Supplementary Information: The Economic Impact of Lower Protein Infant Formula for the Children of Overweight and Obese Mothers

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1. Methods

1.1. BMI Trajectory

1.1.1. BMI at 2 Years Old

The regression models for weight and height estimates are reported in Tables S1 and S2, respectively. The functions used for these estimations and the body mass index (BMI) calculation are reported in Equations (S-E1) to (S-E3), respectively.

Weight (kg) = \( \text{Birth Weight} + \text{intercept} + b_1 \times \text{(birth weight)} + b_2 \times \text{(birth height)} + b_3 \times \text{Female} + b_4 \times \text{(Caucasian)} + b_5 \times \text{(mother BMI)} + b_6 \times \text{(education (4 to 8 years))} + b_7 \times \text{(education (8 to 9 years))} + b_8 \times \text{(education (+10 years))} + b_9 \times \text{(mother is smoker)} + b_{10} \times \text{lpIF formula} + b_{11} \times \text{(age in months)} + b_{12} \times \text{(age in months}^2) + b_{13} \times \text{(lpIF formula} \times \text{age in months)} + b_{14} \times \text{(lpIF formula} \times \text{age in months}^2) + b_{15} \times \text{(female} \times \text{age in months)} + b_{16} \times \text{(female} \times \text{age in months}^2) + b_{17} \times \text{(female} \times \text{lpIF formula} \times \text{age in months)} + b_{18} \times \text{(female} \times \text{lpIF formula} \times \text{age in months}^2)

Height (cm) = \( \text{BirthHeight} + \text{intercept} + b_1 \times \text{(square root of age in months)} + b_2 \times \text{(lpIF)} + b_3 \times \text{(square root of age in months} \times \text{lpIF)} + b_4 \times \text{(Birth Height)} + b_5 \times \text{Female} + b_6 \times \text{(mother height)} + b_7 \times \text{(head circumference)} + \text{NormalDist}(0, \sqrt{\text{sigma1}}) + \text{[square root of age in months} \times \text{NormalDist}(0, \sqrt{\text{sigma2}})] + \text{NormalDist}(0, \sqrt{\text{sigma3}}) + 2 \times \text{Covariance[N.Dist(0,}\sqrt{\text{sigma1}}),\text{N.Dist(0,}\sqrt{\text{sigma2}})]\)

Table S1. Regression output for weight estimation at the age of 2 years.

| Parameter               | Mean   | Standard Error |
|-------------------------|--------|----------------|
| Intercept               | -1.44494 | 1.4374         |
| Birth weight            | 0.74178 | 0.13984        |
| Birth height            | 0.05916 | 0.03225        |
| Gender (Female)         | -0.08303 | 0.10749        |
| Race (Caucasian)        | -0.12063 | 0.16784        |
| Mother’s BMI            | 0.00241 | 0.01439        |
| Education (4 to 8 years) | -0.2956 | 0.43465        |
| Education (8 to 9 years) | 0.22165 | 0.42106        |
| Education (+10 years)   | -0.2448 | 0.39849        |
| Mother is smoker        | 0.17417 | 0.08865        |
| lpIF formula            | 0.06003 | 0.1086         |
| Age in months           | 0.79599 | 0.01751        |
| Age in months^2         | -0.01681 | 0.00069        |
| lpIF formula * age      | -0.035  | 0.02371        |
| lpIF formula * age^2    | -0.00005 | 0.00096        |
| Female * age in months  | -0.06204 | 0.02359        |
| Female * age in months^2| 0.00227 | 0.00094        |
| Female and lpIF formula * age | 0.06626 | 0.03115        |
| Female and lpIF formula * age^2 | -0.00103 | 0.0013 |

* Compared to the reference group: education (<4 years).
Table S2. Regression output for height estimation at the age of 2 years.

| Parameter | Mean   | Standard Error |
|-----------|--------|----------------|
| Intercept | -2.824 | 3.1199         |
| √Age (in months) | 8.4893 | 0.0775         |
| BMI Formula (lplf) | 0.03166 | 0.286          |
| BMI Formula (lplf[√Age(in months)]) | -0.1146 | 0.1143         |
| Birth height (cm) | -0.3894 | 0.04947        |
| Gender status (Female) | -0.5712 | 0.1589         |
| Mother’s height (cm) | 0.06574 | 0.01438        |
| Head circumference at birth (cm) | 0.2191 | 0.07691        |
| Sigma 1 (1st correlation parameter for random effects model) | 2.127 | -             |
| Sigma 2 (2nd correlation parameter for random effects model) | 0.332 | -             |
| Sigma 3 (3rd correlation parameter for random effects model) | 1.3545 | -             |

Covariance of normal distribution (0, Sigma 1) and normal distribution(0, Sigma 2) | -0.5689 | -             |

The model uses the functions reported in Tables S1 and S2 to estimate an individual’s weight and height at age 2 years. Equation (S-E3) then uses these estimates to calculate BMI at age 2 years:

\[
BMI = \frac{\text{Weight (kg)}}{\text{[Height(m)/100]}}^2
\]  
(S-E3)

1.1.2. BMI at 17 Years Old

The model uses the function summarised in Equation (S-E4) and Table S3 to predict an individuals’ BMI at 17 years old.

\[
BMI (17 \text{ years}) = \alpha + b1 \times \text{weight gain in infancy} + b2 \times \text{birth weight} + b3 \times \text{gender (female)} + b4 \times \text{gestational age} + b5 \times \text{maternal socioeconomic status} + b6 \times \text{maternal BMI}
\]  
(S-E4)

The Stockholm Weight Development Study (SWEDES) study is based on a sample of 2342 mothers invited to participate between 1984 and 1985 and who were followed during and after their pregnancies. A total of 1423 of these mothers completed the study at the one-year follow-up, and 481 mothers and their children participated in the follow-up study (SWEDES) after 17 years.

A meta-analysis of 10 studies suggested that the analysis of SWEDES may underestimate the impact of weight gain in infancy on BMI at age 17 years [1]. To account for this underestimate, the coefficient on the weight gain variable in the original model was inflated by the difference between the odds ratio from the SWEDES cohort and that from the Philadelphia Blood Pressure Project (PBPP) cohort. The PBPP study was selected as it estimated the relationship between infant weight gain and BMI at 20 years old, the closest age of the studies included in the meta-analysis to that in the model. PBPP is a cohort of 300 African Americans born between 1962 and 1966 in the United States (U.S.) and followed up to 20 years of age.

Table S3. BMI at 17 years based on weight gain between birth and 12 months (Ekelund analysis *).

| Coefficient             | Value  | Standard Error |
|-------------------------|--------|----------------|
| Intercept               | 13.56  | 4.48           |
| Weight gain in infancy  | 1.34 **| 0.18           |
| Birth weight (kg)       | 1.52   | 0.46           |
| Gender status (female)  | 1.12   | 0.35           |
| Gestational age (weeks) | 0.07   | 0.12           |
| Maternal socioeconomic status | -0.27 | 0.18          |
| Maternal BMI (kg/m²)    | -0.01  | 0.04           |

* These analyses were conducted by Dr. Ekelund, in addition to the analyses in his published study [33]. ** The adjustment of the Ekelund equation to match Druet et al. [1] is done by modifying the weight gain in infancy parameter from the original 0.82 to the above 1.34.
1.1.3. BMI at Age 18 Years and Higher

Individuals’ BMI at 48 years old is predicted based on their weight at 17 years old. Østbye (2011) [2] generated a function (Equation (S-E5)) predicting BMI at age 48 years based on BMI at age 17 years.

\[
\text{BMI} = (\text{BMI at age 17}) + \text{linear term} \times \text{age} + \text{quadratic term} \times (\text{age}^2)
\]  
(S-E5)

Østbye (2011) [2] specified Equation (S-E5) for four different subgroups, distinguished by their BMI at age 17 years old. The subgroups and the model parameters are reported in Table S4. In the discrete event simulation (DES), individuals are categorised into one of these subgroups based on their BMI at 17 years old, and the relevant function is selected to estimate the change in their BMI over time until the age of 48 years old.

**Table S4.** BMI classifications (kg/m²) used in the estimation of BMI between the ages 18 and 48 years [2].

| Subgroup [Range of BMI] | Linear Term | SE (Linear Term) | Quadratic Term | SE (Quadratic Term) |
|-------------------------|-------------|------------------|----------------|---------------------|
| Normal weight [0, 20.82] | 0.12        | 0.003            | 0              | 0                   |
| Overweight [20.83, 23.17] | 0.31        | 0.013            | -0.003         | 0.0004              |
| Late adulthood [23.18, 26.64] | 0.58 | 0.023            | -0.008         | 0.0007              |
| Early adulthood [26.65, 100] | 1.05       | 0.068            | -0.019         | 0.0024              |

1.1.4. BMI from 49 Years of Age Onwards

Individuals’ BMI from age 49 years onwards is predicted based on a function derived from fitting a polynomial equation (Equation (S-E6)) to WHO data on the cross-sectional average BMI, by gender, for 10-year age groups between 49 and 79 years and the average BMI between 80 and 100 years [3].

\[
\text{BMI} = (\text{BMI at age 49}) + \text{linear term} \times \text{age} + \text{quadratic term} \times (\text{age}^2)
\]  
(S-E6)

An individual’s BMI at age 49 years is predicted by the model (see section BMI between the ages of 18 and 48 years above). The estimates of the linear and quadratic terms for the equation above are provided in Table S5.

**Table S5.** Linear and quadratic terms used in the projection of BMI for ages 49 years and above [4].

| Gender  | Linear Term | Quadratic Term |
|---------|-------------|----------------|
| Males   | 0.0794      | -0.0011        |
| Females | 0.0894      | -0.0012        |

1.2. Disease Risks

1.2.1. Primary Events

Equation (S-E7) and Table S6 report the function used to determine the probability that an individual would experience diabetes over a period of 7.5 years.

\[
P(\text{diabetes}) = \frac{1}{1 + e^{(-1 \times (-13.415 + 0.028 \times \text{age} + 0.661 \times \text{sex} + 0.412 \times \text{(Mexican)} + 0.079 \times \text{(fasting glucose)} + 0.018 \times \text{SBP} - 0.039 \times \text{HDL} + 0.070 \times \text{BMI} + 0.481 \times \text{(prior family history of diabetes)})}}
\]  
(S-E7)

If the individual is not expected to experience a disease-related event in the next 7.5 years, their risk would be re-assessed after this period for the following 7.5 years, and so on, until their death.
Table S6. San Antonio equation used to estimate the probability of diabetes risk [5].

| Parameter                                      | Mean   | Standard Error |
|------------------------------------------------|--------|----------------|
| Intercept                                      | −13.42 | 0.68           |
| Age (years)                                    | 0.03   | 0.00           |
| Gender (female)                                | 0.66   | 0.03           |
| Race (Mexican American)                        | 0.41   | 0.02           |
| Fasting glucose level (mg/dL)                  | 0.08   | 0.00           |
| SBP level (mm Hg)                              | 0.02   | 0.00           |
| HDL level (mg/dL)                              | −0.04  | 0.00           |
| BMI level (kg/m²)                              | 0.07   | 0.00           |
| Family diabetes history (≥1 parent or sibling had diabetes) | 0.48   | 0.02           |

* The standard error is calculated based on the assumption that this variable is normally distributed with 95% of the area within 1.96 standard deviations of the mean.

CHD Risk

Table S7 describes the function (Equation (S-E8)) used to estimate the probability of an initial CHD event.

\[
P(\text{CHD}) = 1 - \exp \left[ - \left( \text{X days} \times \exp \left( -14.9756 - 0.0159 \times \text{BMI} - 0.0571 \times \text{age} - 0.4959 \times \text{(smoker)} - 0.0070 \times \text{SBP} - 0.1432 \times \text{cholesterol to HDL ratio} - 0.3421 \times \text{(diabetic)} + 0.5139 \times \text{([female] ^ (1/0.7303))} \right) \right] \]

(S-E8)

Table S7. Framingham equation used to estimate the probability of initial CHD risk [6].

| Parameter                                      | Mean   | Standard Error |
|------------------------------------------------|--------|----------------|
| Intercept                                      | 14.98  | 0.76           |
| BMI level (kg/m²)                              | −0.02  | 0.00           |
| Age (years)                                    | −0.06  | 0.00           |
| Smoking status (smoker)                        | −0.50  | 0.03           |
| SBP level (mm Hg)                              | −0.01  | 0.00           |
| Cholesterol/HDL-C ratio                        | −0.14  | 0.01           |
| Diabetic status (diabetic)                     | −0.34  | 0.02           |
| Gender (female)                                | 0.51   | 0.03           |
| Weibull lpIF                                   | 0.73   | 0.04           |

* The standard error is calculated based on the assumption that this variable is normally distributed with 95% of the area within 1.96 standard deviations of the mean.

Table S8 shows the probability that an initial CHD is either an MI, an angina or a cardiac death.

Table S8. Probability that an initial CHD event is angina or myocardial infarction (MI) * [7].

| Gender | MI | Angina |
|--------|----|--------|
|        | Mean | Standard Error | Mean | Standard Error |
| Female | 42%  | 2%      | 56%  | 3%             |
| Male   | 53%  | 3%      | 41%  | 2%             |

* These do not add up to 100% since the remaining probability is associated with the initial CHD event being cardiac death.

Stroke Risk

Equation (S-E9) provides the function used to estimate the probability that an individual experiences a stroke.
\[ P \text{ (stroke)} = 1 - \exp \left(-\left[14.6574 - 0.0227 \times \text{BMI} - 0.0450 \times \text{age} - 0.2584 \times \text{(smoker)} - 0.007879 \times \text{SBP} - 0.0596 \times \frac{\text{cholesterol}}{\text{HDL ratio}} \right]^\frac{1}{0.4978}\right) \]  

(S-E9)

The estimates of the coefficients for the equation above are provided in Table S9.

**Table S9.** Framingham equation used to estimate the probability of initial stroke risk [6].

| Parameter                       | Mean  | Standard Error * |
|---------------------------------|-------|------------------|
| Intercept                       | 14.66 | 0.75             |
| BMI level (kg/m²)               | -0.02 | 0.00             |
| Age (years)                     | -0.05 | 0.00             |
| Smoking status (smoker)         | -0.26 | 0.01             |
| SBP level (mm Hg)               | -0.01 | 0.00             |
| Cholesterol/HDL-C ratio         | -0.06 | 0.00             |
| Weibull lpIF                    | 0.50  | 0.03             |

* The standard error is calculated based on the assumption that this variable is normally distributed with 95% of the area within 1.96 standard deviations of the mean.

1.2.2. Secondary Events

The sources used to estimate the risk of secondary events, contingent upon the nature of the primary event and the time since the primary event, are described in Table S10.

**Table S10.** The probability of secondary events after primary event, per three months.

| Primary Event | Secondary Event | Phase     | Mean    | Standard Error | Source |
|---------------|-----------------|-----------|---------|----------------|--------|
| MI            | MI              | Acute     | 2.12%   | 0.11%          | 1      |
| MI            | MI              | Post-acute| 0.52%   | 0.03%          | 8      |
| Stroke        | Stroke          | Acute     | 1.46%   | 0.07%          | 10     |
| Stroke        | Stroke          | Post-acute| 1.46%   | 0.02%          | 11     |
| MI            | Stroke          | Acute     | 0.31%   | 0.02%          | 10     |
| MI            | Stroke          | Post-acute| 0.31%   | 0.02%          | 11     |
| Stroke and MI | Stroke          | Post-acute| 1.46%   | 0.07%          | 10     |
| Stroke and MI | MI              | Post-acute| 0.31%   | 0.02%          | 10     |
| Angina        | MI *            | -         | 0.21%   | 0.01%          | 12     |
| Angina        | Stroke *        | -         | 0.15%   | 0.01%          | 12     |

* These probabilities are used in both acute and post-acute phases.

1.3. Mortality

There are two sources of mortality in the model. First, background mortality, which is assigned to each individual at birth, is the time of death provided the person does not die from any of the modelled disease events. Table S11 shows the functions used to estimate background mortality. These are generated by fitting a Gompertz function (parameters \( \lambda \) and \( \gamma \)) piece-wise to the different age brackets in the all-cause mortality life tables for Mexico [4].
Table S11. Background all-cause mortality functions.

| Gender | Parameter | Part 1 | Part 2 | Part 3 | Part 4 |
|--------|-----------|--------|--------|--------|--------|
| Female | $\lambda$ | -7.663730 | -9.314051 | -10.583913 | -5.072112 |
|        | $\gamma$  | -0.045055 | 0.073045 | 0.092736  | 0.037065 |
| Male   | $\lambda$ | -4.496873 | -8.184782 | -7.455439 | -9.413828 |
|        | $\gamma$  | -1.596605 | 0.012823 | 0.047107  | 0.081203 |

Age Survival cut point: females †
16 72 95 110

Age Survival cut point: males †
2 14 64 105

† These age cut points define the different pieces of the piece-wise Gompertz function that was fitted to the background mortality hazard.

Second, experiencing disease events is associated with a mortality risk. The background mortality is adjusted for death associated with the cardiovascular events predicted separately in the model in order to avoid double counting. The data used to do this are reported in Table S12. Since diseases occur in the model only after the age of 18 years, background mortality was not adjusted prior to that age.

Table S12. Percent of deaths attributable to cardiovascular events.

| Gender | Age (years) | Source |
|--------|-------------|--------|
|        | 18 to 24    | 25 to 34 | 35 to 44 | 45 to 64 | 65+     |
| Females| 2.8%        | 4.6%    | 8.4%    | 15.9%    | 24.1%   | [13]    |
| Males  | 4.4%        | 6.4%    | 9.1%    | 13.1%    | 25.9%   |         |

These disease-specific mortality risks comprises two elements. First, the probability that an initial CHD event is fatal is reported in Table S13.

Table S13. Proportion of initial CHD events that are cardiac death [7].

| Gender | Mean | Standard Error |
|--------|------|----------------|
| Female | 2%   | 0.10%          |
| Male   | 6%   | 0.31%          |

Second, the mortality rate subsequent to experiencing a disease event is reported in Table S14.

Table S14. Mortality rate following disease events (3-month probability).

| Parameter                   | Mean       | Standard Error | Source |
|-----------------------------|------------|----------------|--------|
| MI in Acute                 | 13.7%      | 0.70%          | [8,14]  |
| Stroke in Acute             | 19.9%      | 1.02%          | [10,14] |
| MI in Post-acute            | 0.17%      | 0.01%          | [8,14]  |
| Stroke in Post-acute        | 0.54%      | 0.03%          | [10,14] |
| Stroke + MI in Post-acute   | 0.54%      | 0.03%          | [10]    |
| Angina                      | 0.18%      | 0.01%          | [12]    |

* Code “I63” is used “diag-09-10” worksheet of Hospital Episode Statistics (HES) (2010). ** Code “I21” is used “diag-09-10” worksheet of HES (2010). *** Code “I22” is used “diag-09-10” worksheet of HES (2010).

1.4. Healthcare Costs

Table S15 reports the data used to calculate the costs of diseases. Costs are inflated to 2014 values using the national Mexican price index [15].
Table S15. Direct medical costs of diseases (MXN, 2014).

| Disease | Phase                                             | Mean     | Standard Error | Source |
|---------|---------------------------------------------------|----------|----------------|--------|
| Stroke  | Acute (one-off cost after event)                  | 44,080   | 2,249          | [16]   |
|         | Post-acute (daily)                                | 39.06    | 1.99           | [17]   |
| MI      | Acute (one-off cost after event)                  | 173,112  | 8,832          | [16]   |
|         | Post-acute (daily)                                | 44.69    | 2.28           | [17]   |
| Angina  | All (per day)                                     | 181.38   | 9.25           | [17]   |
| Diabetes| All (per day)                                     | 37.24    | 1.90           | [18]   |

* The standard error is calculated based on the assumption that this variable is normally distributed with 95% of the area within 1.96 standard deviations of the mean.

1.5. Health-Related Quality-of-Life Impacts

Table S16 reports the parameter values, dispersion parameters, descriptions and sources for the utility decrements.

Table S16. Utility decrements.

| Parameters                           | Mean Decrement | Standard Error | Description                                                                 | Source |
|--------------------------------------|----------------|----------------|------------------------------------------------------------------------------|--------|
| Age                                  | −0.0036        | 0.0002 *       | Age-based annual utility decrement (applied starting from age 18)            | [19]   |
| BMI, non-diabetic                     | −0.0143        | 0.0008 *       | Applied per unit increase in BMI for non-diabetic individual (applied starting from age 18) | [20]   |
| BMI, diabetic                         | −0.0285        | 0.0015 *       | Applied per unit increase in BMI, for diabetic individual (applied starting from age 18) | [20]   |
| Acute MI                             | −0.0626        | 0.0132         | Applied after the occurrence of the event                                   | [20]   |
| Acute stroke                         | −0.1171        | 0.0121         | Applied after the occurrence of the event                                   | [19]   |
| Post-acute MI                         | −0.0627        | 0.0131         | Applied in post-acute phase (3 months following the event) until time of death | [19]   |
| Angina                               | −0.0854        | 0.0134         | Applied until time of death                                                 | [19]   |
| Post-acute stroke                    | −0.0732        | 0.0244         | Applied in post-acute phase (3 months following the event) until time of death | [19]   |

* This value is calculated based on the assumption that this variable is normally distributed with 95% of the area within 1.96 standard deviations of the mean.

1.6. Productivity Impacts

Productivity impacts are incorporated into the model in two ways. First, before the age of 13 years, an individual’s BMI will impact their probability of missing school, with a knock-on impact on their parents’ ability to attend work. Second, after the age of 18 years, employment status and productivity are impacted by the experience of health events.

1.6.1. School Absenteeism

Table S17 describes the function used to estimate the number of days individuals miss from school between the ages of 4 years and 12 years. Geier et al. (2007) [21] estimated the function from data collected from a cohort of 1069 fourth to sixth graders in the U.S. BMI was estimated by assuming a linear relationship between BMI at 2 years old and 17 years old.

The impact of school absence on productivity is estimated by assuming that a day off school would cause one parent to miss work for the 20.7% of children in Mexico for whom both parents work [22].
Table S17. Regression model of a day’s absence from school [21].

| Parameter                | Mean | Standard Error |
|--------------------------|------|----------------|
| Intercept                | 2.22 | 3.86           |
| Obese *                  | 1.92 | 0.77           |
| Overweight               | 1.04 | 0.86           |
| Underweight              | −1.41| 2.21           |
| Normal-weight            | 0    | 0              |
| Black                    | −2.19| 1.11           |
| Asian                    | −7.5 | 1.22           |
| Hispanic (Mexican American) | −1.68| 1.19           |
| Other                    | −2.36| 1.86           |
| White                    | 0    | 0              |
| Gender (Female)          | −0.06| 0.63           |
| Age                      | 1.1  | 0.32           |

* Obese here was defined as BMI for age ≥95th percentile.

1.6.2. Disease-Related Productivity Impacts

After the age of 18 years, for those individuals who are employed (Table S18), productivity loss is estimated based on days missed from work due to disease events. In a small proportion of instances, disease events will lead to individuals being permanently out of employment. In most instances, disease events are associated with a period off work. Table S19 summarises the data used to estimate these productivity impacts. Productivity losses are accrued until the individual retires at 65 years old [21] and assuming 257 working days per year.

For chronic conditions, such as diabetes and angina, a certain number of days is expected to be missed from work every year [23,24]. If, for example, diabetes causes 40 days off work per year, the patient is assumed to be off work 10 days at each quarter of the year.

If two disease events are experienced simultaneously, the highest number of days off work associated with these events is applied.

Table S18. Productivity impacts of obesity-related diseases.

| Obesity-Related Diseases | Days off Work | Standard Error | Source | % Patients Permanently Disabled | Source |
|--------------------------|---------------|----------------|--------|--------------------------------|--------|
| Myocardial infarction    | 168 per event | 8.6            | [25]   | 0.32%                          | [23]   |
| Stroke                   | 270 per event | 13.8           | [26]   | 0.28%                          | [24]   |
| Diabetes                 | 38 per year   | 1.9            | [27]   | 0.00%                          | Assumption |
| Angina                   | 2.0 per year  | 5.0            | [28]   | 0.00%                          | Assumption |

Table S19. Employment rate in Mexico by age and gender [29].

| Age (Years) | Males (%) | Females (%) |
|-------------|-----------|-------------|
| 18 to 24    | 55.6%     | 30.7%       |
| 25 to 34    | 90.1%     | 52.6%       |
| 35 to 44    | 92.6%     | 55.9%       |
| 45 to 54    | 90.3%     | 51.6%       |
| 55 to 64    | 76.6%     | 37.2%       |
| 65+         | 0.0%      | 0.0%        |

1.6.3. Valuing Productivity Impacts

The value of the productivity impact is estimated using the capital approach in the base case and with the friction approach in a scenario analysis. The capital approach assumes that an absent employee will never be replaced at work by another individual and is estimated using Equation (S-E10):
Productivity cost loss = total days of work loss × (elasticity of productivity × mean daily salary) \hspace{1cm} \text{(S-E10)}

where the elasticity of productivity is 0.8, the proportion of the day during which the individual is actually productive [30] and the average daily salary is MXN 268.10 [31].

The friction approach assumes that absent employees will be replaced after a “friction” period, the time required to replace a person at work. If an individual is absent from work for a period less than the friction period, the friction method reduces to the capital method. If, however, the period of absence is greater than the friction period, the friction method estimates productivity costs using Equation (S-E11).

Productivity cost loss = (friction days × (elasticity of productivity × mean daily salary) + friction costs \hspace{1cm} \text{(S-E11)}

where the friction period is 68.32 days (assumed to be the same in Mexico as in the U.K. [31]), and the friction cost (one-off cost of replacing an employee: vacancy cover, redundancy cost, recruitment and selection, training and induction cost) is MXN 26,266 [30].

2. Sensitivity Analysis for the Base Case Results

Figure S1 shows the outcome of the PSA. Each blue diamond point on the figure is the outcome of a model run, undertaken to capture the parameter uncertainty in the model by randomly sampling from parameter distributions of the input parameters. The red square indicates the point at which the mean cost and mean QALY values intersect.

![Cost-effectiveness plane for the outcome of the probabilistic sensitivity analysis (discounted).](image-url)

Figure S1. Cost-effectiveness plane for the outcome of the probabilistic sensitivity analysis (discounted).

Table S20 shows the PSA outcomes by quadrant. Southeast is the quadrant with the most model runs, where lpIF is less expensive and more effective.
Table S20. Allocation of PSA outcomes by quadrants of the cost-effectiveness plane.

| Quadrant                              | Allocation |
|---------------------------------------|------------|
| Northeast quadrant: lpIF is more expensive and more effective | 20.1%      |
| Northwest quadrant: lpIF is more expensive and less effective | 16.0%      |
| Southeast quadrant: lpIF is less expensive and more effective | 32.7%      |
| Southwest quadrant: lpIF is less expensive and less effective | 31.2%      |

3. Validation

In order to assess the validity of the predictions of the model, Table S21 compares the result of the model specified for the current situation in Mexico (individual characteristics based on descriptive statistics for the Mexican population and using standard high-protein formula) with the observed outcomes for the Mexican population. It demonstrates that the model fairly accurately predicts the current life expectancy in Mexico and is the same ballpark for the other BMI and disease risk outcomes.

Table S21. Comparison of model predictions with the observed characteristics of the Mexican population [32].

| Model Outcome | Model Prediction (Standard High Protein Formula) | Observed |
|---------------|--------------------------------------------------|----------|
| Life years (LYs) | 77.5 years | 77 years |
| % diabetes     | 14.8%     | 17% to 21% |
| % angina       | 8.6%      | 4.8% to 9.2% |
| % MI           | 3.3%      |          |
| % stroke       | 0.27%     | 0.21%    |
| % becoming obese (BMI ≥30) | 17.1% | 32.8% |
| Average lifetime BMI | 28.2 | 31.3 |

Table S22 provides the individual characteristics considered in the model, broken down by age groups.

Table S22. Age-dependent individual characteristics.

| Age Range | Males (mg/dL) | Standard Error | Female (mg/dL) | Standard Error | Source |
|-----------|---------------|----------------|----------------|----------------|--------|
|            | Fasting Glucose Level (FGL) | | | | |
| [18, 29]  | 88.7          | 4.53           | 80.9           | 4.13           | [34]   |
| [30, 39]  | 90.3          | 4.61           | 89.1           | 4.55           |        |
| [40, 49]  | 90.1          | 11.60          | 87.2           | 10.70          |        |
| [50, 59]  | 90.1          | 11.60          | 87.2           | 10.70          |        |
| [60, 69]  | 90.1          | 11.60          | 87.2           | 10.70          |        |
| [70, 79]  | 117.4         | 5.99           | 109.2          | 5.57           |        |
| [80, 100] | 96.4          | 4.92           | 89.5           | 4.57           |        |
| [101, 199]| 96.4          | 4.92           | 89.5           | 4.57           |        |

| Systolic Blood Pressure (SBP) | | | | | |
| [18, 29]    | 120.40       | 6.14           | 113.80         | 5.81           | [34]   |
| [30, 39]    | 122.30       | 6.24           | 116.90         | 5.96           |        |
| [40, 49]    | 124.90       | 6.37           | 123.10         | 6.28           |        |
| [50, 59]    | 128.30       | 6.55           | 129.00         | 6.58           |        |
| [60, 69]    | 132.50       | 6.76           | 133.60         | 6.82           |        |
| [70, 79]    | 134.70       | 6.87           | 137.50         | 7.02           |        |
| [80, 100]   | 132.90       | 6.78           | 137.70         | 7.03           |        |
| [101, 199]  | 132.90       | 6.78           | 137.70         | 7.03           |        |

Table S22. Cont.
| Age Range | Males (mg/dL) | Standard Error | Female (mg/dL) | Standard Error | Source |
|-----------|---------------|----------------|----------------|----------------|--------|
| [18, 29]  | 36.70         | 0.66           | 40.00          | 0.59           |        |
| [30, 39]  | 36.70         | 0.71           | 39.40          | 0.66           | [35]   |
| [40, 49]  | 38.40         | 0.87           | 39.90          | 0.64           |        |
| [50, 59]  | 37.80         | 1.02           | 43.30          | 1.02           |        |
| [60, 100] | 36.20         | 0.94           | 43.00          | 1.25           |        |
| [101, 199]| 36.20         | 0.94           | 43.00          | 1.25           |        |

### Cholesterol/HDL-ratio

| Age Range | Males (mg/dL) | Standard Error | Female (mg/dL) | Standard Error | Source |
|-----------|---------------|----------------|----------------|----------------|--------|
| [18, 29]  | 5.04          | 0.26           | 4.75           | 0.24           | [35]   |
| [30, 39]  | 5.12          | 0.26           | 5.02           | 0.26           |        |
| [40, 49]  | 5.35          | 0.27           | 5.10           | 0.26           |        |
| [50, 59]  | 5.32          | 0.27           | 5.26           | 0.27           |        |
| [60, 100] | 5.49          | 0.28           | 5.09           | 0.26           |        |
| [101, 199]| 5.49          | 0.28           | 5.09           | 0.26           |        |

### Smoking Status

| Age Range | Males (%) | Standard Error | Female (%) | Standard Error | Source |
|-----------|-----------|----------------|------------|----------------|--------|
| [18, 29]  | 34.7%     | 1.77%          | 10.7%      | 0.55%          | [34]   |
| [30, 39]  | 33.1%     | 1.69%          | 9.7%       | 0.49%          |        |
| [40, 49]  | 30.9%     | 1.58%          | 11.1%      | 0.57%          |        |
| [50, 59]  | 28.9%     | 1.47%          | 10.1%      | 0.52%          |        |
| [60, 69]  | 25.3%     | 1.29%          | 5.1%       | 0.26%          |        |
| [70, 79]  | 15.9%     | 0.81%          | 6.2%       | 0.32%          |        |
| [80, 100]| 11.0%     | 0.56%          | 2.8%       | 0.14%          |        |
| [101, 199]| 34.7%     | 1.77%          | 10.7%      | 0.55%          |        |

Values for ages 18 to 20 were unavailable and, thus, assumed to be the same as those for the age range of 20 to 29. The standard error is calculated based on the assumption that this variable is normally distributed with 95% of the area within 1.96 standard deviations of the mean.

### References

1. Druet, C.; Stettler, N.; Sharp, S.; Simmons, R.K.; Cooper, C.; Smith, G.D.; Ekelund, U.; Lévy-Marchal, C.; Jarvelin, M.R.; Kuh, D.; et al. Prediction of childhood obesity by infancy weight gain: An individual-level meta-analysis. *Paediatr. Perinat. Epidemiol.* 2012, 26, 19–26.
2. Østbye, T.; Malhotra, R.; Landerman, L.R. Body mass trajectories through adulthood: Results from the National Longitudinal Survey of Youth 1979 Cohort (1981–2006). *Int. J. Epidemiol.* 2011, 40, 240–250.
3. World Health Organization. *Non-Communicable Diseases Indicators*. May 2015. Available online: https://apps.who.int/infobase/indicators.aspx (accessed on 4 May 2015).
4. World Health Organization. Global Health Observatory Data Repository. Segmented Life Tables for Mexico, 2011. Available online: http://apps.who.int/gho/athena/data/GHO/LIFE_0000000029,LIFE_0000000030,LIFE_0000000031,LIFE_0000000032,LIFE_0000000033,LIFE_0000000034,LIFE_0000000035?filename=NGA&format=xml&profile=excel (accessed on 4 May 2015).
5. Stern, M.P.; Williams, K.; Haffner, S.M. Identification of persons at high risk for type 2 diabetes mellitus: Do we need the oral glucose tolerance test? *Ann. Intern Med.* 2002, 136, 575–581.
6. Wilson, P.W.; Bozeman, S.R.; Burton, T.M.; Hoaglin, D.C.; Ben-Joseph, R.; Fashos, C.L. Prediction of first events of coronary heart disease and stroke with consideration of adiposity. *Circulation* 2008, 118, 124–130.
7. D’Agostino, R.B.; Russell, M.W.; Huse, D.M.; Ellison, R.C.; Silbershatz, H.; Wilson, P.W.; Hertz, S.C. Primary and subsequent coronary risk appraisal: New results from the Framingham study. *Am. Heart J.* 2000, 139, 272–281.
8. Bonaca, M.P.; Braunwald, E.; de Ferrari, G.M.; Isaza, D.; Lewis, B.S.; Mehrhof, F.; Merlini, P.A.; Murphy, S.A.; Sabatine, M.S.; et al. Vorapaxar for secondary prevention of thrombotic events for patients with previous myocardial infarction: A prespecified subgroup analysis of the TRA 2 P-TIMI 50 trial. *Lancet* 2012, 380, 1317–1324.
9. Wallentin, L.; Becker, R.C.; Budaj, A.; Cannon, C.P.; Emanuelsson, H.; Held, C.; Horrow, J.; Husted, S.; James, S.; Katus, H.; et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N. Engl. J. Med. 2009, 361, 1045–1057.

10. Diener, H.-C.; Bogousslavsky, J.; Brass, L.M.; Cimminiello, C.; Csiba, L.; Kaste, M.; Leys, D.; Matias-Guiu, J.; Rupprecht, H.J.; MATCH Investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): Randomised, double-blind, placebo-controlled trial. Lancet 2004, 364, 331–337.

11. Trueman, P.; Lowson, K.; Bending, M.; Ganderton, M.; Chaplin, S.; Wright, D.; Duffy, S.; Saxby, R.; Bowel Cancer Services: Costs and Benefits. Final Report to the Department of Health. Available online: https://www.shef.ac.uk/polopoly_fs/1.44049!/file/FinalBowelCancerSummaryReport-Apr07.pdf (accessed on 4 May 2015).

12. Ridker, P.M.; Manson, J.E.; Gaziano, J.M.; Buring, J.E.; Hennekens, C.H. Low-dose aspirin therapy for chronic stable angina: A randomized, placebo-controlled clinical trial. Ann. Internal Med. 1991, 114, 835–839.

13. Instituto Nacional de Estadistica y Geografía. Main Causes of Mortality Habitual Residence, Age and Sex of the Deceased, 2012 Available online: http://www.inegi.org.mx/est/contenidos/proyectos/registros/ vitales/mortalidad/tabulados/PC.asp?t=14&c=11817 (accessed on 4 May 2015).

14. Hospital Episode Statistics. 2009/2010 Provisional Linked HES-ONS Mortality Data Aggregated by Diagnosis/Procedure, 2010. Available online: http://www.hscic.gov.uk/ hesonsmortality (accessed on 4 May 2015).

15. Instituto Nacional de Estadística y Geografía. National Consumer Price Index and its Components, 2014. Available online: http://www.inegi.org.mx/sistemas/IndicePrecios/Cuadro.aspx?nc=CA55&T=%C3%8 (accessed on 4 May 2015).

16. Instituto Mexicano del seguro Social Grupos Relacionados con el Diagnostico (DRG)—Cedula Medico-Economica (CME), 2012. Available online: http://201.144.108.20/profesionales/Pages/grd-cme.aspx (accessed on 4 May 2015).

17. Reynales-Shigematsu, L.M.; Rodríguez-Bolaños Rde, L.; Jiménez, J.A.; Juárez-Márquez, S.A.; Castro-Rios, A.; Hernández-Avila, M. Health care costs attributable to tobacco consumption on a national level in the Mexican Social Security Institute. Salud Pública Méx. 2006, 48, s48–s64.

18. Bolaños, R.; de los Ángeles, R.; Myriam, R.S.L.; Alberto, J.R.J.; Arturo, J.M.S.; Mauricio, H.A. Costos directos de atención médica en pacientes con diabetes mellitus tipo 2 en México: Análisis de microcosteo. Rev. Panam. Salud Publica 2010, 28, 412–420.

19. Sullivan, P.W.; Slejko, J.F.; Sculpher, M.J.; Ghushchyan, V. Catalogue of EQ-5D scores for the United Kingdom. Med. Dec. Making 2011, 31, 800–804.

20. Hakim, Z.; Wolf, A.; Garrison, L.P. Estimating the effect of changes in body mass index on health state preferences. Pharmaco economics 2002, 20, 393–404.

21. Geier, A.B.; Foster, G.D.; Womble, L.G.; McLaughlin, J.; Borradaile, K.E.; Nachmani, J.; Sherman, S.; Kumanyika, S.; Shults, J. The relationship between relative weight and school attendance among elementary schoolchildren. Obesity 2007, 15, 2157–2161.

22. Organisation for Economic Co-Operation and Development OECD Family Database: 2. The Labour Market Position of Families (LMF). Available online: http://www.oecd.org/els/family/database.htm#labour_market (accessed on 4 May 2015).

23. Brink, E.; Brändström, Y.; Cliffordsson, C.; Herlitz, J.; Karlson, B.W. Illness consequences after myocardial infarction: Problems with physical functioning and return to work. J. Adv. Nurs. 2008, 64, 587–594.

24. Kersten, P.; George, S.; Low, J.; Ashburn, A.; McLellan, L. The Subjective Index of Physical and Social Outcome: Its usefulness in a younger stroke population. Int. J. Rehabil. Res. 2004, 27, 59–63.

25. Froelicher, E.; Kee, L.L.; Newton, K.M.; Lindskog, B.; Livingston, M. Return to work, sexual activity, and other activities after acute myocardial infarction. Heart Lung 1993, 23, 423–435.

26. Daniel, K.; Wolfe, C.D.; Busch, M.A.; McKevitt, C. What are the social consequences of stroke for working-aged adults? A systematic review. Stroke 2009, 40, e431–e440.

27. Plou, U.J. The Cost of Diabetes-Related Complications: Registry-Based Analysis of Days Absent from Work. Econ. Res. Int. 2013, doi:10.1155/2013/618039.

28. Brown, R.; Kendall, M.; Halpern, M. Cost Analysis of Once-Daily ISMN versus twice-daily ISMN or transdermal patch for nitrate prophylaxis. J. Clin. Pharmacy Ther. 1997, 22, 67–76.
29. Organisation for Economic Co-operation and Development. OECD Employment Outlook. Available online: http://www.oecd.org/els/emp/oecdemploymentoutlook.htm (accessed on 4 May 2015).
30. Hakkaart-van Rooijen, L.; Tan, S.; Bouwmans, C. Dutch Costing Manual; Institute for Medical Technology Assessment (By order of the Board of Health Insurances): Rotterdam, The Netherlands, 2010.
31. Chartered Institute of Personnel and Development. Recruitment, Retention and Turnover. Annual Survey Report 2007; Chartered Institute of Personnel and Development: London, UK, 2007.
32. World Health Organization. Global Health Observatory. Available online: http://www.who.int/gho/publications/world_health_statistics/en/ (accessed on 4 May 2015).
33. Ekelund, U.; Ong, K.; Linne, Y.; Neovius, M.; Brage, S.; Dunger, D.B.; Wareham, N.J.; Rössner, S. Upward weight percentile crossing in infancy and early childhood independently predicts fat mass in young adults: The Stockholm Weight Development Study (SWEDES). Am. J. Clin. Nutr. 2006, 83, 324–330.
34. World Health Organization. WHO Global Infobase. Available online: https://apps.who.int/infobase/Indicators.aspx (accessed on 4 May 2015).
35. Aguilar-Salinas, C.A.; Gómez-Pérez, F.J.; Rull, J.; Villalpando, S.; Barquera, S.; Rojas, R. Prevalence of dyslipidemias in the Mexican National Health and Nutrition Survey 2006. Salud Públxica Méx. 2010, 52 (Suppl. 1), S44–S53.

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