



Global Sensitivity Analysis of a Model Simulating an Individual's Health State through Their Lifetime

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ABSTRACT: In public health, model predictions are used by decision-makers to minimise health burdens and monetary costs of non-communicable diseases. Fully understanding the uncertainty underlying those predictions is thus crucial. One-parameter-at-a-time methods are typically used

for model uncertainty analysis but are often impractical for large-scale nonlinear models containing a very large number of parameters and cannot be used to examine the uncertainty associated with parameter interaction. An individual-based chronic disease model was developed to model the impact of Body Mass Index (BMI) trends on the rates of non-communicable diseases. The model was simulated for overweight and obese male case studies and used to predict their life expectancy, disease-free life expectancy and quality-adjusted life years. Uncertainty was estimated by carrying out a global sensitivity analysis by assessing the contribution to the overall uncertainty from a selection of parameters individually and from their interactions. Results show that the uncertainty of the BMI input parameter had the greatest impact on the disease-free life expectancy and quality-adjusted life year uncertainty compared to the relative risks of colorectal cancer and stroke. Life expectancy uncertainty was influenced by BMI and colorectal cancer relative risks. Global sensitivity analysis enables the assessment of the parametric uncertainty for individual parameters and their interaction. This allows the communication of the uncertainty of different policy options. A strategy for scaling-up uncertainty analysis from an individual to a population level is discussed.

KEYWORDS: MICROSIMULATION MODEL, GLOBAL SENSITIVITY ANALYSIS, UNCERTAINTY ANALYSIS, PUBLIC HEALTH POLICY PREDICTIONS

JEL classification: C15, C53, C54, C63

1 INTRODUCTION

Microsimulation models are becoming increasingly popular in public health (Atella, Belotti, Carrino, & Piano Mortari, 2017; Goldman et al., 2009; Gonzalez-Gonzalez, Tysinger, Goldman, & Wong, 2017; Hennessy et al., 2015; Hunt et al., 2017; McPherson, Marsh, & Brown, 2007; Rogers et al., 2014). These models have been used to predict the future epidemiological and economic impacts of risk factors (e.g. Body Mass Index (BMI), smoking, alcohol consumption) on rates of non-communicable diseases in a given population (Ahern et al., 2017; Hunt et al., 2017). Typically these models simulate the health profile of between 5,000 and 100 million individuals. Due to the increasing availability of health-related 'big' data and computing power, these models are becoming increasingly more complex and data driven. Model input data are commonly extracted from multiple sources each with varying levels of uncertainty. In general, a quantification of the uncertainty of outputs from public health microsimulation models is not analysed. Uncertainty estimates of model outputs which reflect the uncertainty of the model input parameters are important to include because they provide more detail about the confidence of these outputs (Mathijssen, Petersen, Besseling, Rahman, & Don, 2008).

There are two main methods for analysing the parametric uncertainty of complex models such as microsimulation: deterministic and probabilistic (there is another method which uses fuzzy mathematics but it is not as widely used). Deterministic analysis considers fixed variation in parameter values whereas probabilistic analysis considers random variations in parameter values. Local deterministic sensitivity analysis such as one-at-a-time can be used to analyse the impact of the uncertainty from one input parameter on the model output (Saltelli, 1999). However, these methods are unrealistic for models with many complex interactions and with a large number of input parameters. Probabilistic methods such as the classical Monte Carlo sensitivity analysis can be used to analyse the overall output uncertainty from the uncertainty of the input parameters (Rutter, Zaslavsky, & Feuer, 2011). However, this does not give direct information about which input parameters contribute most to the output uncertainty and the contribution from parameter interaction. Global sensitivity analysis (Sobol indices) provides a direct way of assessing the relative contribution to the overall uncertainty from each input parameter and their interactions (Kucherenko, 2009; Saltelli, 2002; Saltelli et al., 2008, 2010; Sobol, 2001).

In this study, an individual-based chronic disease model has been developed based on a previously developed microsimulation model (Hunt et al., 2017; McPherson et al., 2007). This model has been used to evaluate the impact of an individual's BMI on their life expectancy, disease-free life

expectancy and quality-adjusted life year. The model simulates single individuals through time and calculates the probability of different events (e.g. disease prevalence, death) similar to a life table approach. These individuals would be equivalent to an individual unit in a large-scale microsimulation model. The uncertainty of the model input parameters has been incorporated into the simulation for each individual to calculate the uncertainty of the model output. This model has been simulated within the Problem Solving environment for Uncertainty Analysis and Design Exploration (PSUADE) programming framework to analyse the parametric uncertainty by estimating the Sobol indices (Tong, 2005). The Sobol indices provide information about the uncertainty from model input parameters and their interaction on the model outputs. To our knowledge, this method has not been applied to public health microsimulation models (Hennessy et al., 2015; Lymer, Schofield, Lee, & Colagiuri, 2016; Manuel et al., 2014). Some studies have analysed the uncertainty on an output, however, the contribution from individual parameters and their interactions has not been presented (Kypridemos et al., 2016; Sharif et al., 2012).

2 METHODS

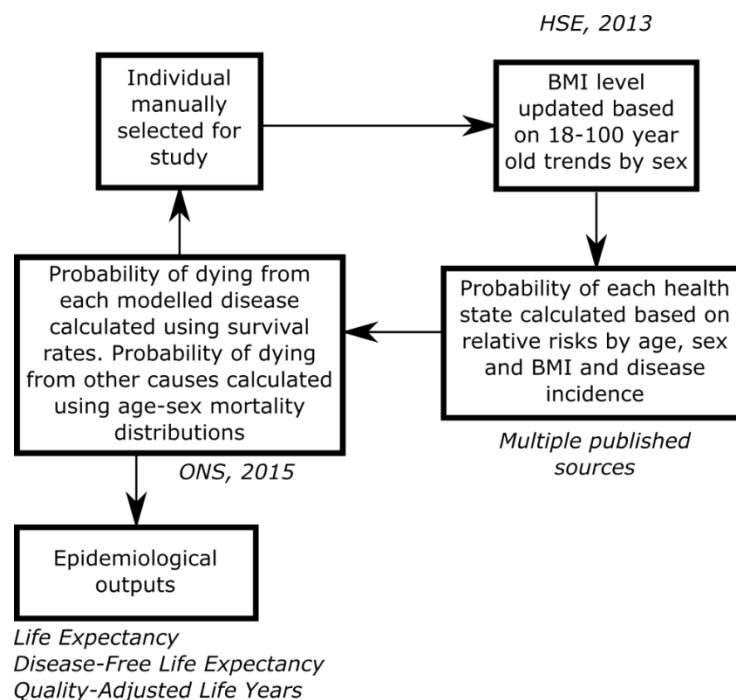
2.1 The individual-based chronic disease model

Two individual case studies were simulated in an individual-based chronic disease model through time as opposed to several million which would routinely be simulated in the larger microsimulation model. Moreover, this model was adapted to probabilistically model the health profile of individuals through time. At each time point, the probability that an individual was in a given health state was calculated and used to compute the output health metrics (life expectancy, disease-free life expectancy and quality-adjusted life years).

Figure 1 provides a summary of the main processes and data sources that were used in the individual-based model. An individual's starting age, BMI and health status were pre-defined. Each year an individual's BMI levels were updated based on the 18 to 100 year old BMI distribution trends disaggregated by sex. In this study the trends were assumed to be static, so the BMI distribution was assumed to be stationary, i.e. to not change over time. The 18 to 100 year old trends were computed by fitting a non-linear multivariate categorical regression model using individual level age, sex and BMI data from the 2013 Health Survey for England (HSE). The regression methods are described in the online supplementary material (Appendix). The model used an individual's BMI, age and sex to calculate their risk of disease. The risk of disease was calculated from BMI-age-sex relative risks and age-sex incidence rates. Five obesity-related diseases were included in the simulation: coronary heart disease; stroke; type 2 diabetes; hypertension; and

colorectal cancer. The individual-based model calculated the probability of each health state ranging from the probability of not having a disease to the probability of death. The probability of an individual living with multi-morbidities was also assessed up to a combination of four diseases at any one time. The probability of an individual dying was calculated from the survival rates of a given disease and the mortality rates of other causes (more technical details are provided in the online supplementary material - Appendix). The total mortality statistics and some of the survival statistics were sourced from the Office for National Statistics (ONS). In cases, where the survival statistics were unavailable the rates were estimated from prevalence and mortality statistics. Further details about these data sources are provided in the online supplementary material - Appendix. A utility weight was associated with each disease and these were used to estimate the mean Quality Adjusted Life Year (QALY) each year. The sources for this data are summarised in the online supplementary material - Appendix.

Figure 1: Schematic of the individual-based chronic disease model used to simulate individuals through time.



Source: The figure has been adapted from Lymer et al. (2016).

2.1.1 Case studies

Two 20-year-old case-studies were investigated: an overweight male (BMI=27.5 kg/m²) and an obese male (BMI=37.5 kg/m²). Both individuals had no health conditions in the start year of the

simulation (2016). The model was simulated between 2016 and 2116 to ensure that the individuals are simulated far enough into the future to estimate life expectancy.

2.1.2 Model outputs

Obesity is a major risk factor for fatal (e.g. coronary heart disease) and non-fatal (e.g. type 2 diabetes) diseases and has been shown to have an impact on an individual's healthy life expectancy (disease-free life expectancy) (Stenholm et al., 2017). Three outputs were assessed in this study: life expectancy, disease-free life expectancy and quality-adjusted life years. Life expectancy was calculated from the sum of the probabilities of the individual being alive in each year of the simulation and was initialised with the age of the individual in the start year of the simulation (see Equation 1). The disease-free life expectancy was calculated from the sum of the probability of an individual being alive without a disease in each year of the simulation (see Equation 2). This health metric was also initialised with the starting age of the individual. The quality-adjusted life year was initialised with the age of the individual in the start year of the simulation. It was calculated by summing the probability of being alive without a disease and the probability of being alive with a disease multiplied by the average quality of life (QoL) in the given year (see Equation 4). The average QoL was calculated from the utility weights which were specific to the diseases that an individual may have in a given year (see Equation 3). The average QoL was weighted based on the probability of having each disease.

$$\text{Life expectancy} = \text{age}(t_{\text{start}}) + \sum_{t=t_{\text{start}}}^{t_{\text{end}}} P_{\text{alive}}(t) \quad (1)$$

$$\text{Disease free life expectancy} = \text{age}(t_{\text{start}}) + \sum_{t=t_{\text{start}}}^{t_{\text{end}}} (P_{\text{alive}}(t) - P_{\text{alive+disease}}(t)) \quad (2)$$

$$QoL_{\text{average}}(t) = \frac{\sum_{d=0}^{N_{\text{diseases}}} P_{\text{disease}}(t) \times QoL_{\text{disease}}}{\sum_{d=0}^{N_{\text{diseases}}} P_{\text{disease}}(t)} \quad (3)$$

$$\text{Quality-adjusted life year} = \text{age}(t_{\text{start}}) + \sum_{t=t_{\text{start}}}^{t_{\text{end}}} (P_{\text{alive+no disease}}(t) + P_{\text{alive+disease}}(t) \times QoL_{\text{average}}(t)) \quad (4)$$

Equations 1, 2 and 4 are discrete time dynamic equations in steps of one year. The first term on the right hand side of these equations gives the age of the individual at the start of the simulation. The summation term of Equation 1 sums the probabilities that the individual is alive at each year. The summation term of Equation 2 only sums the probabilities that the individual is disease-free.

The summation term of Equation 4 sums the probabilities that the individual is alive with no disease and the probabilities that the individual is alive with a disease scaled by the average QoL.

2.1.3 *Model input parameter uncertainty*

Information on the uncertainty from three different model input parameters was available in the literature and included in this analysis. The first model parameter was the BMI distribution trends. BMI trends by 5 year age groups were created for males, providing information on the probability of individuals in each BMI category (healthy weight, overweight and obese) across each 5 year age group from 2003 to 2116. The mean and standard deviation for each BMI category were calculated across all of the adult age groups (≥ 20 years old) between 2003 and 2116 (see Table 1). The overall mean probability and standard deviation across all of the BMI categories were also calculated from the mean and standard deviation from each BMI category. The upper and lower bounds for the healthy weight, overweight, obese and average BMI category probabilities were calculated by assuming a uniform distribution of uncertainty around each probability. Uniform distribution is often used as an uninformed prior distribution when there is a lack of precise information on parameter uncertainty. This provided an estimation of the uncertainty around the proportions of individuals within each BMI category.

In general, BMI distributions in a population are represented by a log-normal distribution. A log-normal distribution of the average adult male BMI levels was constructed from the mean probabilities of each BMI category. The mean BMI level (25.192) at the percentile corresponding to the mean BMI category probability (0.333) was estimated. In addition, the lower and upper bounds for the mean BMI level were estimated at the lower and upper bounds of the mean BMI category probability. The mean BMI level and the corresponding lower and upper bounds were used to estimate the lower and upper bounds around the BMI of each case study. It was assumed that the difference between the mean BMI level and the lower and upper bounds was the same as the difference between the BMI level of each case study and the corresponding lower and upper bounds (see Table 1).

Table 1: Summary of the BMI model parameters and their variances used in the sensitivity analysis.

Model parameter	Mean	Standard deviation	Lower bound	Upper bound
Healthy weight BMI probability (BMI < 25 kg/m ²)	0.252	0.078	0.117	0.387
Overweight BMI probability (25 ≤ BMI < 30 kg/m ²)	0.314	0.083	0.170	0.459
Obese BMI probability (BMI ≥ 30 kg/m ²)	0.434	0.107	0.248	0.619
Mean BMI category probability	0.333	0.090	0.177	0.490
Mean BMI ¹ level	25.192		20.591	27.028
Case study 1 BMI level	27.5		22.899	29.336
Case study 2 BMI level	37.5		35.207	41.644

The second and third parameters used in the uncertainty analysis were the relative risk of stroke and colorectal cancer, respectively. These were chosen because there were uncertainty estimates available in the literature. Granular relative risks were available by age and sex groups from the DYNAMO-HIA project (World Obesity Federation, 2008). An average of the overweight (25-30 kg/m²) and obese (≥ 30-45 kg/m²) groups was calculated for males. Variance estimates around each of these relative risks were not provided. The variance of the relative risk of stroke and colorectal cancer for overweight and obese were sourced from Guh et al. (2009) and used as a proxy for the variances around the DYNAMO-HIA relative risks. As this dataset contained only a single relative risk estimate for the overweight and obese categories, the estimates did not vary with age. The uncertainty was represented by a uniform distribution around each mean relative risk (see Table 2). The upper and lower bounds of each uniform distribution are presented in Table 2.

Table 2: Summary of the relative risk model parameters and their variances used in the sensitivity analysis.

Model parameter	Mean	Standard deviation	Lower bound	Upper bound
Relative risk stroke for overweight	1.213	0.056	1.116	1.310
Relative risk stroke for obese	1.758	0.107	1.573	1.944
Relative risk colorectal cancer for overweight	1.231	0.082	1.089	1.373
Relative risk colorectal cancer for obese	1.823	0.224	1.435	2.211

2.2 Sobol (Global) Sensitivity Indices

Denote the uncertain input parameters by $x_1 \dots x_n$ where n is the number of uncertain parameters. The three uncertain input parameters used in this study represented the BMI value, relative risk of stroke and relative risk of colorectal cancer. Denote further by y the output (outcome) of interest and by f the analytical model or the black-box model (i.e. computer model) which maps the input parameters to the output (Equation 5):

$$y = f(x_1, x_2, \dots, x_n) \quad (5)$$

where the output parameter y represents life expectancy, disease-free life expectancy and quality-adjusted life years. The aim of the global sensitivity analysis method is to determine the contribution of the uncertainty (variance) in each of the input parameters $x_1 \dots x_n$ ($V_i(x_i)$) and their interactions ($V_{ij}(x_i, x_j)$) to the uncertainty (variance) of the output y . The total number of parameters m of the model can of course be much larger than n , i.e. $m \gg n$. However, what is important here are the parameters which are considered to be uncertain. The variance of the output can be decomposed as follows (Equation 6):

$$V(f(\mathbf{x})) = \sum_{i=1}^n V_i(x_i) + \sum_{1 \leq i < j \leq n} V_{ij}(x_i, x_j) + \sum_{1 \leq i < j < k \leq n} V_{ijk} \dots + V_{1\dots n} \quad (6)$$

Where $V(f(x))$ is the variance of the output, i.e. the variance of the life expectancy, disease-free life expectancy and quality-adjusted life year. This variance is composed of the variance from individual input model parameters ($V_i(x_i)$), variance from the interaction of two input model parameters ($V_{ij}(x_i, x_j)$) and the variance from the interaction of three or more input model parameters. In other words, the total variance of the output is the sum of the variances of the input parameters and all the orders of their interactions.

Sobol indices are a measure of global sensitivity analysis (Kucherenko, 2009; Saltelli, 2002; Saltelli et al., 2008, 2010; Sobol, 2001). They enable the quantification of the contribution of individual model input parameters and their interaction to the total variance of the model output parameter (V). The first order Sobol indices (S_i) relate to the individual contribution from each parameter (see Equation 7).

$$S_i = \frac{V_i}{V} \quad (7)$$

The second order Sobol indices relate to the interaction between two parameters i and j . The contribution from each pair of interactions is described in Equation 8.

$$S_{ij} = \frac{V_{ij}}{V} \quad (8)$$

Each Sobol index must be less than one and the sum of all the sensitivity indices is one (Equation 9).

$$\sum_i^n S_i + \sum_{i<j}^n S_{ij} + \sum_{i<j<k}^n S_{ijk} + \dots = 1 \quad (9)$$

The main assumption of the global sensitivity analysis method is that these parameters are independent. If required, the global sensitivity analysis method can be modified to handle dependence between the parameters by using Copulas (Kucherenko, Tarantola, & Annoni, 2012).

2.3 Analysing the Sobol indices for each model output

The first and second order Sobol indices for each model output were analysed with PSUADE, an open-source software package developed by Charles Tong (Tong, 2005). The software was used to generate auxiliary variables (z_1 , z_2 and z_3) which were used as scalar additives to vary the true model input parameters within the uncertainty bounds. This was required because the relative risks for stroke and colorectal cancer varied with age and the uncertainty estimates for these model parameters were extracted from a source which only provided the uncertainty around single relative risks for all age groups. The uncertainties provided around these single relative risks were used as a proxy for the uncertainty around all the relative risks which varied with age and BMI. As an individual aged through the course of the simulation, they would be assigned a new probability of acquiring a disease based on their current age, sex and BMI. The distribution of each variable z_1 , z_2 and z_3 sampled randomly with PSUADE in the start year of the simulation are summarised in Table 3. The variables z_1 , z_2 and z_3 were used to scale the BMI, relative risk of stroke and relative risk of colorectal cancer, respectively in the model as shown in Equations 10 to 12.

Table 3: Scalar additives z_1 , z_2 and z_3 sampled by PSUADE.

PSUADE parameter	Lower bound for overweight	Upper bound for overweight	Lower bound for obese	Upper bound for obese
z_1	22.899	29.336	35.207	41.644
z_2	1.116	1.310	1.573	1.944
z_3	1.089	1.373	1.435	2.211

$$BMI(t) = (z_1 - BMI_{mean}) + BMI_{trend}(t) \quad (10)$$

$$RR_{stroke}(BMI, age) = (z_2 - RR_{StrokeMean}) + RR_{stroke}(BMI, age) \quad (11)$$

$$RR_{bowel}(BMI, age) = (z_3 - RR_{ColorectalCancerMean}) + RR_{ColorectalCancer}(BMI, age) \quad (12)$$

The BMI prevalence and relative risk were correlated in the model because the relative risk was dependent on the BMI level. Constraints were applied on the parameters z_2 and z_3 which were scalar additives for the relative risks of stroke and colorectal cancer, respectively to account for this dependency. The relative risks for both diseases varied for two different age groups and by BMI. For each age group, a linear function was fitted to the relative risk by BMI level. For each disease, an average linear function was calculated from the linear functions approximated for the two age groups (further details are provided in online supplementary material). These average linear functions for stroke (see Equation 13) and colorectal cancer (see Equation 14) were used to define constraints on the sampled variables (z_1 , z_2 and z_3).

$$|z_2 + 0.26095 - 0.0539 * z_1| < 0.1 \quad (13)$$

$$|z_3 + 0.36905 - 0.0585 * z_1| < 0.1 \quad (14)$$

3 RESULTS

In this section, the uncertainty analysis for life expectancy, disease-free life expectancy and quality-adjusted life year will be shown for both case studies: an overweight and an obese male aged 20 in 2016. The uncertainty for each of the model outputs will be shown in terms of the first- and second-order Sobol indices. For each model input parameter that has been studied, it will be checked if they are strictly positive and contribute to the uncertainty of each model output.

3.1 Disease-free life expectancy

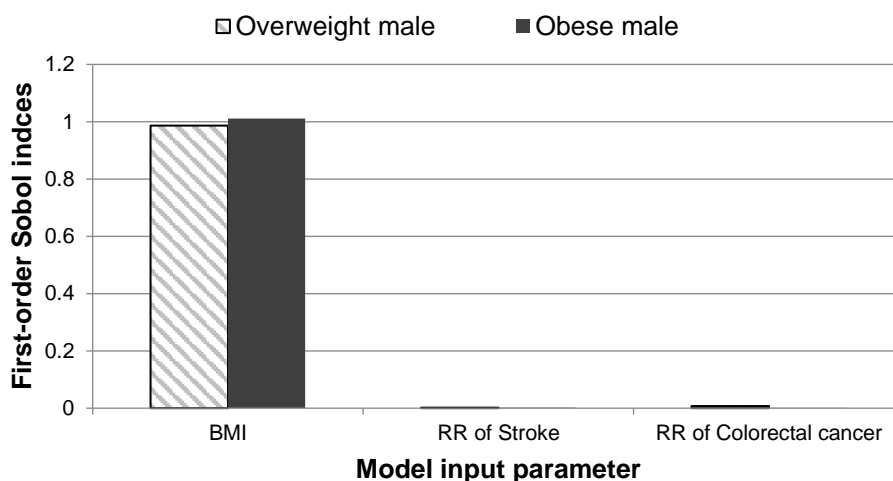
The mean, standard deviation and variance of the disease-free life expectancy are summarised in Table 4. The mean number of year's disease free was shown to be greater for the overweight male compared to the obese male 63 and 48 years, respectively. The standard deviation around the obese male mean disease-free life expectancy was similar to the standard deviation around the overweight disease-free life expectancy mean.

Table 4: Summary of the mean, standard deviation and variance for the disease-free life expectancy for the two case studies.

Case study	Mean (years)	Standard deviation (years)	Variance (years ²)
Overweight male	63.47	3.41	11.59
Obese male	48.32	3.14	9.87

The individual impact of the uncertainty of the three input parameters on the disease-free life expectancy is shown in Figure 2. The graph shows the first-order Sobol indices for each of the three input parameters. The first parameter, which relates to the BMI value, is shown to have the greatest impact on the overall uncertainty of the disease-free life expectancy output for both the overweight and obese males. The smallest impact is from the parametric uncertainty of the relative risk of stroke for both case studies. For the overweight male, there was shown to be a much larger difference between the BMI and relative risk first-order Sobol indices.

Figure 2: A graphical illustration of the first-order Sobol indices for each model input parameter: BMI, relative risk of stroke and relative risk of colorectal cancer for disease-free life expectancy.



The second-order Sobol indices were not strictly positive and did not contribute to the uncertainty of the disease-free life expectancy.

3.2 Life expectancy

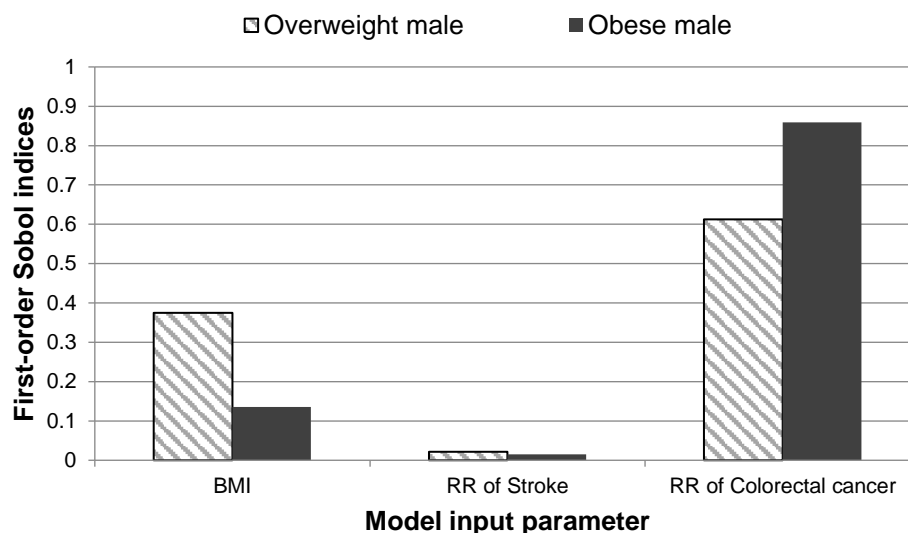
The impact of the parametric uncertainty of the three model input parameters on the life expectancy was much smaller compared to the disease-free life expectancy. Table 5 shows the mean, standard deviation and variance life expectancy for each case study.

Table 5: Summary of the mean, standard deviation and variance for the life expectancy for the two case studies.

Case study	Mean (years)	Standard deviation (years)	Variance (years ²)
Overweight male	79.76	0.11	0.01
Obese male	79.17	0.31	0.09

There was a mean life expectancy difference of approximately 0.6 years between the overweight and obese individuals. The standard deviations for the overweight and obese individuals were 0.11 and 0.31 years, respectively. The first-order Sobol indices were analysed for both case studies and the results are presented in Figure 3. The results show that the uncertainty from the relative risk of colorectal cancer contributes the most to the overall uncertainty of the life expectancy. However, the BMI also contributes to the uncertainty.

Figure 3: A graphical illustration of the first-order Sobol indices for each model input parameter: BMI, relative risk of stroke and relative risk of colorectal cancer for life expectancy.



The second-order Sobol indices were not strictly positive and did not contribute to the uncertainty of the life expectancy.

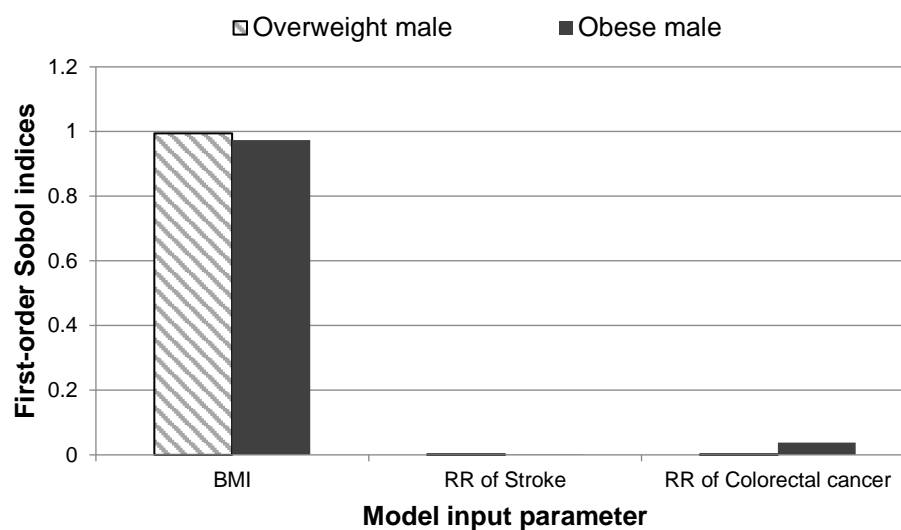
3.3 Quality-adjusted life years

The mean quality-adjusted life years for an overweight and an obese male were 75 and 70 years, respectively (Table 6). The standard deviations around each of the case studies were similar.

Table 6: Summary of the mean, standard deviation and variance for the quality-adjusted life years for the two case studies.

Case study	Mean (years)	Standard deviation (years)	Variance (years ²)
Overweight male	75.09	1.01	1.02
Obese male	70.06	1.06	1.12

The impact from each of the model parameters is shown in Figure 4. The relative impact from each of the three model parameters on the uncertainty of the quality-adjusted life year outputs were similar to the results observed for disease-free life expectancy. BMI has the greatest contribution to the overall uncertainty of the quality adjusted life years for both the overweight and obese case studies. In the overweight case study, BMI is the only model parameter which contributes to the quality-adjusted life year uncertainty when compared to the relative risk of stroke and relative risk of colorectal cancer. For the obese male both BMI and the relative risk of colorectal cancer have an impact on the uncertainty of this model output.

Figure 4: A graphical illustration of the first-order Sobol indices for each model input parameter: BMI, relative risk of stroke and relative risk of colorectal cancer for quality-adjusted life year.

The second-order Sobol indices were not strictly positive and did not contribute to the uncertainty of the quality adjusted life year.

4 DISCUSSION

We have estimated the uncertainty of three model outputs: life expectancy, disease-free life expectancy and quality-adjusted life years in an individual based model. Global sensitivity analysis was carried out to calculate the contribution from BMI trends, relative risk of stroke and relative risk of colorectal cancer on the uncertainty of the life expectancy, disease-free life expectancy and quality-adjusted life years. An overweight and an obese male were modelled as case studies. BMI is

shown to have an impact on the mean disease-free life expectancy and quality-adjusted life years and only a small impact on mean life expectancy. From the three input parameters investigated only the uncertainty from the BMI trends contributed to the uncertainty of the disease-free life expectancy and the uncertainty of the quality adjusted life year for the overweight case study. However, the life expectancy uncertainty was influenced by the BMI trends and relative risk of colorectal cancer uncertainties. To our knowledge, this is the first time that global sensitivity analysis has been applied to an individual-based chronic disease model (Hennessy et al., 2015; Lymer et al., 2016; Manuel et al., 2014).

4.1 Disease-free life expectancy

An individual's disease-free life expectancy was calculated by the summing over the annual probabilities that an individual lived without a disease in their lifetime. The model simulated additional obesity-related diseases which were not included in the global sensitivity analysis. The uncertainties for these parameters were not included because the uncertainty estimates around these model input parameters were difficult to reliably source. These model parameters included the relative risks of type 2 diabetes, hypertension and coronary heart disease. The probability that an individual acquired a disease was primarily driven by BMI. The uncertainty of the relative risk of stroke and colorectal cancer did not have an effect on the incidence of type 2 diabetes, hypertension and coronary heart disease. The uncertainty of the BMI trends was therefore likely to have a larger influence on the disease-free life expectancy uncertainty.

A large difference in the mean disease-free life expectancy was observed between an overweight and an obese male. This was expected because obese individuals have a greater probability of acquiring obesity related diseases. The uncertainty of the disease-free life expectancy for the obese male was relatively larger than the overweight male disease-free life expectancy. This is related to there being a greater uncertainty around the model input parameters for the obese male.

4.2 Life expectancy

The contribution from the model input parameters to the uncertainty of life expectancy was more distributed amongst the model inputs for the overweight and obese male. The uncertainty of the life expectancy estimate was much smaller compared to the uncertainty of the disease-free life expectancy. The model also takes account of deaths from other causes. The uncertainty of the mortality rates from other causes was not incorporated into this uncertainty analysis. Therefore, uncertainty reported in this study is likely to underestimate the total uncertainty. The BMI trends

are likely to have had a smaller effect on life expectancy compared to disease-free life expectancy because of the type of additional diseases that were modelled in this study. Type 2 diabetes and hypertension were non terminal diseases, which would not impact on the life expectancy. As previously discussed these diseases did have an impact on disease-free life expectancy. Moreover, each case study had vastly different BMI levels, 27.5 kg/m² and 37.5 kg/m² and only a small difference was observed in the mean life expectancy. This evidence suggests that the uncertainty in BMI levels would only have a small impact on the life expectancy uncertainty. The uncertainty of the relative risk of colorectal cancer also contributed to the uncertainty of life expectancy compared to the relative risk of stroke. The uncertainties around relative risks for colorectal cancer were greater than the uncertainties for the stroke relative risks. Therefore, the colorectal cancer relative risk uncertainties were more likely to contribute to the life expectancy uncertainties compared to the stroke relative risks.

4.3 Quality-adjusted life year

The total quality-adjusted life years for an individual were calculated based on the probability that an individual had a particular disease and the probability that an individual was disease free. The probability that an individual had a particular disease was scaled by the QoL of the individual in a given year. The average QoL was estimated from the diseases that an individual may have in a given year. The QoL for an individual varies between zero (dead) and one (alive and disease-free). The quality-adjusted life year for an obese individual was lower compared to the overweight individual. This is because an obese individual is more likely to be living with obesity related diseases. It is unlikely that the probability of death had an impact on this difference in the quality-adjusted life years between the overweight and obese individual because there were only very small differences between the mean life expectancies of the two case studies.

BMI was the only model parameter to contribute to the uncertainty of quality-adjusted life year for the overweight case study. A similar outcome was observed for the disease-free life expectancy. BMI and the relative risk of colorectal cancer contributed to the uncertainty of the quality adjusted life years for the obese individual. Colorectal cancer had a QoL equal to 0.68 compared to stroke which had a QoL equal to 0.713. The diseases that have a lower QoL are likely to have a larger impact on the quality-adjusted life years. In addition, the obese individual had a higher chance of acquiring colorectal cancer compared to the overweight individual. Therefore, it was more likely that the uncertainty of the colorectal cancer relative risks would have a larger impact on the uncertainty of this model output for the obese individual. Additional diseases were included in the

simulation but not in the uncertainty analysis. Diseases such as type 2 diabetes also have a relatively low QoL equal to 0.66. It is highly likely that the uncertainty of the relative risks for type 2 diabetes would also have an influence on the uncertainty of the quality-adjusted life years if they were included in the uncertainty analysis.

4.4 Limitations

There are limitations in this study with regards to the sources of uncertainty, the assumptions used to approximate the uncertainty and the small subset of parameters assessed. One limitation relates to the estimation of the uncertainty from the BMI trends. The average uncertainty was obtained from averaging the uncertainty across each five year age group and BMI category and up to 100 years into the future. However, the uncertainty in the BMI projections did not remain constant and actually increased over time. The uncertainty of the BMI used in this analysis is likely to be an overestimate. Further work will investigate whether a time varying uncertainty can be included in the global sensitivity analysis. This is particularly important because the time horizon of interest will vary depending on the starting age of an individual. Future work will need to adapt the uncertainty estimation based on the time horizon of interest. Another limitation relates to the sample size used by the PSUADE program. This was set to 20,000 samples. However, after the samples were filtered based on the constraints, the sample size was reduced to 31% and 12% of the original samples for the overweight and obese case studies, respectively. In order to scale this process to the microsimulation, an optimal number of samples required will need to be assessed to minimise the computational time taken to run the model.

We were unable to obtain uncertainty estimates for all of the parameters used in the model. A high number of model input parameters were sourced from published literature (see the online supplementary material for further details). In many cases the uncertainties of these point estimates were not provided. In this study it was only possible to obtain the standard deviations around one overweight and one obese relative risk for stroke and colorectal cancer (Guh et al., 2009). The uncertainties were not disaggregated by age or sex. However, a different source was used to approximate the mean point estimates for the model (World Obesity Federation, 2008). Overweight and obese case studies were chosen based on the uncertainty data available for relative risks. These data were more granular and were broken down by age, sex and BMI groups. More granular data was preferred for the individual based model, as the relative risks varied between different age, sex and BMI groups. The standard deviations obtained from the less granular relative risks were used as a proxy for the granular relative risks. These uncertainties may have been

overestimated because age, sex and BMI may have contributed to the uncertainty around the less granular relative risks. In general, the risk of these diseases increases with age. Therefore, the uncertainty used when the individual was in their 20's to 40's may have overestimated the uncertainty from these parameters. Although, when an individual reached an older age, this uncertainty may have been underestimated. This will depend on the original cohort used to estimate the relative risks and their associated uncertainties.

We have addressed only parametric uncertainty in this study. We did not address structural uncertainty. By their nature, model parameters are, however, conditional on model structure. Structural uncertainty is concerned with the uncertainty in the structure of the model. This can take several forms such as the uncertainty in the high-level methodological assumptions made to construct the model (e.g. in relation to characterising the health trajectory of an individual), the uncertainty in the number of state variables in the model (e.g. number of disease and health states), the uncertainty in the relationships governing the associations between the model variables (e.g. the associations between disease relative risk and BMI and age). There are various methods to address structural uncertainty but we have not incorporated any of them in this study (Bojke, Claxton, Sculpher, & Palmer, 2009; Strong, Oakley, & Chilcott, 2012).

This study has focused on a method for assessing parametric uncertainty in complex nonlinear models. This is important for models where the outputs are used by decision makers and therefore need to be trusted. Modelling standards for good research practices have been developed by the International Society for Pharmacoeconomics and Outcomes Research to improve the reliability and transparency of models reported in the literature (Caro, Briggs, Siebert, & Kuntz, 2012). These good research practices highlight the need to include uncertainty analysis in addition to validation and comparisons with other models in the field. Internal and external validation is an important and consistent theme across a number of modelling guidelines (American Diabetes Association Consensus Panel, 2004; Caro et al., 2012; Palmer et al., 2013). The uncertainty analysis method described in this study will contribute towards standardising dissemination of modelling outputs.

4.5 Future work

This study has focused on a small subset of model input parameters to demonstrate the application of applying global sensitivity analysis techniques to an individual based model, a simplified version of the UK Health Forum (UKHF) microsimulation model. This study is a precursor for applying global sensitivity analysis to the UKHF microsimulation model. Future work will increase the number of model input parameters that are incorporated into the global sensitivity analysis. In

addition, the method will be scaled up in order to incorporate differences from within a population in the microsimulation model. However, future analyses will optimise this process by identifying the key model input parameters that contribute to the uncertainty of different model outputs and assess the sample and population sizes required to obtain accurate uncertainty estimates which can help inform public health policies.

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NOTES

¹ The average BMI was approximated from the BMI distribution in 2013 as predicted by the static trend. The BMI was calculated from the average BMI category percentile mean, lower and upper bounds.