate
40 to 44 years	3.64216E-05
45 to 49 years	4.64842E-05
50 to 54 years	5.93269E-05
55 to 59 years	7.57179E-05
60 to 64 years	9.66373E-05
65 to 69 years	0.000123336
70 to 74 years	0.000157412
75 to 79 years	0.000200902
80 years and over	0.000256408

Table 7. Hepatocellular carcinoma incidence rate from cirrhosis.[14-25]

Age	Incidence rate
40 to 44 years	0.008844339
45 to 49 years	0.011287867
50 to 54 years	0.014406497
55 to 59 years	0.018386746
60 to 64 years	0.023466665
65 to 69 years	0.029950073
70 to 74 years	0.038224725
75 to 79 years	0.048785512
80 years and over	0.062264050

Table 8. Overweight and obesity prevalence percentages at the start of the simulation.[11]

Sex	Ethnicity	Age	Overweight percentage	Obesity percentage
Male	Hispanic	20-44	39.5	36.8
Male	Hispanic	45-64	43.8	41.0
Male	Hispanic	65+	42.8	44.7
Male	White	20-44	35.7	31.6
Male	White	45-64	40.8	39.0
Male	White	65+	42.5	36.9
Male	Black	20-44	28.7	36.9
Male	Black	45-64	34.3	40.6
Male	Black	65+	37.0	36.7
Female	Hispanic	20-44	33.2	36.8
Female	Hispanic	45-64	32.9	52.9
Female	Hispanic	65+	33.0	49.3
Female	White	20-44	25.3	28.0
Female	White	45-64	32.6	37.4
Female	White	65+	29.5	44.3
Female	Black	20-44	22.3	56.1
Female	Black	45-64	27.1	61.8
Female	Black	65+	25.8	53.7

Table 9. Type 2 diabetes prevalence percentage at the start of the simulation.[11]

Sex	Ethnicity	Age	Percentage with T2D
Male	Hispanic	20-24	0.90
Male	Hispanic	25-44	3.50
Male	Hispanic	45-54	14.20
Male	Hispanic	55-64	25.80
Male	Hispanic	65-74	32.80
Male	Hispanic	75-84	31.30
Male	Hispanic	85+	23.80
Male	NH-White	20-24	0.90
Male	NH-White	25-44	2.40
Male	NH-White	45-54	8.20
Male	NH-White	55-64	14.70
Male	NH-White	65-74	20.10
Male	NH-White	75-84	20.50
Male	NH-White	85+	17.90
Male	NH-Black	20-24	1.00
Male	NH-Black	25-44	5.00
Male	NH-Black	45-54	15.00
Male	NH-Black	55-64	24.00
Male	NH-Black	65-74	26.50
Male	NH-Black	75-84	39.00
Male	NH-Black	85+	18.70
Female	Hispanic	20-24	0.90
Female	Hispanic	25-44	3.60
Female	Hispanic	45-54	10.30
Female	Hispanic	55-64	24.00
Female	Hispanic	65-74	34.80
Female	Hispanic	75-84	32.40
Female	Hispanic	85+	22.80
Female	NH-White	20-24	1.20
Female	NH-White	25-44	2.80
Female	NH-White	45-54	7.30
Female	NH-White	55-64	12.10
Female	NH-White	65-74	17.00
Female	NH-White	75-84	17.10
Female	NH-White	85+	12.10
Female	NH-Black	20-24	1.00
Female	NH-Black	25-44	5.20
Female	NH-Black	45-54	10.90
Female	NH-Black	55-64	24.10
Female	NH-Black	65-74	32.60
Female	NH-Black	75-84	31.60
Female	NH-Black	85+	20.20

Table 10. Type 2 diabetes incidence rate.[33,34]

Age	Incidence rate
20-24	0.000447
25-29	0.000762
30-34	0.001090
35-39	0.001625
40-44	0.002880
45-49	0.003575
50-54	0.004957
55-59	0.005071
60-64	0.004662
65-69	0.004450
70-74	0.003925
75-79	0.003609
80+	0.003240

Table 11. Coronary heart disease prevalence percentage at the start of the simulation.[11]

Sex	Ethnicity	Age	Percentage with CHD
Male	Hispanic	20-35	0.00
Male	Hispanic	35-44	1.30
Male	Hispanic	45-54	3.90
Male	Hispanic	55-64	10.60
Male	Hispanic	65-74	19.20
Male	Hispanic	75-84	23.50
Male	Hispanic	85+	23.80
Male	NH-White	20-35	0.00
Male	NH-White	35-44	1.20
Male	NH-White	45-54	6.00
Male	NH-White	55-64	13.80
Male	NH-White	65-74	23.30
Male	NH-White	75-84	31.80
Male	NH-White	85+	38.60
Male	NH-Black	20-35	0.00
Male	NH-Black	35-44	1.70
Male	NH-Black	45-54	7.50
Male	NH-Black	55-64	14.20
Male	NH-Black	65-74	16.90
Male	NH-Black	75-84	22.10
Male	NH-Black	85+	18.80
Female	Hispanic	20-35	0.00
Female	Hispanic	35-44	1.20
Female	Hispanic	45-54	3.00
Female	Hispanic	55-64	6.70
Female	Hispanic	65-74	16.20
Female	Hispanic	75-84	20.30
Female	Hispanic	85+	23.90
Female	NH-White	20-35	0.00
Female	NH-White	35-44	0.90
Female	NH-White	45-54	3.30
Female	NH-White	55-64	6.70
Female	NH-White	65-74	11.20
Female	NH-White	75-84	18.40
Female	NH-White	85+	24.30
Female	NH-Black	20-35	0.00
Female	NH-Black	35-44	1.20
Female	NH-Black	45-54	5.30
Female	NH-Black	55-64	11.20
Female	NH-Black	65-74	17.40
Female	NH-Black	75-84	19.80
Female	NH-Black	85+	21.80

Table 12. Coronary heart disease incidence rate (in %).[30,31]

Year	<35	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
2010	0.0	0.0516	0.0516	0.2007	0.2007	0.3519	0.3519	0.5869	0.5869	1.4447	1.4447	3.0621
2011	0.0	0.0508	0.0508	0.1976	0.1976	0.3466	0.3466	0.5781	0.5781	1.4230	1.4230	3.0162
2012	0.0	0.0501	0.0501	0.1947	0.1947	0.3414	0.3414	0.5694	0.5694	1.4017	1.4017	2.9709
2013	0.0	0.0493	0.0493	0.1918	0.1918	0.3363	0.3363	0.5609	0.5609	1.3806	1.3806	2.9263
2014	0.0	0.0486	0.0486	0.1889	0.1889	0.3312	0.3312	0.5525	0.5525	1.3599	1.3599	2.8825
2015	0.0	0.0478	0.0478	0.1860	0.1860	0.3262	0.3262	0.5442	0.5442	1.3395	1.3395	2.8392
2016	0.0	0.0471	0.0471	0.1833	0.1833	0.3214	0.3214	0.5360	0.5360	1.3194	1.3194	2.7966
2017	0.0	0.0464	0.0464	0.1805	0.1805	0.3165	0.3165	0.5280	0.5280	1.2997	1.2997	2.7547
2018	0.0	0.0457	0.0457	0.1778	0.1778	0.3118	0.3118	0.5201	0.5201	1.2802	1.2802	2.7134
2019	0.0	0.0450	0.0450	0.1751	0.1751	0.3071	0.3071	0.5123	0.5123	1.2610	1.2610	2.6727
2020	0.0	0.0444	0.0444	0.1725	0.1725	0.3025	0.3025	0.5046	0.5046	1.2420	1.2420	2.6326
2021	0.0	0.0437	0.0437	0.1699	0.1699	0.2980	0.2980	0.4970	0.4970	1.2234	1.2234	2.5931
2022	0.0	0.0430	0.0430	0.1674	0.1674	0.2935	0.2935	0.4896	0.4896	1.2051	1.2051	2.5542
2023	0.0	0.0424	0.0424	0.1649	0.1649	0.2891	0.2891	0.4822	0.4822	1.1870	1.1870	2.5159
2024	0.0	0.0418	0.0418	0.1624	0.1624	0.2848	0.2848	0.4750	0.4750	1.1692	1.1692	2.4781
2025	0.0	0.0411	0.0411	0.1600	0.1600	0.2805	0.2805	0.4679	0.4679	1.1516	1.1516	2.4410
2026	0.0	0.0405	0.0405	0.1576	0.1576	0.2763	0.2763	0.4608	0.4608	1.1344	1.1344	2.4043
2027	0.0	0.0399	0.0399	0.1552	0.1552	0.2721	0.2721	0.4539	0.4539	1.1174	1.1174	2.3683
2028	0.0	0.0393	0.0393	0.1529	0.1529	0.2681	0.2681	0.4471	0.4471	1.1006	1.1006	2.3328
2029	0.0	0.0387	0.0387	0.1506	0.1506	0.2640	0.2640	0.4404	0.4404	1.0841	1.0841	2.2978
2030	0.0	0.0381	0.0381	0.1483	0.1483	0.2601	0.2601	0.4338	0.4338	1.0678	1.0678	2.2633
2031	0.0	0.0376	0.0376	0.1461	0.1461	0.2562	0.2562	0.4273	0.4273	1.0518	1.0518	2.2293
2032	0.0	0.0370	0.0370	0.1439	0.1439	0.2523	0.2523	0.4209	0.4209	1.0360	1.0360	2.1959
2033	0.0	0.0364	0.0364	0.1417	0.1417	0.2485	0.2485	0.4146	0.4146	1.0205	1.0205	2.1630
2034	0.0	0.0359	0.0359	0.1396	0.1396	0.2448	0.2448	0.4084	0.4084	1.0052	1.0052	2.1305
2035	0.0	0.0354	0.0354	0.1375	0.1375	0.2411	0.2411	0.4022	0.4022	0.9901	0.9901	2.0986

Table 13. Added sugar consumption distributions.[12,13]

Sex	Ethnicity	Consumption group	% in low vs high risk group
Male	Hispanic	Low sugar consumption	36.40%
Male	Hispanic	High sugar consumption	63.60%
Male	Non-hispanic White	Low sugar consumption	36.40%
Male	Non-hispanic White	High sugar consumption	63.60%
Male	Non-hispanic Black	Low sugar consumption	34.10%
Male	Non-hispanic Black	High sugar consumption	65.90%
Female	Hispanic	Low sugar consumption	52.80%
Female	Hispanic	High sugar consumption	47.20%
Female	Non-hispanic White	Low sugar consumption	49.30%
Female	Non-hispanic White	High sugar consumption	50.70%
Female	Non-hispanic Black	Low sugar consumption	41.70%
Female	Non-hispanic Black	High sugar consumption	58.30%

Table 14. Type 2 diabetes mortality rate.[32-34]

Age	Mortality rate
20-24	0.006177
25-29	0.009399
30-34	0.009399
35-39	0.009399
40-44	0.009399
45-49	0.013706
50-54	0.013706
55-59	0.020137
60-64	0.020137
65-69	0.031904
70-74	0.031904
75-79	0.068313
80+	0.068313

Table 15. Coronary heart disease mortality rate (in %).[30-32]

Year	<35	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
2010	0.0000	0.5067	0.8506	0.9493	1.3778	1.4767	1.4179	1.1071	2.1109	2.2865	3.9970	9.4859
2011	0.0000	0.4960	0.8327	0.9293	1.3489	1.4457	1.3881	1.0839	2.0665	2.2385	3.9130	9.2867
2012	0.0000	0.4856	0.8152	0.9098	1.3205	1.4153	1.3590	1.0611	2.0231	2.1914	3.8309	9.0917
2013	0.0000	0.4754	0.7981	0.8907	1.2928	1.3856	1.3304	1.0388	1.9807	2.1454	3.7504	8.9007
2014	0.0000	0.4654	0.7813	0.8720	1.2657	1.3565	1.3025	1.0170	1.9391	2.1004	3.6717	8.7138
2015	0.0000	0.4557	0.7649	0.8537	1.2391	1.3280	1.2751	0.9956	1.8983	2.0563	3.5946	8.5308
2016	0.0000	0.4461	0.7489	0.8358	1.2131	1.3002	1.2484	0.9747	1.8585	2.0131	3.5191	8.3517
2017	0.0000	0.4367	0.7331	0.8182	1.1876	1.2728	1.2221	0.9543	1.8195	1.9708	3.4452	8.1763
2018	0.0000	0.4275	0.7177	0.8010	1.1626	1.2461	1.1965	0.9342	1.7812	1.9294	3.3728	8.0046
2019	0.0000	0.4186	0.7027	0.7842	1.1382	1.2199	1.1714	0.9146	1.7438	1.8889	3.3020	7.8365
2020	0.0000	0.4098	0.6879	0.7677	1.1143	1.1943	1.1468	0.8954	1.7072	1.8492	3.2326	7.6719
2021	0.0000	0.4012	0.6735	0.7516	1.0909	1.1692	1.1227	0.8766	1.6714	1.8104	3.1648	7.5108
2022	0.0000	0.3927	0.6593	0.7358	1.0680	1.1447	1.0991	0.8582	1.6363	1.7724	3.0983	7.3531
2023	0.0000	0.3845	0.6455	0.7204	1.0456	1.1207	1.0760	0.8402	1.6019	1.7352	3.0332	7.1987
2024	0.0000	0.3764	0.6319	0.7053	1.0236	1.0971	1.0534	0.8225	1.5683	1.6987	2.9695	7.0475
2025	0.0000	0.3685	0.6187	0.6905	1.0021	1.0741	1.0313	0.8052	1.5353	1.6631	2.9072	6.8995
2026	0.0000	0.3608	0.6057	0.6760	0.9811	1.0515	1.0096	0.7883	1.5031	1.6281	2.8461	6.7546
2027	0.0000	0.3532	0.5929	0.6618	0.9605	1.0294	0.9884	0.7718	1.4715	1.5939	2.7864	6.6128
2028	0.0000	0.3458	0.5805	0.6479	0.9403	1.0078	0.9677	0.7556	1.4406	1.5605	2.7278	6.4739
2029	0.0000	0.3385	0.5683	0.6343	0.9206	0.9867	0.9474	0.7397	1.4104	1.5277	2.6706	6.3380
2030	0.0000	0.3314	0.5564	0.6209	0.9012	0.9659	0.9275	0.7242	1.3808	1.4956	2.6145	6.2049
2031	0.0000	0.3245	0.5447	0.6079	0.8823	0.9457	0.9080	0.7090	1.3518	1.4642	2.5596	6.0746
2032	0.0000	0.3176	0.5332	0.5951	0.8638	0.9258	0.8889	0.6941	1.3234	1.4335	2.5058	5.9470
2033	0.0000	0.3110	0.5220	0.5826	0.8456	0.9064	0.8703	0.6795	1.2956	1.4034	2.4532	5.8221
2034	0.0000	0.3044	0.5111	0.5704	0.8279	0.8873	0.8520	0.6652	1.2684	1.3739	2.4017	5.6998
2035	0.0000	0.2981	0.5004	0.5584	0.8105	0.8687	0.8341	0.6513	1.2417	1.3450	2.3513	5.5801

Table 16. Non-disease related mortality rate (in %).[32]

Year	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+
2010	0.086	0.093	0.105	0.128	0.178	0.275	0.411	0.583	0.822	1.242	1.909	3.038	4.952	11.162
2011	0.086	0.093	0.105	0.125	0.174	0.269	0.403	0.571	0.797	1.205	1.851	2.947	4.804	10.828
2012	0.086	0.093	0.105	0.123	0.171	0.264	0.395	0.560	0.773	1.169	1.796	2.859	4.660	10.503
2013	0.086	0.093	0.105	0.120	0.167	0.259	0.387	0.548	0.750	1.133	1.742	2.773	4.520	10.188
2014	0.086	0.093	0.105	0.118	0.164	0.253	0.379	0.537	0.728	1.099	1.690	2.690	4.384	9.882
2015	0.086	0.093	0.105	0.115	0.161	0.248	0.372	0.527	0.706	1.066	1.639	2.609	4.253	9.586
2016	0.086	0.093	0.105	0.113	0.158	0.243	0.364	0.516	0.685	1.034	1.590	2.531	4.125	9.298
2017	0.086	0.093	0.105	0.111	0.154	0.239	0.357	0.506	0.664	1.003	1.542	2.455	4.002	9.019
2018	0.086	0.093	0.105	0.109	0.151	0.234	0.350	0.496	0.644	0.973	1.496	2.381	3.881	8.749
2019	0.086	0.093	0.105	0.106	0.148	0.229	0.343	0.486	0.625	0.944	1.451	2.310	3.765	8.486
2020	0.086	0.093	0.105	0.104	0.145	0.225	0.336	0.476	0.606	0.916	1.408	2.241	3.652	8.231
2021	0.086	0.093	0.105	0.102	0.142	0.220	0.329	0.467	0.588	0.888	1.365	2.173	3.543	7.985
2022	0.086	0.093	0.105	0.100	0.140	0.216	0.323	0.457	0.570	0.862	1.324	2.108	3.436	7.745
2023	0.086	0.093	0.105	0.098	0.137	0.211	0.316	0.448	0.553	0.836	1.285	2.045	3.333	7.513
2024	0.086	0.093	0.105	0.096	0.134	0.207	0.310	0.439	0.537	0.811	1.246	1.984	3.233	7.287
2025	0.086	0.093	0.105	0.094	0.131	0.203	0.304	0.430	0.521	0.786	1.209	1.924	3.136	7.069
2026	0.086	0.093	0.105	0.092	0.129	0.199	0.298	0.422	0.505	0.763	1.172	1.866	3.042	6.857
2027	0.086	0.093	0.105	0.090	0.126	0.195	0.292	0.413	0.490	0.740	1.137	1.810	2.951	6.651
2028	0.086	0.093	0.105	0.089	0.124	0.191	0.286	0.405	0.475	0.718	1.103	1.756	2.862	6.451
2029	0.086	0.093	0.105	0.087	0.121	0.187	0.280	0.397	0.461	0.696	1.070	1.703	2.776	6.258
2030	0.086	0.093	0.105	0.085	0.119	0.183	0.275	0.389	0.447	0.675	1.038	1.652	2.693	6.070
2031	0.086	0.093	0.105	0.083	0.116	0.180	0.269	0.381	0.434	0.655	1.007	1.603	2.612	5.888
2032	0.086	0.093	0.105	0.082	0.114	0.176	0.264	0.374	0.421	0.635	0.977	1.555	2.534	5.711
2033	0.086	0.093	0.105	0.080	0.112	0.173	0.258	0.366	0.408	0.616	0.947	1.508	2.458	5.540
2034	0.086	0.093	0.105	0.079	0.110	0.169	0.253	0.359	0.396	0.598	0.919	1.463	2.384	5.374
2035	0.086	0.093	0.105	0.077	0.107	0.166	0.248	0.352	0.384	0.580	0.891	1.419	2.313	5.213

Table 17. IHME health-adjusted life expectancy and discounted life expectancy for females. [94,95]

Age of death	WHO HALE	Discounted by 3%
20	51.138	25.981
21	51.138	25.981
22	51.138	25.981
23	51.138	25.981
24	51.138	25.981
25	46.766	24.966
26	46.766	24.966
27	46.766	24.966
28	46.766	24.966
29	46.766	24.966
30	42.466	23.832
31	42.466	23.832
32	42.466	23.832
33	42.466	23.832
34	42.466	23.832
35	38.214	22.560
36	38.214	22.560
37	38.214	22.560
38	38.214	22.560
39	38.214	22.560
40	34.033	21.144
41	34.033	21.144
42	34.033	21.144
43	34.033	21.144
44	34.033	21.144
45	29.960	19.584
46	29.960	19.584
47	29.960	19.584
48	29.960	19.584
49	29.960	19.584
50	26.017	17.884
51	26.017	17.884
52	26.017	17.884
53	26.017	17.884
54	26.017	17.884
55	22.214	16.045
56	22.214	16.045
57	22.214	16.045
58	22.214	16.045
59	22.214	16.045
60	18.574	14.081
61	18.574	14.081
62	18.574	14.081
63	18.574	14.081
64	18.574	14.081
65	15.167	12.042
66	15.167	12.042
67	15.167	12.042
68	15.167	12.042
69	15.167	12.042
70	12.020	9.968
71	12.020	9.968
72	12.020	9.968
73	12.020	9.968
74	12.020	9.968
75	9.169	7.912
76	9.169	7.912
77	9.169	7.912
78	9.169	7.912
79	9.169	7.912
80	6.646	5.942
81	6.646	5.942
82	6.646	5.942
83	6.646	5.942
84	6.646	5.942
85	4.512	4.159
86	4.512	4.159
87	4.512	4.159
88	4.512	4.159
89	4.512	4.159
90	2.915	2.751
91	2.915	2.751
92	2.915	2.751
93	2.915	2.751
94	2.915	2.751
95	1.868	1.789
96	1.868	1.789
97	1.868	1.789
98	1.868	1.789
99	1.868	1.789
100	1.231	1.189
101	1.231	1.189
102	1.231	1.189
103	1.231	1.189
104	1.231	1.189
105	1.000	0.971
106	1.000	0.971
107	1.000	0.971
108	1.000	0.971
109	1.000	0.971
110	1.000	0.971

Table 18. IHME health-adjusted life expectancy and discounted life expectancy for males.[94,95]

Age of death	WHO HALE	Discounted by 3%
20	48.035	25.275
21	48.035	25.275
22	48.035	25.275
23	48.035	25.275
24	48.035	25.275
25	43.802	24.200
26	43.802	24.200
27	43.802	24.200
28	43.802	24.200
29	43.802	24.200
30	39.589	22.989
31	39.589	22.989
32	39.589	22.989
33	39.589	22.989
34	39.589	22.989
35	35.374	21.616
36	35.374	21.616
37	35.374	21.616
38	35.374	21.616
39	35.374	21.616
40	31.217	20.085
41	31.217	20.085
42	31.217	20.085
43	31.217	20.085
44	31.217	20.085
45	27.195	18.412
46	27.195	18.412
47	27.195	18.412
48	27.195	18.412
49	27.195	18.412
50	23.347	16.614
51	23.347	16.614
52	23.347	16.614
53	23.347	16.614
54	23.347	16.614
55	19.705	14.714
56	19.705	14.714
57	19.705	14.714
58	19.705	14.714
59	19.705	14.714
60	16.256	12.716
61	16.256	12.716
62	16.256	12.716
63	16.256	12.716
64	16.256	12.716
65	13.080	10.688
66	13.080	10.688
67	13.080	10.688
68	13.080	10.688
69	13.080	10.688
70	10.208	8.680
71	10.208	8.680
72	10.208	8.680
73	10.208	8.680
74	10.208	8.680
75	7.680	6.767
76	7.680	6.767
77	7.680	6.767
78	7.680	6.767
79	7.680	6.767
80	5.524	5.019
81	5.524	5.019
82	5.524	5.019
83	5.524	5.019
84	5.524	5.019
85	3.723	3.471
86	3.723	3.471
87	3.723	3.471
88	3.723	3.471
89	3.723	3.471
90	2.388	2.269
91	2.388	2.269
92	2.388	2.269
93	2.388	2.269
94	2.388	2.269
95	1.521	1.462
96	1.521	1.462
97	1.521	1.462
98	1.521	1.462
99	1.521	1.462
100	1.000	0.971
101	1.000	0.971
102	1.000	0.971
103	1.000	0.971
104	1.000	0.971
105	1.000	0.971
106	1.000	0.971
107	1.000	0.971
108	1.000	0.971
109	1.000	0.971
110	1.000	0.971

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Additional file 1

EVEREST Statement: Checklist for health economics paper

	Study section	Additional remarks
Study design		
(1) The research question is stated	Introduction	Page 2
(2) The economic importance of the research question is stated	Introduction	Page 2
(3) The viewpoint(s) of the analysis are clearly stated and justified	Introduction, Methods	Page 2 and page 4-5 (interventions)
(4) The rationale for choosing the alternative programmes or interventions compared is stated	Methods	Page 4-5 (interventions)
(5) The alternatives being compared are clearly described	Methods	Page 4-5 (interventions)
(6) The form of economic evaluation used is stated	Methods	Page 3
(7) The choice of form of economic evaluation is justified in relation to the questions addressed	Introduction, Methods	Page 3
Data collection		
(8) The source(s) of effectiveness estimates used are stated	Methods; Table 1, Table 2	Page 5 and 6
(9) Details of the design and results of effectiveness study are given (if based on single study)	N/A	Data derived from peer reviewed literature and national health surveys
(10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	Methods	Page 6
(11) The primary outcome measure(s) for the economic evaluation are clearly stated	Methods	Page 5
(12) Methods to value health states and other benefits are stated	Methods	Page 5; table 1
(13) Details of the subjects from whom valuations were obtained are given	N/A	
(14) Productivity changes (if included) are reported separately	N/A	
(15) The relevance of productivity changes to the study question is discussed	N/A	
(16) Quantities of resources are reported separately from their unit costs	Methods; stated per person; Table 1, Table 2	Page 5 and 6
(17) Methods for the estimation of quantities and unit costs are described	Methods; Table 1, Table 2	Page 5 and 6; Adopted from literature

(18) Currency and price data are recorded	Methods; Table 1, Table 2	Page 5 and 6
(19) Details of currency of price adjustments for inflation or currency conversion are given	Methods	Page 5
(20) Details of any model used are given	Methods	Page 3
(21) The choice of model used and the key parameters on which it is based are justified	Methods	Page 3
Analysis and interpretation of results		
(22) Time horizon of costs and benefits is stated	Methods	Page 5
(23) The discount rate(s) is stated	Methods	Page 5
(24) The choice of rate(s) is justified	Methods	Page 5
(25) An explanation is given if costs or benefits are not discounted	N/A	
(26) Details of statistical tests and confidence intervals are given for stochastic data	N/A	
(27) The approach to sensitivity analysis is given	Methods	Page 6
(28) The choice of variables for sensitivity analysis is justified	Methods; Table 1, Table 2	Page 6
(29) The ranges over which the variables are varied are stated	Table 1, Table 2	Page 6
(30) Relevant alternatives are compared	Methods, Results	Page 4 and 5
(31) Incremental analysis is reported	N/A	
(32) Major outcomes are presented in a disaggregated as well as aggregated form	Table 3, 4 and 5	Page 7 and 9
(33) The answer to the study question is given	Discussion, Conclusion	Page 10
(34) Conclusions follow from the data reported	Conclusion	Page 11
(35) Conclusions are accompanied by the appropriate caveats	Discussion, Conclusion	Page 10