1 PRIMEtime: an epidemiological model for informing diet and obesity policy

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Abstract

Background: Mathematical modelling can play a vital role in guiding public health action. In this paper, we provide an overview of the revised and updated PRIMEtime model, a tool for evaluating health and economic impacts of policies impacting on diet and obesity. We provide guidance on populating PRIMEtime with country-specific data; and illustrate its validation and implementation in evaluating a combination of interventions in the UK: a sugar-sweetened beverage (SSB) tax; a ban on television advertising of unhealthy foods; and a weight loss program.

Methods: PRIMEtime uses routinely available epidemiological data to simulate the effects of changes in diet and obesity on 19 non-communicable diseases, in open- or closed-population cohorts, over time horizons from 1 year to a lifetime. From these simulations, the model can estimate impact of a policy on population health (obesity prevalence, cases of disease averted, quality-adjusted life years), health and social care costs, and economic measures (net monetary benefit, cost-effectiveness ratios). We populated PRIMEtime with UK data and validated epidemiological predictions against two published data collections. We then evaluated three current obesity intervention policies based on estimates of effectiveness from published evaluation studies.

Results: There was considerable variation in the modelled impact of interventions on prevalence of obesity and subsequent changes in health and the need for health care: restrictions on TV advertising of unhealthy foods to children led to the largest reductions in obesity prevalence; but the SSB tax, which also targeted adults, had the biggest benefits in reducing obesity-related disease; and the weight loss program, while having very small impact on obesity prevalence at the population scale, had large and immediate benefits in improving health and reducing health sector spending. From a health sector perspective, the combination of interventions produced a favourable net monetary benefit of £31,400 (12,200 to 50,700) million. But the combined effect in reducing prevalence of overweight and obesity, was not estimated to reach more than 0.81 percentage points (95%

46   uncertainty interval: 0.21 to 1.4) for males and 0.95 percentage points (0.24 to 1.7) for females by

47   2050.

48   **Conclusions**:

49   Diet and obesity interventions have the potential to improve population health and reduce health

50   sector spending both immediately and in the long-term. Models such as PRIMEtime can be used to

51   evaluate the economic merits of intervention strategies and determine how best to combine

52   interventions to achieve maximum population benefit. But with almost a third of children and two-

53   thirds of adults currently overweight or obese, we need to broaden the application of public health

54   models to evaluating the structural and systemic changes that are needed in our society to address

55   the underlying drivers of the obesity epidemic.

56

Introduction

Overweight and obesity have been recognised as a cause of poor health for over 2000 years.[1] But in the early times, it is likely the overall prevalence of obesity in the population was low; with malnutrition and underweight a greater cause of ill-health and premature loss of life. It is only in the last two decades that the number of overweight and obese adults worldwide have outnumbered those who are underweight.[2] Globally, 39% of adults and 18% of children and adolescents are now estimated to be overweight or obese.[3] This is associated with an excess 4.7 million deaths and 147.7 million disability-adjusted life years, with around 90% of this burden due to cardiovascular diseases, diabetes, related kidney diseases, and cancers.[4]

Like many high-income countries, the United Kingdom has been at the leading edge of the transition to obesity. By the time the World Health Organization recognised the growing prevalence of overweight and obesity as a 'global epidemic' in 1998, around 3 in 5 adults in England were already either overweight or obese.[5] While successive governments have attempted to address the problem over the last 30 years, including 14 strategy documents and 689 proposed policies and programs, efforts have so far failed to turn the tide.[6, 7] Although rapid upwards trends in obesity prevalence of the 1990s had flattened by the early 2000s, projection models suggest that prevalence of overweight and obesity will remain high until at least 2035, without more effective action.[8]

Mathematical modelling can play a vital role in guiding public health action,[9] as we have witnessed in the COVD-19 pandemic. While an epidemic of obesity may be slower-moving than an epidemic of an infectious disease, the informative value of modelling is no less important. Models can help us understand what the likely consequences of an intervention are, how confident we can be in the predicted outcomes, and what are the risks associated with the decision to act (or not act).[10] In the absence of modelling, decision-making is little more than blind guesswork; but modelling will only be of value if the model's design, its inputs and outputs are clearly communicated, and there is

81   transparency in the assumptions that have been made, whether explicit in model parameters or

82   implicit in the structural design.[9, 10]

83   PRIMEtime is an epidemiological modelling tool that was developed in the UK for simulating diet and

84   obesity interventions and scenarios. The model was initially developed in 2014 for examining impacts

85   of changes in diet and obesity on population health, including non-communicable disease rates and

86   life expectancy,[11] and this was later expanded to include impacts on quality of life and costs of

87   health and social care.[12] The model has been used to examine potential impacts of a range of

88   interventions and scenarios, including a targeted weight loss program, regulation of television

89   advertising of unhealthy foods to children, salt reduction, evaluating changes to dietary guidelines and

90   identifying most environmentally sustainable dietary patterns.[11-16]

91   In recent years, we have made a number of updates to the PRIMEtime model. These include new

92   features to capture background trends in obesity and disease rates, as well as updates of model

93   parameters to incorporate the latest evidence on risks of disease associated with diet and obesity,

94   and to capture the latest data on risk factor and disease rates in the UK. In addition, we have modified

95   the cohort simulation to include options for both open- and closed-cohort simulation. While

96   previously a closed-cohort simulation model, allowing users to examine changing health and cost

97   consequences for an adult population cohort ageing through time, PRIMEtime now additionally

98   incorporates open-cohort simulation of outcomes for children and future birth cohorts out to 2050.

99   This feature enables users to examine impacts of interventions on population prevalence of

100   overweight and obesity and population rates of disease into the future, and potentially facilitates

101   linkage of PRIMEtime with economic and environmental simulation models.

102   In this paper we describe the updated PRIMEtime model and illustrate its use in evaluating a

103   combination of interventions: a sugar-sweetened beverage tax; a ban on television advertising of

104   unhealthy foods; and a weight loss program. These are all interventions that have been implemented

105   or recommended in the government's latest obesity strategy.[17] This work is not intended to be a

106   comprehensive evaluation of all potential obesity intervention strategies, rather the aim is to provide

107   transparency on the model's design and input parameters, to illustrate how the model can be used,

108   and discuss how this and other modelling may be developed and better integrated into policy in the

109   future.

Methods

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The PRIMEtime model

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Model Design

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113   The PRIMEtime modelling approach (Figure 1) consists of three interlinked components: (1) a risk

114   factor exposure module, which quantifies the effect of change in prevalence of one or more risk

115   factors on incidence of related diseases; (2) a series of disease models, which simulate changing

116   incidence, prevalence and mortality of diseases related to the modelled risk factors; (3) a lifetable,

117   which simulates overall impacts on the population, health and social care system, due to the changing

118   disease epidemiology.

Risk factor exposure

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120   When an intervention is simulated in PRIMEtime, the magnitude of impact on disease associated with

121   a risk factor (e.g. high body mass index) depends on a combination of variables: (1) the baseline

122   population exposure to the risk factor; (2) the measured effect of the intervention on exposure, and

123   the proportion of the population who stand to benefit; and (3) the magnitude of the relative risk of

124   disease associated with the risk factor. This impact is quantified by the population impact fraction

125   (PIF):[18]

126
$$PIF = \frac{\int p \, RR(x) \, dx - \int p'(x) \, RR(x) \, dx}{\int p(x) \, RR(x) \, dx}$$

127   where: x is the units of a risk factor (e.g. body mass index); $p(x)$ is the prevalence of that risk factor;

128     $p'(x)$ is the prevalence of the risk factor after a scenario or intervention; and $RR(x)$ is the relative risk

129   of disease associated with the risk factor. The PIF is age- and sex-dependent. Where there are

130   background trends in the risk factor (e.g. obesity), the PIF is also time-dependent. Where diseases are

131   influenced by multiple independent risk factors, PRIMEtime combines the PIFs multiplicatively:

132    $$PIF_{combined} = 1 - \prod_{i=1}^{n}(1 - PIF_i)$$

133   for $i = 1 \dots n$ diseases.

134   The relative risks of disease associated with each risk factor in PRIMEtime, have been drawn from

135   systematic reviews and meta-analyses. For modelling purposes, it is necessary to establish dose-

136   response relationships across the entire distribution of risk factor exposure in the population of

137   interest. Large, long-term randomised controlled trials are rare, and where they do exist, they provide

138   only limited variance between control and intervention arms in the risk factor of interest. Therefore,

139   establishing causality in the relationship between a risk factor and condition relies heavily on

140   prospective cohort studies, and evaluation of the entirety of evidence against criteria, such as those

141   of Bradford-Hill – strength and consistency of evidence, specificity, temporality, biological gradient,

142   plausibility, coherence, analogy and supporting experimental evidence.[19] In developing and

143   updating PRIMEtime we have preferentially drawn on systematic reviews and meta-analyses that take

144   these factors into account.

145   Disease models

146   Diet- and obesity-related diseases currently included in PRIMEtime include ischaemic heart disease,

147   ischaemic stroke, intracerebral haemorrhage, hypertensive heart disease, diabetes mellitus type 2,

148   colorectal cancer, breast cancer, uterine cancer, oesophageal cancer, kidney cancer, pancreatic

149   cancer, liver cancer, multiple myeloma, asthma, low back pain, osteoarthritis of the hip and knee,

150   depression, atrial fibrillation/flutter, and gallbladder/biliary diseases.

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151   Cardiovascular diseases, diabetes and cancers are modelled in a three-state Markov model, in which

152   the population is either in a healthy state, a diseased state or dead (from the disease or from other

153   un-related causes).[20] The initial distribution of the population between the healthy and diseased

154   states is determined by the prevalence of the disease in the baseline year. Further transition between

155   states over time is based on annual rates of incidence, remission and case fatality. However, for the

156   remaining PRIMEtime diseases that are chiefly characterised by morbidity rather than mortality (low

157   back pain, osteoarthritis, depression, and gallbladder and biliary diseases) we do not model

158   progression to mortality.

159   PRIMEtime is designed to evaluate the effects of interventions, scenarios or system shocks in

160   *preventing* disease and the consequent effects on population health and society. Therefore, we model

161   the effects of a change in risk factor exposure, which is quantified by the PIF, as a change in disease

162   incidence rate (I):

163 $$I'_{lag} = I \times (1 - PIF_{combined})$$

164   The calculation of I'_{lag} allows for a time lag in the reversal of disease risk. While there is an absence

165   of direct evidence examining the time course for changes in disease rates following population

166   changes in dietary intake or obesity, the World Health Organization has estimated it takes three to

167   five years to achieve full reversal of stroke risk and around two-thirds of heart disease risk, from trials

168   of blood pressure treatments.[21] Risk reversibility of cancers is likely to be longer, based on follow-

169   up of patients around ten years after bariatric surgery or intentional weight loss.[22]

170   Population lifetable

171   In the population lifetable component of PRIMEtime, the population is divided into five-year age and

172   sex cohorts that are simulated through time. In a closed cohort simulation, the model is typically run

173   until everyone in the starting population is dead. In an open cohort simulation, which incorporates

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174   future birth cohorts, the model can be run until the desired time horizon is reached or until there are

175   no further birth cohorts entering the simulation.

176   Each population age- and sex- cohort is simulated in a proportional multi-state lifetable.[23] This

177   consists of a standard lifetable model, which simulates the survival experience of a cohort based on

178   age- and sex-specific mortality rates, connected with the series of disease-specific models described

179   above. There are three key actions that occur in the proportional multi-state lifetable model.

180   First, when we simulate a change in prevalence of obesity, this influences incidence of obesity-related

181   diseases, which, over time, lead to changes in disease-specific mortality rates. These changes in

182   disease-specific mortality rates modify the total mortality rate in the main lifetable, while holding the

183   proportion of mortality due to all other causes (i.e. causes not related to obesity) constant.

184   Second, everyone in the lifetable cohort who is alive has a utility weight, which reflects average

185   'quality of life' at each age and sex. In the same way that total mortality in the lifetable is modified by

186   changes in disease-specific mortality, the total utility in the lifetable is modified by changes in disease-

187   specific utility, which are derived in the disease-specific models from the change in incidence and/or

188   prevalence of the disease and the disease-specific utility weight(s).

189   Third, everyone in the lifetable cohort who is alive has an average cost associated with their health

190   care. This cost increases or decreases, based on changes in rates of obesity-related diseases, which

191   are derived in the disease-specific models from the change in incidence and/or prevalence of the

192   disease and the disease-specific health care cost.

193   Together, the lifetable, disease-specific and risk factor exposure models simulate each cohort ageing,

194   over time, until everyone is dead, has reached 100 years of age, or the simulation has reached the end

195   of its time horizon. From these simulations, PRIMEtime can determine the effect of a change in

196   prevalence of a risk factor on: (a) population life expectancy; (b) gain or loss of quality-adjusted life

197   years (QALYs); and (c) impact on costs to the health or social care system.

Country-specific input data

Population and mortality

200 PRIMEtime can be adapted for any country context with a number of country-specific inputs.

201 Population is entered by sex and 5-year age group, with the exception of the 0 to 4 year old group,

202 which is split into 0 year olds and 1 to 4 years olds to facilitate calculation of life expectancy at birth.

203 To run a closed cohort analysis, only the population in the baseline year of analysis is required. If

204 running an open cohort analysis, future cohorts of 0 to 4 years olds can be estimated from population

205 projections. The model currently has capacity to accept new entrants into the modelling until 2050.

206 PRIMEtime also requires mortality rates from all causes by sex and single year of age, from age 0 to

207 100+.

208 Both mortality rates and population numbers can be downloaded in the required format from the

209 Human Mortality Database[24] for 41 countries and, in some cases, also by population sub-groups,

210 e.g. by ethnicity. The Institute of Health Metrics Results Tool[25] also provides links to their collations

211 of population, mortality and life table data for Global Burden of Disease analyses, which is an

212 alternative source of data for countries not included in the Human Mortality Database or if within-

213 country data collections are not accessible. These sources currently provide data up to 2019.

214 Population estimates for later years (e.g. for open cohort analyses incorporating future birth cohorts)

215 are based on population projections. The United Nations provide a database of global population

216 projections if local estimates are not available.

Disease epidemiology

218 Population-specific disease rates can be derived from a variety of sources such as death and disease

219 registries and disease-specific studies. Alternatively, PRIMEtime users can draw on Global Burden of

220 Disease (GBD) syntheses of these sources. Cause-specific incidence, prevalence and mortality rates

221 can be downloaded, by age and sex, using the GBD Results Tool.[25] These data can be used in

222   PRIMEtime for non-commercial purposes under the Creative Commons Attribution-Non Commercial

223   4.0 International License.[26]

224   A key challenge in populating the PRIMEtime model is the requirement for cause-specific case fatality

225   rates. In the PRIMEtime model, the case fatality reflects the excess mortality of someone with the

226   disease compared with someone who does not have the disease. These rates are rarely reported,

227   however they can be derived from cause-specific incidence, prevalence and mortality rates, together

228   with population numbers and all-cause mortality rates, using the *disbayes* R package, which can be

229   found on the GitHub repository.[27] This package is recommended as, using a Bayesian approach, it

230   estimates case fatality using the same three-state model and assumptions that underpin disease

231   simulation in the PRIMEtime model, so consistency in approach is maintained.

232   Background trends in cause-specific incidence and case fatality rates can be estimated by fitting

233   models to rates derived over multiple years. The GBD Results Tool[25] contains yearly estimates of

234   rates from 1990.

235   Risk factor exposure

236   Prevalence of risk factors can be derived from population survey data. PRIMEtime is designed to take

237   the mean and standard deviation of the distribution of risk in the population, by age and sex. This

238   allows the population impact fraction to be calculated continuously (e.g. where the relative risk is

239   defined per unit of BMI) or categorically (e.g. where relative risks are defined for overweight and obese

240   categories of prevalence). There is also an option for taking background trends in risk factors into

241   account.

242   Derivation of risk factor prevalence and trends depend on the availability of survey data, which is

243   highly country-specific. Cobiac et al[8] provides an example of deriving trends in body mass index from

244   health survey data in England. However, some global collations of data also exist, such as the World

245   Health Organization Global Health Observatory[3] and the Global Dietary Database.[28]

246   Costs

247   There is currently no global database of age- and sex-specific costs of disease treatment in different

248   countries. For PRIMEtime analyses in the UK, the unit costs of treatment for the explicitly modelled

249   diseases and the average costs associated with health care for all other diseases, have been derived

250   from a range of administrative datasets. Briggs et al.[29] have published a detailed description of these

251   methods.

252   Model Implementation

253   Simulation options

254   PRIMEtime provides a number of options for evaluation. The user can:

255   −   define discount rates for health and cost impacts;

256   −   define time horizons for population simulation and for output of data;

257   −   set time lags on the effects of a risk factor on diseases;

258   −   include or exclude background trends in risk factors;

259   −   include or exclude diseases; and

260   −   select population cohorts for simulation (a closed cohort analysis only simulates outcomes for

261   the population alive in the baseline year of analysis, whereas an open cohort analysis also

262   simulates outcomes for those born in future years).

263   These choices depend on the purpose of the PRIMEtime simulation. For example, calculating cost-

264   effectiveness or return-on-investment of an intervention, will generally require discounting of cost

265   and health outcomes. Comparing cost-effectiveness of multiple preventive interventions can generally

266   be performed using a closed cohort simulation, since the relative performance of different

267   interventions is unlikely to be greatly impacted by the addition of future birth cohorts who will not

268   experience health benefits until well into the future. However, an open cohort simulation may be

269   preferred if PRIMEtime is being used to simulate impacts of a scenario on rates of obesity-related

270   diseases or costs of treating these diseases, over time into the future.

271   Scenario specification

272   PRIMEtime currently allows for simultaneous simulation of up to five scenarios or population sub-

273   groups. While the model can be run any number of times for different evaluations, simultaneous

274   simulation facilitates analyses where uncertainty in the relative order of or difference between

275   scenarios or sub-groups is important. For example, by simultaneously simulating outcome by quintile

276   of Index of Multiple Deprivation, it is possible to estimate uncertainty in the slope index of inequality,

277   a measure of health inequality.

278   Probabilistic Sensitivity Analysis

279   The PRIMEtime model is designed to be run iteratively. If only one iteration is performed, the model

280   will produce point-estimates of outputs based on the mean values of model input parameters.

281   However, when run many times, the model will randomly select from uncertain distributions around

282   input parameters to produce a range of outputs, from which mean or median values and 95%

283   uncertainty intervals can be determined. The degree of uncertainty in outputs depends on the number

284   of inputs that are uncertain, and the distribution of uncertainty around those inputs. As a rule-of-

285   thumb, we recommend running as many iterations as are required to achieve stability in outputs to

286   the desired number of significant figures. Typically, this is between 2000 and 5000 iterations.

287   PRIMEtime evaluation of obesity interventions

288   Intervention specification

289   We demonstrate use of the PRIMEtime model in evaluating three interventions for addressing obesity

290   in the UK population:

291   1. Implementing a Soft Drinks Industry Levy (SSB tax)

292   2. Banning television advertising of foods and drinks high in fat, sugar, and salt (HFSS) between

293   5:30 AM and 9:00 PM (TV ad bans).

294   3. Offering total diet replacement to adults (18+ years) with a BMI greater than 30 kg/m^2 (Weight

295   loss program).

296   Intervention effects were derived from previously published analyses as described in Table 1. For this

297   study, we evaluated the interventions individually and additionally evaluated a combination of all

298   three interventions, as if rolled out in the UK population from a baseline year of 2015.

299   UK data inputs

300   For the obesity intervention evaluation, we populated the PRIMEtime model with data for the UK.

301   Table 2 described the data sources and assumptions made, and Text S1 provides the data as entered

302   into PRIMEtime.

303   *Table 1 Intervention scenarios*

Target group	Per person effect	Source
SSB tax		
Whole population	-1.8 kcal (-3.1 to -0.50)*	Estimated from the results of interrupted time series analyses of weekly household reductions in purchasing of sugar in drinks before and after the SDIL,[30] assuming an average of 2.4 people per household,[31] and a calorie content of 3.75 kcal per gram of sugar.[32]
TV ad bans		
Children aged 5 to 17 years	-9.1 kcal (-18 to -0.50)*	Estimated by Mytton et al,[14] assuming a complete withdrawal of HFSS advertising between 5:30 AM and 9:00 PM, a mean ad duration of 25.9 seconds (standard

deviation 11.9 seconds) and an association between a child's daily energy intake and ad viewing for high fat, sugar and salt foods and drinks of 14.2 kcal per minute (0.7 to 27.7).

We assumed that modelled changes in BMI at age 17 years would be sustained through adulthood.

Weight loss program

Adults aged ≥18 years with a BMI>30 kg/m^2	-7.2 kg (-9.4 to -4.9) at a cost of 2017GDP796 per person	Estimated by Kent et al.[13] from the results of a randomised controlled trial of a total diet replacement programme for weight management in primary care. We assumed a weight regain of 27.2 grams per month (18.4 to 35.9) based on the results of a systematic review and meta-analysis of trials reporting weight regain following weight loss intervention.[33] We assumed the intervention would be offered to all registered patients with a BMI>30kg/m^2. Rates of eligibility and willingness to participate, were based on the results of the randomised controlled trial.[34, 35]

Combination

As per individual interventions	As per individual interventions	The calorie effect of the SSB tax (via sugar reduction) and the calorie effect of the TV ad bans are assumed to be additive in childhood. As with the individual analysis of the TV ad bans intervention, the difference in BMI due to the intervention at age 17, is assumed to be maintained into adulthood when the interventions are

	combined. The combined analysis takes into account the impact of the SSB tax and TV ad bans on the proportion of adults who are obese and therefore eligible for the weight loss program.

NB. Values are expressed as means and 95% confidence intervals, except where otherwise noted.

* Impact on body weight (kg) estimated using energy balance model predictions from Hall et al.[36, 37]

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305   *Table 2 PRIMEtime data inputs*

PRIMEtime data input	Source
Population numbers	UK population numbers were determined by 5-year age group and sex from the Human Mortality Database.[24] Future cohorts of 0-4 year olds were derived by sex from the Office for National Statistics (principal projection).[38]
All-cause mortality rates	UK all-cause mortality rates were taken from the Human Mortality Database,[24] by single year of age and sex.
Background trends in overweight and obesity	Predicted trends in overweight and obesity were taken from models fitted to 27 years of Health Survey for England data, by Cobiac et al.[8] We assumed BMI trends in PRIMEtime would follow the non-linear model in base case analyses and the linear model in sensitivity analyses.
Disease rates – incidence, case fatality and starting prevalence	Incidence and case fatality rates were derived from Global Burden of Disease[39] estimates of incidence, prevalence and mortality, using *disbayes*.[27] Spline models were used to smooth data by age.

Background trends in disease incidence and case fatality	We approximated average annual trends in incidence and case fatality rates, by sex and age group (0-34 years; 35-64 years; 65+ years), from the difference in rates between 1995 and 2005 for model validation, and between 2005 and 2015 for intervention analyses.
Relative risks	We derived relative risks of obesity-related diseases from systematic reviews that had been published up to January 2021.
Utility weights	Parameters for estimating disease-specific and background utility weights were taken from a UK catalogue of EQ-5D scores.[40]
Disease costs	We estimated an average cost per prevalent case of each modelled disease, by determining: (a) the total costs of disease treatment from Department of Health and Social Care budget allocations to primary, hospital, community and specialised care services in England; then (b) dividing the total cost by the average number of prevalent cases.[25] We also estimated an overall average cost of health care from the total budget allocation for all diseases, divided by the number of people in the population.[24] Further details of these methods are provided in Text S2. The health care costs were estimated for the 2018-19 budget year and adjusted to the 2015 modelling baseline year using CPI adjustors.[41]

306

Model validation

308   To validate the epidemiological modelling, we additionally populated PRIMEtime with UK data for a

309   baseline year of 2005, then ran the model forward in time to 2015 and compared simulated

310   prevalence estimates for all cardio-metabolic diseases and cancers with other published data. For

311   comparison we used: (1) GBD estimates of prevalence in the year 2015;[7] and (2) estimates of

312   prevalence for the period 2010-2015, from an analysis of linked clinical datasets by Kuan et al.[42]

Intervention evaluation

314   To simulate impact of the interventions on obesity prevalence, we ran an open cohort analysis from

315   2015 to 2050, adding new entrants to the population based on UK population projections. To simulate

316   overall impact on population health (QALYs) and health care costs, we ran a closed cohort analysis

317   over the lifetime of the population alive in 2015. QALYs and costs were discounted using HM Treasury

318   rates of 3.5% costs and 1.5% health (0 to 30 years), 3% costs and 1.29% health (31-75 years) and 2.5%

319   costs and 1.07% health (76-125 years).[43] We also calculated the net monetary benefit of each

320   intervention and the combination of interventions, which reflects the value of each option in

321   monetary terms, assuming a willingness-to-pay threshold for health.[44] For these calculations we

322   assumed a value of £60,000 per QALY, as recommended by HM Treasury.[45]

Results

Model validation

325   Figure 2 illustrates the results of the model validation runs, and full results can be found in Table S1

326   (PRIMEtime vs. GBD) and Table S2 (PRIMEtime vs. Kuan et al) in the supplementary appendix (Text

327   S3). Overall, estimates from PRIMEtime were slightly higher than estimates from GBD for 13 out of 14

328   diseases, and slightly lower than estimates from Kuan et al for 12 out of 13 diseases (Kuan et al did

329   not have a comparable disease category for hypertensive heart disease). The absolute difference in

330   the prevalent proportion of the population with disease was less than 1 percentage point for 12 out

331   of 14 diseases in comparison with the GBD estimates, and for 11 out of the 13 diseases in the

332   comparison with the Kuan et al estimates. We found the largest percentage differences for diabetes

333   (Kuan et al 2.7 percentage points lower; GBD 2.5 percentage points higher) and atrial fibrillation and

334   flutter (Kuan et al 2.5 percentage points higher). The mean absolute percentage error across all

335   outcomes was 0.12 percentage points.

Prevalence of overweight and obesity

337   The modelling shows that all of the interventions are likely to reduce population prevalence of

338   overweight and obesity over time, but the pattern of impact varies between interventions (Figure 3).

339   Restricting television advertising of unhealthy foods has the largest impact in reducing overweight and

340   obesity overall, with effects concentrated during childhood. The reduction in prevalence starts at

341   around 0.31 percentage points (95% uncertainty interval: 0.021 to 0.58) for males and 0.34 percentage

342   points (0.023 to 0.65) for females, then increases over time as more children are born and exposed to

343   the intervention. The sugar-sweetened beverage tax also has a slightly smaller impact; benefiting both

344   children and adults, it achieves a reduction in prevalence of overweight and obesity of around 0.19

345   percentage points (0.058 to 0.31) for males and 0.20 percentage points (0.063 to 0.34) for females

346   initially, and remains relatively stable through time (Text S3 – Table S3). The weight loss program,

347   while very effective for the obese adult population who participate in the program, has the smallest

348   overall effect on population prevalence of overweight and obesity, initially reducing prevalence by just

349   0.022 percentage points (0.015 to 0.030) for males and 0.027 percentage points (0.018 to 0.037) for

350   females, with lessening benefit over time due to weight regain among participants. The best outcomes

351   are achieved by combining the interventions, which leads to an initial reduction in population

352   prevalence of overweight and obesity of 0.51 percentage point (0.20 to 0.82) for males and 0.57

353   percentage points (0.22 to 0.90) for females. This reduction increases over time, to around 0.81

354   percentage points (0.21 to 1.4) for males and 0.95 percentage points (0.24 to 1.7) for females by the

355   end of the simulation in 2050.

Cases of disease

357   Due to the modelled improvements in overweight and obesity prevalence, all of the modelled

358   interventions lead to a reduction in incidence of disease (Table 3). The size of the impact of each

359   intervention, in the first ten years of implementation is strongly influenced by the nature of the target

360   population. The sugar-sweetened beverage tax, which is designed to have an effect across all groups

361   in the population, has the largest benefits in reducing disease in the first ten years. The biggest impact

362   is on cases of type 2 diabetes, followed by cardiovascular diseases and cancers. While restricting

363   television advertising of unhealthy foods to children has larger impacts on overweight and obesity

364   than the SSB tax, it has relatively little effect on cases of disease in the first ten years, since it is

365   targeting children, who will not experience the benefits of disease prevention until some years into

366   the future. The weight loss program, on the other hand, has immediate benefits in reducing cases of

367   type 2 diabetes, cardiovascular diseases and cancers, since it is targeting obese adults, who are at

368   highest risk of developing obesity-related diseases. When combined, the interventions are predicted

369   to prevent 15,000 (95% uncertainty interval: 6,600 to 24,000) cases of type 2 diabetes, 4,900 (2,200

370   to 7,700) cases of cardiovascular diseases and 460 (220 to 720) cases of cancer in the first ten years of

371   implementation.

372   *Table 3 Impact of the intervention scenarios on incident cases of disease in the first ten years (rounded to two significant*
373   *figures).*

Disease group*	Female	Male	Total
SSB tax			
Type 2 diabetes	-5,300 (-9,200 to -1,600)	-6,400 (-11,000 to -1,900)	-12,000 (-20,000 to -3,500)
Cardiovascular diseases	-1,500 (-2,600 to -480)	-2,300 (-4,000 to -730)	-3,900 (-6,600 to -1,200)
Cancers	-240 (-410 to -75)	-110 (-190 to -33)	-350 (-600 to -110)
TV ad bans			
Type 2 diabetes	0.0039 (0.0003 to 0.0078)	0.0047 (0.0003 to 0.0094)	0.0086 (0.0005 to 0.017)
Cardiovascular diseases	-0.16 (-0.32 to -0.011)	-0.23 (-0.46 to -0.015)	-0.38 (-0.79 to -0.026)

Cancers	-6.9 (-14 to -0.48)	-1.3 (-2.6 to -0.08)	-8.2 (-16 to -0.56)
Weight loss program			
Type 2 diabetes	-1,500 (-2,200 to -920)	-1,700 (-2,400 to -1,000)	-3,200 (-4,600 to -1,900)
Cardiovascular diseases	-440 (-640 to -270)	-650 (-930 to -400)	-1,100 (-1,600 to -670)
Cancers	-73 (-100 to -46)	-32 (-46 to -20)	-110 (-150 to -66)
Combination			
Type 2 diabetes	-6,800 (-11,000 to -3,100)	-8,100 (-13,000 to -3,500)	-15,000 (-24,000 to -6,600)
Cardiovascular diseases	-2,000 (-3,100 to -890)	-3,000 (-4,700 to -1,300)	-4,900 (-7,700 to -2,200)
Cancers	-320 (-500 to -150)	-140 (-230 to -67)	-460 (-720 to -220)

* Table S4 in the supplementary appendix (Text S3) shows modelled impact on individual diseases within each group.

374

Population health and health care costs

376 When modelled over the lifetime of the UK population, all of the interventions lead to a health gain

377 for the population and a reduction in health care spending, and all interventions have a positive net

378 monetary benefit from a health sector perspective (Table 4). The combination of interventions is

379 estimated to produce a population health gain of 519,000 (201,000 to 837,000) QALYs and offset £299

380 (£121 to £515) million in health sector spending, achieving a net monetary benefit of £31,400 (12,200

381 to 50,700) million.

382   *Table 4 Lifetime impact of the intervention scenarios on population health and health care costs, and the net monetary benefit*
383   *of the scenarios*

Scenario	Health impact (QALYs)	Cost offsets (£million)	Net monetary benefit (£million)
SSB tax	200,000 (61,200 to 345,000)	-128 (-237 to -37.5)	12,100 (3,710 to 20,900)
TV ad bans	302,000 (19,900 to 588,000)	-159 (-331 to -11.2)	18,300 (1,200 to 35,600)
Weight loss program	18,600 (8,580 to 33,300)	-12.2 (-26.2 to -2.82)	1,130 (519 to 2,020)
Combination	519,000 (201,000 to 837,000)	-299 (-515 to -121)	31,400 (12,200 to 50,700)

384

Uncertainty

386   Uncertainty around intervention effects on sugar intake (SSB tax), calorie intake (TV ad bans) or weight

387   change (Weight loss program) have the biggest influence on uncertainty in the model predictions of

388   health gain, health sector cost offsets and net monetary benefit (Figure 4). The uncertainty in relative

389   risks of obesity-related diseases, utility values quantifying quality of life, and disease unit costs are less

390   influential. Results are similar when the interventions are evaluated individually (Text S3 – Figure S1).

Sensitivity

392   The modelled net monetary benefit remained positive in all sensitivity scenarios we evaluated (Text

393   S3 – Figure S2). The magnitude of net monetary benefit is most strongly influenced by the preferred

394   discount rates. The outcome is more favourable with lower or no discounting, since this effectively

395   gives more weight to future health gains and averted health care costs. Whereas the net monetary

396   benefit is less favourable (although still positive) with a higher discount rate overall, or when the rate

397   of discounting of health gains is increased more than costs, (e.g. when changing to NICE rates). Net

22

398 monetary benefit does not vary substantially with variations in the modelled background trends in

399 BMI distribution, background trends in disease incidence and case fatality rates, and assumed lags in

400 effect of BMI changes on disease incidence. Increasing the number of modelled obesity-related

401 diseases included in the simulation does influence the magnitude of impact on health and health care

402 costs, but the overall impact on net monetary benefit is small.

Discussion

403

Main findings and interpretation

404

405 In this paper we have described the PRIMEtime model, a tool for evaluating health and economic

406 impacts of diet and obesity policies. The model uses routinely available epidemiological data to

407 simulate the effects of changes in diet and obesity on 19 non-communicable diseases, over the lifetime

408 of the population, or out to the year 2050 if including future birth cohorts. From these simulations,

409 the model can estimate impact of a policy on population health (overweight and obesity prevalence,

410 cases of disease averted, quality-adjusted life years gained), health and social care costs, and

411 economic measures (net monetary benefit, cost-effectiveness ratios).

412 The PRIMEtime modelling of a SSB tax, a ban on television advertising of unhealthy foods, and a weight

413 loss program illustrates the potentially wide variation in impact of interventions on prevalence of

414 overweight and obesity, and subsequent changes in health and the need for health care. This variation

415 is due to both the characteristics of the intervention and population that is targeted.

416 While reductions in TV advertising of unhealthy foods to children has the largest impact in reducing

417 prevalence of overweight and obesity, the SSB tax has much larger and more immediate benefits in

418 reducing disease. The weight loss program also has immediate benefits in improving health despite

419 relatively small benefits in reducing overweight and obesity on a population-scale. The variability in

420 impact, both by age and over time, demonstrates the importance of using models to determine how

421 best to combine intervention strategies to achieve maximum population benefit.

422   From a health sector perspective, the modelling shows that all three policies will likely have a positive

423   net monetary benefit. This would suggest that all three of the obesity interventions are a good

424   investment for HM Treasury. However, even when combined these three interventions are predicted

425   to reduce prevalence of overweight and obesity by less than 1 percentage point by 2050. With almost

426   a third of children and two-thirds of adults currently overweight or obese,[5] much more will be

427   needed to address the problem.

Study strengths and limitations

429   While PRIMEtime is not primarily designed for forecasting disease rates, the accuracy of the

430   underlying epidemiological model will nevertheless impact on the absolute magnitude of its outputs,

431   such as QALYs and health care costs. Therefore it is reassuring that in validation PRIMEtime simulated

432   future prevalence of diseases close to estimates from GBD and Kuan et al.[42] (<1 percentage point

433   difference for 85% of estimates). For the majority of diseases, prevalence estimates from PRIMEtime

434   were slightly higher than those from GBD and slightly lower than those from Kuan et al. This may partly

435   relate to differences in the way that the two comparison studies have arrived at their estimates. The

436   GBD collates data from a variety of sources, such as surveys, registries and published studies, and uses

437   statistical models to estimate country-specific disease rates that are regionally and globally consistent.

438   Whereas, Kuan et al have derived prevalence by analysing electronic health records from the primary

439   care Clinical Practice Research Datalink linked with hospital admissions records from Hospital Episode

440   Statistics, using a newly developed system of algorithmic phenotyping to identify cases of disease.[46]

441   The linked databases are considered representative of the English population,[47] which constitutes

442   around 85% of the UK population that we simulated in PRIMEtime.

443   Other reasons for differences between PRIMEtime predictions and later estimates may include

444   changes in incidence or case fatality rates that were not captured by trend estimates (e.g. due to

445   increased or decreased funding of prevention or treatment practices) and assumptions embedded in

446   the epidemiological modelling. PRIMEtime simulates the epidemiology using a *proportional* multi-

447   state lifetable design.[23] In a standard multi-state lifetable model, an individual or population cohort

448   transition from one state to another (e.g. from healthy, to having disease *X*, to dying from disease *X*

449   or other causes). But as additional diseases are added to the simulation, the model quickly becomes

450   intractable due the need for additional disease states (e.g. having disease *X* only, having disease *Y* only

451   and having diseases *X* and *Y*) and data required to quantify rates of transition between these many

452   states. A *proportional* multi-state lifetable model overcomes this problem by allowing the individual

453   or population cohort to proportionally exist in multiple disease states. This approach potentially has

454   an advantage in modelling health impacts of *preventive* interventions, where a change in population

455   exposure to a risk factor, can influence many diseases. However, implicit in allowing a population

456   cohort to proportionally exist across multiple disease states is the assumption that the diseases are

457   independent. In some cases, this assumption is clearly violated. For example, prevalence of diabetes

458   increases risk of both heart disease[48] and stroke,[49] even when adjusted for baseline

459   cardiovascular risks such as obesity. In PRIMEtime, we adjust for the dependence between diabetes

460   and cardiovascular disease outcomes, by treating diabetes as both a risk factor and a disease in the

461   model structure. But data to explicitly incorporate other possible relationships, such as between

462   cancer prevalence and cardiovascular outcomes, are limited.

463   While the proportional multi-state lifetable approach does involve some trade-offs, the methods are

464   widely used in modelling tools designed to evaluate health and economic impacts of diet and obesity

465   interventions (e.g.[50-55]). Models that do not take this approach, typically only simulate one disease

466   (e.g. the Coronary heart disease (CHD) policy model[56, 57]) or estimate changes in incidence and/or

467   mortality of diseases without addressing co-morbidity (e.g. the Foresight model,[58]) thus sacrificing

468   capacity to simulate changing effects on quality of life and health care costs through time.

469   PRIMEtime is primarily designed for scenario evaluation. It is a tool that can be used to compare future

470   impacts of policies, under a common set of assumptions about future unknowns, and to explore

471   uncertainties in potential outcomes, in order to help set priorities for action and better understand

472   risks associated with decisions. Uncertainty bounds reflect best estimates of the likely range of

473   outcomes, but will never capture impacts of future unpredictable events, such as the emergence of

474   new pandemic diseases. Thus, the true strength of simulation is in comparison of alternative policy

475   options under the same set of assumptions. And these assumptions must be updated as knowledge

476   develops. For example, the selection of diet- and obesity-related diseases in PRIMEtime, and

477   quantification of the dose-response relationships, as captured in Table S4 and Table S5

478   (supplementary appendix Text S1) should be regularly revisited and updated as new systematic

479   reviews and meta-analyses are published.

Potential policy and research implications

480

481   The three interventions we have evaluated in PRIMEtime are all components of the UK government's

482   latest obesity strategy.[17] The SSB tax was implemented as a Soft Drinks Industry Levy in 2018;[59]

483   and a 9pm watershed on advertising of high fat, salt and sugar foods, is scheduled to come into effect

484   at the end of 2022.[60] While weight loss programs for those who are already obese are

485   recommended, as of mid-2021, there do not appear to be specific plans for added funding. While the

486   modelling indicates that all three are a good investment, the relatively small overall impact on the

487   high prevalence of overweight and obesity in the UK suggests that much more will be required to

488   improve health and reduce the associated costs of care.

489   A broader range of interventions targeting dietary intake and obesity may be beneficial for health in

490   the UK, but it is likely that we also need to give greater consideration to the structural and systemic

491   changes that are needed in our society to address the underlying drivers of the obesity epidemic. With

492   globalisation has come enormous shifts in the way that we work, travel, produce and distribute food,

493   which have impacted on both our dietary intake and energy expenditure.[61] While the underlying

494   drivers and feedback mechanisms are sometime complex,[62] the last decade has seen big advances

495   in the way that we can collect and make use of data to better understand these forces, as well as big

496   advances in the tools available to build and run models. Since the early 2000s there has been rapid

497   growth in the development and use of models to find cost-effective interventions that directly target

498   physical activity, dietary intake and obesity.[63, 64] But models can potentially now play a much

499   broader role in simulating impacts of policies or trends that impact on the food system or active

500   environment, either directly or indirectly. In the future, integration of health models, such as

501   PRIMEtime, with models the simulate the complexities of our economies and changing climate, may

502   help us better understand and address the underlying drivers of the obesity epidemic.

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665

Risk factor exposure	Diet — Obesity
Disease models	Disease 1 - - - Disease 2 · · · Disease *x*
Population lifetable	Lifetable