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Assessing the health and economic burden of obesity-related complications in East-Asian populations: implementation of risk equations in the Core Obesity Model for Japan and model validation

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ABSTRACT

Objective Obesity is associated with a significant clinical and economic burden and its prevalence has reached epidemic proportions worldwide. An ethnicity-specific impact of excess weight has been demonstrated, with Asian individuals exhibiting weight-related health problems at lower body mass indexes (BMIs) than Caucasians. We aimed to adapt the core obesity model (COM) to predict incidences of weight-associated diseases, including type 2 diabetes, acute coronary syndrome (ACS), stroke, cancers, sleep apnoea, hyperuricaemia/gout, total knee replacement (TKR) and non-alcoholic fatty liver disease (NAFLD) in a Japanese population.

Methods and analysis Literature was searched to identify studies reporting the association between risk factors and comorbidities in Japanese populations. Data were extracted to update the COM risk prediction equations. Internal and external validation were performed.

Results Overall, good internal validity was achieved, with mild underestimation for diabetes, cardiovascular and all-cause death taken together (ordinary least squares linear regression [OLS-LRL] 0.8844), moderate overestimation of TKR and cancers (OLS-LRL 1.267) and a slight underestimation for NAFLD and hyperuricaemia (OLS-LRL 0.934). External validation results were aligned with known geographical patterns: complications occurred at lower BMI in Japanese individuals, with a threefold higher incidence of diabetes and twofold higher obstructive sleep apnoea, gout prevalence and colorectal cancer at equal BMI. Conversely, the 10-year cumulative ACS incidences predicted in a Japanese population were less than half of those in a Western population.

Conclusion The Japanese COM adaptation addresses ethnicity-specific patterns of overweight/obesity, with better sensitivity to lower BMIs for several associated complications. It may support regional public health policy and research.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The core obesity model (COM), which quantifies the association between risk factors and incidence of obesity-related complications, is based on data specific to Caucasian/Western populations.

⇒ As Japanese individuals exhibit health burdens from excess weight at a lower body mass index (BMI) than Caucasian populations, the objective of the current work was to identify relevant data sources and use these to expand and validate the COM for use in a Japanese clinical setting.

WHAT THIS STUDY ADDS

⇒ An adapted model for prediction of weight-related complications in a Japanese population was developed.

⇒ The adapted model had good external validity, showing an increased risk of type 2 diabetes, total cardiovascular events, sleep apnoea, colorectal cancer and gout starting from lower BMI levels in Japan compared with Western populations.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study will facilitate obesity-related health and economics research in Japan, facilitating analyses of the risk of obesity-related complications and the impact of therapeutic interventions on these complications in a Japanese population.

INTRODUCTION

Obesity is a multifactorial disease characterised by excessive adiposity and defined internationally by a body mass index (BMI) of ≥30 kg/m^2.[1 2] Individuals with obesity experience direct and significant impairments of their well-being and functioning[3 4] and are at increased risk of non-communicable, disabling and life-threatening health conditions, particularly cardiovascular (CV) disease (CVD) and type 2 diabetes (T2D), several types of cancers and musculoskeletal disorders.[1] The rise in overweight and obesity is a

global public health challenge, with a high prevalence in the USA[5] and Europe[1] and a robust rising trend observed in Asia.[6 7]

The ethnicity-specific impact of excess weight adds to the complexity of the disease, for example, at the same BMI level, Asian individuals may have larger areas of abdominal and visceral adiposity[8 9] and an increased risk of CVD and glucose intolerance than Caucasians.[10] Furthermore, it was demonstrated that the health burden of excess weight was present at a lower BMI level in a Japanese vs an Australian population.[11] Reflecting this, alternative BMI cut-offs were proposed by the WHO for Asian individuals, with a BMI of 23 to <27.5 kg/m² classified as overweight and a BMI of 27.5 kg/m² or above for obesity.[12] Since 2002, the Japan Society for the Study of Obesity (JASSO) adopted an even lower threshold for 'first-degree obesity' of BMI≥25 kg/m²,[13] corresponding to the Western threshold for 'overweight'.

In its guidelines, the JASSO specifies the comorbidities associated with obesity and overweight. These include hyperuricaemia and gout, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), the spectrum of menstrual disorders and severe chronic kidney disease (CKD) or kidney failure.

Another example of a well-established geographical pattern is the inverse ratio of coronary heart disease (CHD) to stroke, with stroke occurring more frequently than CHD in Asia.[14 15]

Due to the increased risk of developing acute and chronic complications, obesity carries a high economic burden to healthcare payers and patients.[16 17] Japanese adults with obesity were reported to have an 8.2% higher medical expenditure compared with individuals of normal weight.[18]

Given the known differences in the type and incidence of complications between Western and Japanese populations, combined with a lower BMI threshold for obesity, the objectives of the current study were to identify relevant sources for clinical event rates and adapt an existing, published, cost-effectiveness model, the core obesity model (COM),[19 20] as well as to validate its use in Japanese populations.

MATERIALS AND METHODS

The COM[19 20] is a Markov cost-effectiveness model whereby costs and quality-adjusted life-years (QALYs) can be estimated and compared across various weight-loss interventions. The association between changes in risk factors and transition probabilities (ie, incidence of complications) in the COM is quantified via published, landmark studies, so far specific to Caucasian/Western populations.[21–23] A change in BMI is modelled to result in a change in the incidence of obesity-related complications. Other time-dependent mediators in the COM are glycaemic status (or glycated haemoglobin A_{1c} in T2D), systolic blood pressure (SBP) and lipids.

Targeted literature search and data extraction

A targeted literature search was conducted in June 2021 to identify studies reporting the association of risk factors (weight, SBP, lipids and glycaemic levels) and comorbidities (including T2D, acute coronary syndrome (ACS), including myocardial infarction (MI) and unstable angina (UA), stroke, including transient ischaemic attack (TIA), total knee replacement (TKR) surgery following osteoarthritis, obstructive sleep apnoea (OSA) and cancers) existing in the COM. The search was extended to include comorbidities identified by the JASSO as being associated with obesity and preobesity. The search scope and terms are shown in online supplemental appendix S1, tables S1 and S2.

Selection criteria were defined to retain in priority large, prospective, population-based, recent (published in the last 10 years) studies establishing a quantitative link between BMI as a continuous variable and the risk of having or developing targeted complications, adjusted based on demographic and clinical factors. The link between BMI and health-related quality of life (HRQoL) as measured by the EuroQoL-5 Dimension (EQ-5D) utility index was also targeted. Predicted events having a tangible, measurable impact on patient HRQoL and/or medical management cost were preferred over the medical condition: TKR rather than 'osteoarthritis', gout incidence rather than 'hyperuricaemia', use of continuous positive airway pressure (CPAP) device rather than 'OSA', liver cancer or cirrhosis or transplantation rather than earlier NAFLD/NASH stages. Additional parameters that were expected to be region-specific, such as the ratios of CHD to stroke and fatality rates for CV events, were also searched in East-Asian literature, favouring recent publications of large, prospective cohorts.

Where necessary, published curves were read and data points were extracted into Microsoft Excel using WebPlotDigitizer online tool V.4.5. A clinical expert from the Chiba Prefecture University (Japan) critically reviewed the choice of studies and validated the outcomes.

Validation methods

General population age-specific and sex-specific mortality were sourced in alignment with the population of the source studies. The impact of time preferences on outcomes, referred to as 'discounting' in economic evaluations, was not considered, that is, the discount rate on future outcomes was set to zero, as the intention was to validate clinical endpoints 'as they occur' without confounding by time valuation.

Test cohorts

For each predicted complication, model baseline characteristics were set equal to the baseline characteristics of the cohort enrolled in the source studies to control for any potential differences between the observed and predicted outcomes attributable to population-adjustable risk factors in the COM. In total, six profiles were defined from the Japan Epidemiology Collaboration on

Table 1 Baseline characteristics of the cohorts used for model validation, male

Source study		Hu *et al*[24]			Bae *et al*[25]	Yu *et al*[26]
	Time	Men	Men	Men	Men	Men
Baseline characteristics*	Dependent	m1	m2	m3	m4	m5
Age, years	Yes	45.4	45.6	42.9	51.8	58.8
BMI, kg/m^2	Yes	22.1	26.8	32.4	24.2	23.5
SBP, mm Hg	Yes	119.6	126.6	132.8	117.5	117.50
Total cholesterol, mg/dL	Yes	201	212	216	198	191
HDL-C, mg/dL	Yes	59.0	51.1	47.7	45.1	55.3
HbA_{1c} from T2D onset, %†	Yes	7.6	7.6	7.6	7.6	7.6
T2D duration, years†	Yes	4.5	4.5	4.5	4.5	4.5
TG, mg/dL	No	117	160	175	173	95
% with dyslipidaemia‡	No	40	65	75	53	53
% with WC≥80 or 90 cm	No	5	58	97	20	20
Smokers, %	No	42	42	46	49	59
On lipid-lowering drugs, %	No	3	7	12	6	6
On antihypertensive medication, %	No	7	14	23	13	13
High blood pressure, %§	No	16	30	47	24	28
NGT, %	Yes	67	54	50	49	50
Pre-diabetes, %¶	Yes	33	46	50	36	36
T2D, %	Yes	0	0	0	15**	14
Utility score, predicted	Yes	0.933	0.928	0.926	0.922	0.911

*Statistics for numerical variables are means.
†Estimated from the study by Luo *et al*.[79]
‡Dyslipidaemia is defined as TG ≥150 mg=dL, LDL-C ≥140 mg=dL, HDL-C<40 mg=dL or as receiving medical treatment for dyslipidaemia, based on the criteria of the Japan Atherosclerosis Society.[80]
§Hypertension is defined as SBP≥140 mm Hg, DBP ≥90 mm Hg or as receiving medical treatment for hypertension, based on the criteria of The Japanese Society of Hypertension guidelines for the management of hypertension.[81]
¶Estimated based on the mean SD fasting glucose (FG) measured at study baseline and assuming a normal distribution with a threshold of 100 mg/L defined as pre-diabetes FG.
**Set to zero in the validation of T2D cumulative incidence.
BMI, body mass index; DBP, diastolic blood pressure; HbA_{1c}, glycated haemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; m1–5, male profiles; NGT, normal glucose tolerance; SBP, systolic blood pressure; T2D, type 2 diabetes; TG, triglycerides; WC, waist circumference.

Occupational Health (J-ECOH) study[24]: three for males (m1–3; table 1) and three for females (w1–3; table 2), each with a different starting BMI. Two further profiles (one male (m4) and one female (w4)) were defined for the internal validation of T2D and CVD incidences from the Korean Genome and Epidemiology Study (KoGES),[25] and two profiles (one male (m5) and one female (w5)) were defined for the internal validation of CV events from the China Health and Nutrition Survey (HNS).[26] Throughout the analysis time horizon, the average BMI of the cohort was assumed to increase by 0.5 kg per year in the m2–5 and w2–5 profiles while it was kept equal to baseline in the normal weight (m1, w1) profiles.

Internal validation

For internal validation of the model predictions, (1) the model was run with all risk equations set to Japanese/East-Asian sources and (2) predicted outcomes (eg, event rates at study horizon) were compared with the observed outcomes in the source studies for each endpoint and for cohort profiles aligned with source studies.

There is no consensus on the best statistical method for comparing model predictions with observed outcomes.[27] Here, model concordance was assessed by plotting the predicted outcomes (y-axis) against the observed study endpoints (x-axis). A 45° identity line (IL), representing a situation whereby the predicted and observed results matched perfectly, was plotted. Overpredictions or underpredictions were indicated by large numbers of points above or below the IL, respectively. Additionally, an ordinary least squares linear regression line (OLS-LRL) was fitted to the observed data. This had an intercept of zero to attribute more weight to the OLS-LRL slope. A value for the slope markedly lower than 1.0 suggests underprediction by the model and a value greater than 1.0 suggests overprediction. The coefficient of determination (R-squared (R^2)) was checked, to assess

Table 2 Baseline characteristics of the cohorts used for model validation, female

Source study		Hu *et al*[24]			Bae *et al*[25]	Yu *et al*[26]
	Time	Women	Women	Women	Women	Women
Baseline characteristics*	Dependent	w1	w2	w3	w4	w5
Age, years	Yes	43.9	45.9	44.7	52.7	58.8
BMI, kg/m^2	Yes	20.6	26.9	32.7	24.9	23.9
SBP, mm Hg	Yes	113.7	124.6	132.2	117.5	117.50
Total cholesterol, mg/dL	Yes	197	211	212	195	199
HDL-C, mg/dL	Yes	71.3	59.9	56.3	47.4	57.2
HbA_{1c} from T2D onset, %†	Yes	7.6	7.6	7.6	7.6	7.6
T2D duration, years†	Yes	4.5	4.5	4.5	4.5	4.5
TG, mg/dL	No	72	104	117	144	83
% with dyslipidaemia‡	No	20	48	54	47	47
% with WC≥80 or 90 cm	No	18	92	100	58	58
Smokers, %	No	11	11	14	4	3
On lipid-lowering drugs, %	No	3	7	7	6	6
On antihypertensive medication, %	No	3	10	13	13	13
High blood pressure, %§	No	8	21	39	26	26
NGT, %	Yes	89	74	59	63	63
Pre-diabetes, %¶	Yes	11	26	41	24	24
T2D, %	Yes	0	0	0	13**	13
Utility score, predicted	Yes	0.923	0.916	0.901	0.913	0.904

*Statistics for numerical variables are means.
†Estimated from the study by Luo *et al*.[79]
‡Dyslipidaemia is defined as TG ≥150mg=dL, LDL-C ≥140 mg=dL, HDL-C<40 mg=dL or as receiving medical treatment for dyslipidaemia, based on the criteria of the Japan Atherosclerosis Society.[80]
§Hypertension is defined as SBP ≥140 mm Hg, DBP ≥90 mm Hg or as receiving medical treatment for hypertension, based on the criteria of The Japanese Society of Hypertension guidelines for the management of hypertension.[81]
¶Estimated based on the mean SD fasting glucose (FG) measured at study baseline and assuming a normal distribution with a threshold of 100 mg/L defined as pre-diabetes FG.
**Set to zero in the validation of T2D cumulative incidence.
BMI, body mass index; DBP, diastolic blood pressure; HbA_{1c}, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NGT, normal glucose tolerance; SBP, systolic blood pressure; T2D, type 2 diabetes; TG, triglycerides; w1–5, female profiles; WC, waist circumference.

the relevance of the linear model (R^2 closer to 1 is indicative of better linear fit).

External validation

For external validation of the model predictions, (1) the model was run with all risk equations set to Western sources with a time horizon of 10 years and using the six profiles of the J-ECOH study described above and (2) predicted outcomes within each cohort were compared between Western and Japan to check whether known regional specificities are reflected in the results.

The following Western risk equations were used, as available in the COM: QDiabetes[22] for predicting the incidence of T2D, and QRisk3[23] and Framingham Recurring[28] for predicting the incidence of first and recurrent CV events, respectively, in both non-T2D and T2D. Meta-analyses were used to predict the incidence of colon,[29] postmenopausal breast[30] and endometrial cancer[31] in a Western population. Studies by Wendelboe *et al*,[32] Kuwabara *et al*[33] and Chen *et al*[34] were used to predict TKR surgery as a result of debilitating osteoarthritis, hyperuricaemia and gout, respectively. OSA prevalence was predicted using the Sleep Heart Study.[35] UK life-tables[36] were used in the Western setting.

Patient and public involvement

There was no patient or public involvement in the study.

RESULTS

Implementation of risk equations for Japan

The studies identified in the targeted literature review and used to predict event rates are shown in online supplemental table S3 and figure S1. The steps undertaken to make published results suitable for risk prediction in the model are summarised here and in online supplemental table S4 and are described in full in online supplemental appendix S2. The updated COM structure

accounting for Japan-specific complications is shown in online supplemental figure S2.

Type 2 diabetes

Risk in individuals with normal glucose tolerance

Two risk functions were implemented in the COM to estimate the risk of T2D development in the Japanese population: the J-ECOH[24] and the KoGES.[25] Separate risk equations including age and BMI as parameters were developed for males and females using the cumulative incidences at 35 years published in the J-ECOH.

A similar approach was taken for the implementation of the KoGES study. However, this study did not report age-specific incidences, thus, age-dependent ratios were recalculated using data from Hu *et al*[24] and taking the baseline age in KoGES as a reference and recomputing age-dependent incidences within each of the eight BMI categories reported. This resulted in two incidence functions (for males and females separately) by log-transformed age and BMI.

Adjustment for baseline pre-diabetes

Both studies, J-ECOH and KoGES, reported a total incidence of T2D reflecting the cohorts' glycaemic status at baseline. Given that normal glucose tolerance (NGT) and pre-diabetes represent distinct health states in the COM, each of them requires a specific transition probability to the T2D state. The total risk of T2D was thus corrected, that is, adjusted considering a relative risk (RR) of 2:1 for T2D development in pre-diabetes versus NGT.[37]

Cardiovascular disease

Risk of first CV event in individuals with NGT

There was a paucity of studies to predict the risk of incident CV events as a function of BMI in Japan, and more generally East Asian populations. Based on the evidence identified to date, the prediction of transition probabilities and event rates in the COM was done sequentially, aiming to preserve the relative weight of each event in the overall CVD risk. The incidences of ischaemic and haemorrhagic strokes were predicted via a multivariable risk model from the China HNS.[26] As this was a study in a Chinese population, the proportion of total strokes predicted was redistributed by subtype to ensure a Japanese representative number of ischaemic strokes in the total stroke events (64% ischaemic, 36% haemorrhagic) based on Japanese data from the Shiga Stroke and Heart Attack Registry.[38] Next, the stroke rate was adjusted upwards to include TIAs based on a prospective study in Japan[39] reporting a TIA rate of 6.4% among a total of 16 922 acute ischaemic stroke or TIA events. Finally, a total CV event rate was calculated by adjusting the stroke plus TIA rate upwards to also include ACS, representing 25% of total CV events.[40] ACS was further split into MI and UA, respecting a ratio of 1.56.[41]

First CV event in individuals with T2D

In patients with T2D, the total CV risk was increased vs NGT using an RR of 2.27 (95% CI 1.95 to 2.65) for ischaemic stroke and an RR of 1.56 (95% CI 1.19 to 2.15) for haemorrhagic stroke.[42] Risks of TIA and CHD were recalculated from the risk of stroke using the same ratios, and the same repartition of MI/UA, as described for the NGT population.

Recurrent CV events in individuals with NGT or T2D

In patients with established CVD, the risk of further CV events was estimated using the modified Essen stroke model,[43] and the annual probability of an event was redistributed between stroke/TIA and CHD (MI/UA) using the same ratios by subtype as described above. The prediction model included age, sex, hypertension, diagnosis of T2D, previous MI and smoking status among other factors not modelled in the COM.

Cancers

Colorectal cancer

The risk of developing colorectal cancer (CRC) was estimated from a prospective study of eight Japanese cohorts.[44] In the study, the incidence increased with participants' BMI, with an RR of incident CRC of 1.03 (95% CI 1.02 to 1.04) per unit BMI increase above the reference in males and 1.07 (95% CI 1.05 to 1.08) in females. Multiplying the incidence in the reference group with the RR per unit BMI, a sex-specific CRC incidence was calculated for the COM.

Breast cancer, postmenopause

In postmenopausal women, the risk of developing breast cancer was estimated from a pooled analysis of eight Japanese cohorts.[45] The observed incidence was 79.7 per 100 000 person-years, at a reference mean BMI of 23.3 kg/m^2. The RR of incident breast cancer per unit BMI increase was 1.05 (95% CI 1.04 to 1.07). Then, the incidence rate in the reference group was multiplied by the RR per unit BMI. The average menopausal age was assumed to be 51 years in the East-Asian region.[46]

Endometrial cancer, postmenopause

In postmenopausal women, the risk of developing endometrial cancer was estimated from a Mendelian randomisation analysis using the Genome-Wide Association Study (GWAS) of the BioBank Japan (BBJ) project.[47] For uterine endometrial cancer, a significant OR of 1.22 (95% CI 1.08 to 1.38) per unit BMI increase was found. This was applied to a calculated baseline endometrial cancer rate of 40.11 per 100 000 female-person-years aged ≥45[48] in the reference BMI (23.3 kg/m^2) in the GWAS BBJ.[49]

Obstructive sleep apnoea

The prevalence of OSA was informed via a multifactorial risk equation[50] including BMI, age, sex, hypertension and T2D. Considering the distribution of Apnoea-Hypopnoea Index (AHI) in the study (mean±SD 24.1±24.3), the predicted OSA prevalence was restricted to only include severe OSA (AHI≥20), expected to require a CPAP device.[51]

Total knee replacement

The TKR incidence in a large claims analysis in Japan was 65.2 per 100 000 person-years (at a mean BMI of 23 kg/m^2).[52] The total incidence was redistributed as per the Japanese population structure, to reflect a lower TKR rate in males versus females (ratio of 1:4), and in those aged below 65 vs those above 65 years (ratio of 1:10) reported in the same study. The RR per unit increase in BMI was sourced from a prospective population-based cohort of the Singapore Chinese Health Study.[53] A strong association between BMI and TKR risk across the range 15–32 kg/m² was observed in this study with an estimated HR of 1.28 in males and 1.27 in females per unit BMI increase. The incidence rate in the reference group was multiplied by the HR per unit BMI up to a maximum of 32 kg/m². Beyond this BMI value, the predicted incidence was 'capped' at a constant rate.

Hyperuricaemia and gout

Hyperuricaemia prevalence per unit BMI has been estimated in a Japanese population, adjusting for confounding demographic and clinical factors, such as T2D, hypertension and dyslipidaemia.[33] The OR 1.157 (95% CI 1.148 to 1.166) per unit BMI was applied (after being transformed to an RR) to the prevalence of hyperuricaemia in the reference population (BMI 22.4 kg/m^2), being 13.5%. The findings of Chen *et al*[34] confirmed that hyperuricaemia is a significant risk factor for gout, especially in males and females aged 50 or older, and provide age-specific and sex-specific estimates of gout incidence in the COM. The combined findings of these studies were used to include hyperuricaemia and gout in the Japanese COM.

NAFLD/NASH, decompensated liver cirrhosis, liver cancer and transplant

Results from Pang *et al*[54] were used to derive the prevalence of NAFLD in the COM, applying a 1.23 RR per unit BMI increase to a reference group (BMI 23.3 kg/m²) prevalence of 30% and 15%, respectively, in males and females.[55] A multicountry (including Japan), full-disease model by Estes *et al*[56] shows the complexity of a complete NAFLD disease model, that is, the number of transition probabilities required to track the progression from NAFLD until end-stage liver disease. In the COM, the health states distributions predicted by the published model were used to fill in the gap, creating a direct link between NAFLD and the probability of late-stage liver diseases: decompensated liver cirrhosis, liver cancer and liver transplant.

Quality of life

The Chinese study of Xu *et al*[57] was used as an East-Asian alternative to the 'Western' BMI-dependent age and sex-dependent baseline utility curve.[58] In both cases, an inverse U-shaped association was observed between continuous BMI and HRQoL as measured by the EQ-5D 3 levels. The loss in quality of life caused by the events and complications in the COM were found in a catalogue of disease-specific disutilities for the Japanese population[59]: T2D (−0.046), malignant neoplasm, applied to all cancers and to decompensated liver cirrhosis in NAFLD patients (−0.084), acute MI/UA (−0.073), acute stroke (−0.265), gout (−0.012). For other complications, additional published literature was used: OSA (−0.047),[60] chronic, postevent states (−0.040 post-CHD, −0.240 post-stroke)[61] and liver transplant (−0.054).[62] NAFLD was associated with a disutility only in case of liver cancer, decompensated cirrhosis and transplant. No disutility was found related to TKR in the East-Asian literature, thus the value used in Western settings was applied (−0.023).[63]

Mortality

As described in a published abstract,[64] the COM accounts for mortality in three ways: (1) general population, age-specific and sex-specific mortality rates, non-specific to the diseases under study, adjusted to exclude causes later accounted for in the model and to avoid double counting; (2) disease-specific mortality and (3) BMI-dependent HR, that is, an increase or decrease in mortality rates per unit BMI change. In the Japanese setting, the 2020 life tables[65] provided general mortality rates (component 1). Component 2 was based on case fatality rates (death within 1 month of CV event) identified in the Japanese literature: 13.6% for stroke events[39] and 38.8% for CHD events, assuming equal fatality for MI and UA.[66] The HRs of all-cause death post-CV events were kept as per the global COM, using Johansson *et al*[67] and Brønnum-Hansen *et al*.[68] For component 3, the literature on a direct, rather than complications-related link between BMI and all-cause mortality[25] was non-conclusive. Hence, the HR applied in the third component is currently set to 1, meaning no additional effect is implemented in the Japanese adaption of the COM.

Internal validation: predicted versus observed

T2D cumulative incidence was well predicted in males with normal and preobesity weight (m1, m2, m4 profiles, respectively) and was moderately underpredicted in males with obesity (m3). The same trend could be observed in females, with moderate overprediction in females with normal and preobesity weight and moderate underprediction in females with obesity (w3). The cumulative incidence of stroke events tended to be moderately overpredicted in males with preobesity (m5) and underpredicted in females (w5). Total CV events were underpredicted in both males and females with preobesity weight (m4 and w4 profiles, respectively) and so was all-cause mortality. Overall, the results displayed a high degree of linear correlation (R^2=0.9678), and a mild degree of underestimation of validation outcomes (indicated by the OLS-LRL slope 0.8844) (figure 1A).

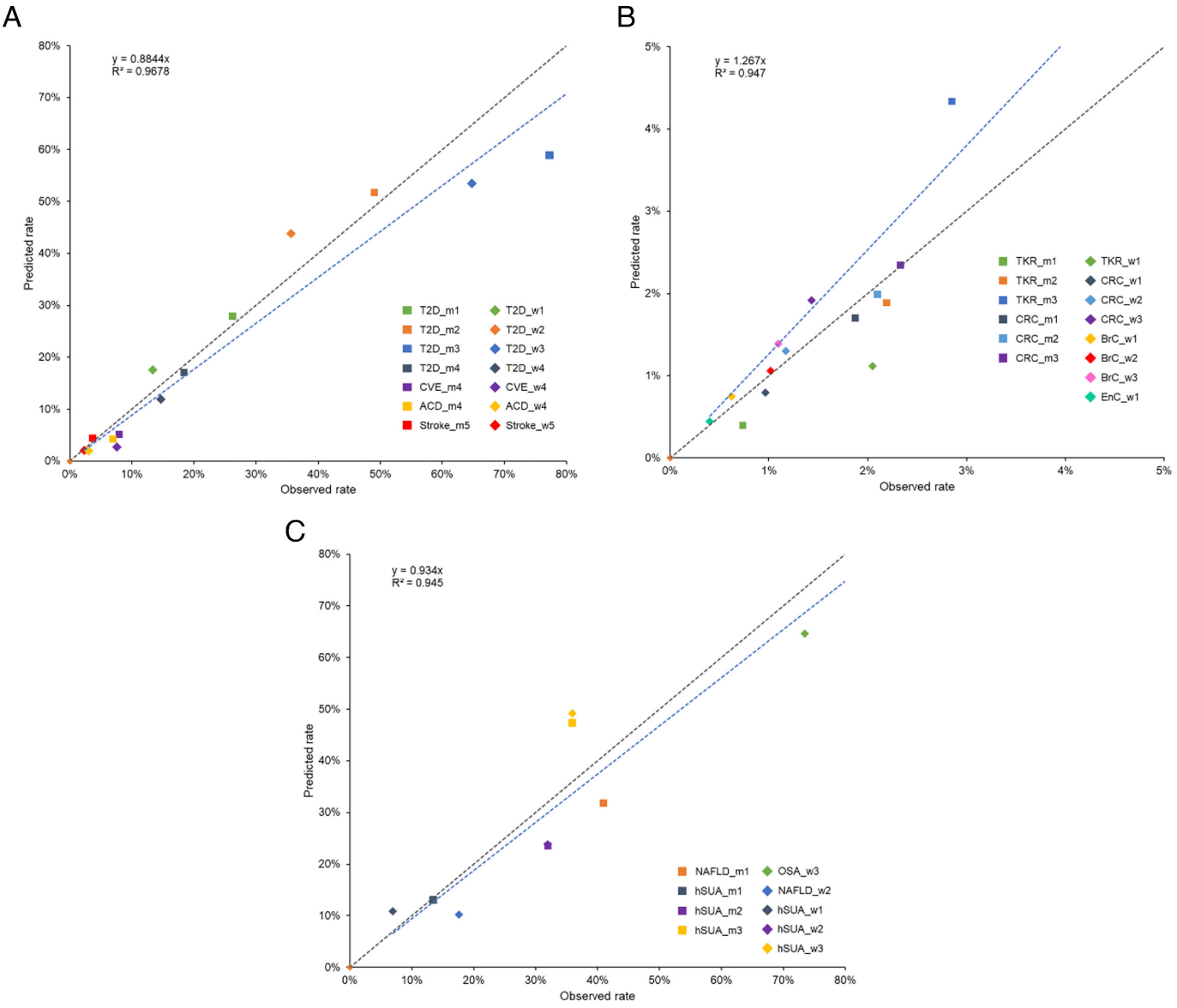

Figure 1 Results of internal validation: observed versus predicted outcomes with Japan/East-Asian settings for T2D and CV complications (A), non-CV complications (CRC, BrC, EnC, TKR; B) and prevalence-based complications (OSA, hyperuricaemia, NAFLD; C). (A) Predicted versus observed cumulative incidence of T2D and targeted CV complications; (B) Predicted versus observed cumulative incidence of non-CV complications across typical East-Asian profiles; (C) Predicted versus observed prevalence of prevalence-based complications across typical East-Asian profiles. For each targeted complication, the scatter plots represent on the x-axis the observed incidence at study horizon and on the y-axis the predicted incidence for a similar profile and time horizon. The legend indicates which complication and profile were tested (cf. tables 1 and 2). The grey dotted line marks the 'perfect' outcome when prediction equals observed value. The blue dotted line is a linear fitting of the dots (trend for underprediction if located below the orange line, trend for overprediction if located above the orange line). The R^2 coefficient next to the equation gives information on the appropriateness of a linear fitting (the closer to 1, the more appropriate is the linear fitting). Dots for TKR in female profiles w2 (obs. 8.4%, pred. 8.0%) and w3 (obs. 10.7%, pred 16.0%) are included in the trendline but not displayed due to scale. ACD, all-cause death; BrC, breast cancer; CRC, colorectal cancer; CV, cardiovascular; CVE, cardiovascular event; EnC, endometrial cancer; hSUA, high serum uric acid (hyperuricaemia); _m, male profile; NAFLD, non-alcoholic fatty liver disease; obs., observed; OSA, obstructive sleep apnoea; pred., predicted; R2, coefficient of determination; T2D, type 2 diabetes; TKR, total knee replacement; _w, female profile.

The predicted cancer incidences were in line with the observed ones, with most of the predicted points being close to the IL. There was a trend for mild overprediction, driven by colorectal and breast cancer incidences in the highest BMI profile for females (w3). Predicted TKR incidences were moderately underpredicted in males and females with normal weight (m1, w1), well predicted in cohorts with preobesity weight (m2, w2) and tended to be overpredicted in males and females with obesity (m3, w3). Overall, there was a moderate overprediction mostly driven by the cumulative incidence of TKR and female cancers in cohorts with obesity. The slope of the

Table 3 External validation, comparison of model predictions at 10 years using Japanese versus Western settings, male

Event	Source study	Results for East Asia			Source study	Results for Western		
Males		**m1**	**m2**	**m3**		**m1**	**m2**	**m3**
Cumulative incidence at 10 years								
T2D	J-ECOH Hu *et al*[24]	12.2%	25.4%	34.9%	QDiabetes[22]	3.4%	8.1%	15.3%
T2D	KoGES Bae *et al*[25]	15.1%	22.9%	26.1%				
Stroke, including TIA	1st event: China HNS; Recurrent: Modified Essen Stroke Risk Score (J-ECOH for T2D incidence)	2.4%	4.3%	6.4%	1st event: Qrisk3[23]; recurrent event: Framingham Recurrent[28]	1.3%	1.9%	2.0%
CHD: MI, UA	1st event: China HNS; Recurrent: Modified Essen (J-ECOH for T2D incidence)	0.8%	1.4%	2.1%	1st event: Qrisk3[23]; recurrent event: Framingham Recurrent[28]	6.1%	8.7%	9.2%
Total CVD	Sum of stroke and CHD	3.2%	5.7%	8.5%	Sum of stroke and CHD	7.4%	10.6%	11.1%
Ratio stroke to CHD		3	3	3		0.2	0.2	0.2
All-cause death	Multiple sources	2.9%	3.7%	3.9%	Multiple sources	4.7%	5.3%	5.8%
Colorectal cancer	Matsuo *et al*[44]	1.0%	1.2%	1.4%	Schlesinger *et al*[29]	0.5%	0.6%	0.7%
TKR	Leung *et al*[53]	0.0%	0.1%	0.3%	Wendelboe *et al*[32]	0.6%	1.1%	3.1%
Gout	Kuwabara *et al*[33] and Chen *et al*[34]	5.3%	7.3%	11.3%	Kuwabara *et al*[33] and Chen *et al*[34]	4.5%	5.1%	6.0%
Decompensated liver cirrhosis and HCC	Pang *et al*[54] and Estes *et al*[56]	0.1%	0.2%	0.2%	Not investigated			
Liver transplant	Pang *et al*[54] and Umeshita *et al*[82]	0.003%	0.027%	0.028%	Not investigated			
Prevalence at 10 years								
Sleep apnoea	Park *et al*[50]	29.8%	41.1%	45.7%	Sleep Heart Study 2002[35]	0.0%	14.3%	22.9%
QALYs at 10 years	Undiscounted model output	8.95	8.76	8.63		9.3	9.3	9.1
Life-years at 10 years	Undiscounted model output	9.87	9.83	9.83		9.8	9.8	9.7

m1, m2, m3: men with baseline BMI 22.1 kg/m^2 (normal weight, WHO), 26.8 kg/m^2 (preobese, WHO) and 32.4 kg/m^2 (obese, WHO), respectively—further details on the validation cohorts' characteristics at baseline are provided in table 1.
BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; HNS, Health and Nutrition Survey; J-ECOH, Japan Epidemiology Collaboration on Occupational Health; KoGES, Korean Genome and Epidemiology Study; MI, myocardial infarction; QALY, quality-adjusted life-year; T2D, type 2 diabetes; TIA, transient ischaemic attack; TKR, total knee replacement; UA, unstable angina.

OLS-LRL was 1.267. A high degree of linear correlation was observed (R^2=0.947) (figure 1B). The prevalence of OSA was well predicted. NALFD prevalence was moderately underpredicted. Hyperuricaemia tended to be underpredicted in males and females with preobesity weight (m2, w2), and moderately overpredicted in males and female cohorts with obesity (m3, w3). Overall, there was a high concordance between predicted and observed outcomes, with an OSL LRL slope of 0.934, and results displayed a high degree of linear correlation (R^2=0.945) (figure 1C).

External validation: Japan versus Western predictions

The results of the external validation are presented in table 3 (male) and table 4 (female). At 10 years, life-years were similar between the Japanese and Western settings while QALYs were marginally lower for Japanese cohorts. A trend of higher 10-year cumulative incidence/prevalence of complications was seen at lower BMI levels in Japanese compared with Western predictions. The predicted cumulative incidences of T2D at 10 years for Japanese profiles with normal weight (m1: 12.2%, w1: 5.9%) were closer to those predicted for Western profiles with overweight (m2: 8.1%, w2: 4.5%). Similar trends could be observed for gout, OSA, breast and colon cancer. Thus, within each profile, the cumulative incidence/prevalence of most complications was higher when using Japanese versus Western risk predictions: approximately threefold higher for T2D (5.9%–34.9% vs 1.1%–15.3%), approximately twofold higher for OSA (12.5%–45.7% vs 0%–25.8%), gout (1.9%–11.3% vs 1.7%–6.0%) and CRC (0.5%–1.4% vs 0.4%–0.7%). Conversely, the 10-year cumulative incidences of CHD predicted in Japanese

Table 4 External validation, comparison of model predictions at 10 years using Japanese vs Western settings, female

Event	Source study	Results for east asia			Source study	Results for western		
Females		**w1**	**w2**	**w3**		**w1**	**w2**	**w3**
Cumulative incidence at 10 years								
T2D	J-ECOH Hu *et al*[24]	5.9%	18.1%	25.7%	QDiabetes[22]	1.1%	4.5%	9.7%
T2D	KoGES Bae *et al*[25]	5.7%	14.2%	19.0%				
Stroke, incl. TIA	1st event: China HNS; Recurrent: Modified Essen (J-ECOH for T2D incidence)	1.0%	1.8%	2.9%	First event: QRisk3[23]; recurrent event: Framingham Recurrent[28]	0.6%	1.1%	1.3%
CHD: MI, UA	1st event: China HNS; Recurrent: Modified Essen (J-ECOH for T2D incidence)	0.3%	0.6%	1.0%	First event: QRisk3[23]; recurrent event: Framingham Recurrent[28]	1.6%	2.8%	3.4%
Total CVD	Sum of stroke and CHD	1.3%	2.4%	3.8%	Sum of stroke and CHD	2.2%	3.9%	4.7%
Ratio stroke to CHD		3.0	3.0	3.0	Ratio stroke to CHD	0.4	0.4	0.4
All-cause death	Multiple sources	1.5%	2.0%	2.7%	Multiple sources	2.7%	2.9%	3.7%
Colorectal cancer	Matsuo *et al*[44]	0.5%	0.8%	1.1%	Schlesinger *et al*[29]	0.4%	0.5%	0.5%
Endometrial cancer, post menopause	Masuda *et al*[47]	0.1%	0.4%	1.0%	Renehan *et al*[31]	0.0%	0.3%	0.9%
Breast cancer, post menopause	Wada *et al*[45]	0.2%	0.4%	0.4%	Renehan *et al*[30]	0.5%	0.9%	0.8%
TKR	Leung *et al*[53]	0.1%	0.4%	1.0%	Wendelboe *et al*[32]	0.4%	1.7%	4.0%
Gout	Kuwabara *et al*[33] and Chen *et al*[34]	1.9%	3.4%	4.6%	Kuwabara *et al*[33] and Chen *et al*[34]	1.7%	2.5%	2.6%
Decompensated liver cirrhosis and HCC	Pang *et al*[54] and Estes *et al*[56]	0.02%	0.10%	0.20%	Not investigated			
Liver transplant	Pang *et al*[54] and Umeshita *et al*[82]	0.0003%	0.0060%	0.0290%	Not investigated			
Prevalence at 10 years								
Sleep apnoea	Park *et al*[50]	12.5%	29.5%	38.9%	Sleep Heart Study 2002[35]	0.0%	14.7%	25.8%
QALYs at 10 years	Undiscounted model output	9.02	8.80	8.51		9.2	9.2	8.9
Life-years at 10 years	Undiscounted model output	9.93	9.90	9.88		9.9	9.9	9.8

w1, w2, w3: women with baseline BMI 20.6 kg/m^2 (normal weight, WHO), 26.9 kg/m^2 (preobese, WHO) and 32.7 kg/m^2 (obese, WHO), respectively—further details on the validation cohorts' characteristics at baseline are provided in table 2.
BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; HNS, Health and Nutrition Survey; J-ECOH, Japan Epidemiology Collaboration on Occupational Health; KoGES, Korean Genome and Epidemiology Study; MI, myocardial infarction; QALY, quality-adjusted life-year; T2D, type two diabetes; TIA, transient ischaemic attack; TKR, total knee replacement; UA, unstable angina.

individuals (range m1–m3 0.8%–2.1%, w1–w3 0.3%–1.0%) were less than half of those predicted in Western individuals (range m1–m3 6.1%–9.2%, w1–w3 1.6%–3.4%) within each profile. The ratio of strokes-to-CHD (Japan 3.0, Western 0.2) is a consequence of the redistribution of total CV events rates in the model according to ethnic-specific patterns. The 10-year cumulative incidence of TKR in Japanese individuals (≤1%) was inferior to the predicted rates in Western settings (range 0.4%–4.0%); TKR, however, remained infrequent in the tested age ranges of 45–55 years, regardless of the geographical area. At equal BMI, the 10-year cumulative incidence of postmenopausal breast cancer was inferior by a factor two in Japanese (range 0.2%–0.4%) vs Western (0.5%–0.8%) females while the predicted postmenopausal endometrial cancer was comparable between the two populations within each profile (0.1%–1.0%, same range across w1–w3). The incidence of gout was up to twofold higher in Japanese males and females affected by obesity (males: 5.3%–11.3%; females: 1.9%–4.6%) compared with Western individuals (males: 4.5%–6.0%; females: 1.7%–2.6%).

DISCUSSION

To our knowledge, this is the first health-economic model in obesity to incorporate predictions of weight-related complications in a Japanese population. Given the known and marked differences in the aetiology and occurrence of certain diseases compared with Western/Caucasian populations, this work is important to ensure a representative estimation of costs and health benefits in the context of cost-effectiveness analyses in obesity for Japan. These results confirm the need to apply specific

prediction models when estimating obesity outcomes in Japanese populations.

The adapted model showed good external validity, showing an increased risk of T2D, OSA, CRC and gout starting from lower BMI levels in Japan compared with Western populations. This pattern has been shown in many studies,[33 69] prompting lower BMI cut-off points to define obesity in Asian individuals. The main cause of this has been hypothesised to relate to a differential body-fat disposition, that is, higher fat accumulation around the abdomen and higher total body fat when compared with white European individuals of the same BMI[70] explaining the higher risk of T2D and all-cause mortality in Asians.[69 71] Other genetic factors, such as craniofacial bony restriction, that is, a shorter cranial base, maxilla and mandible length in Asian compared with Caucasian populations, may explain the higher prevalence of OSA observed even in non-obese individuals.[72] Alcohol usage, as well as a work–life imbalance culture in Japan (eg, constant high levels of stress, nightcap drinking), have been referenced previously as a possible explanation for the higher prevalence of OSA in the non-obese population of Japan. Equally, alcohol usage, as well as a genetic variation altering the function of urate transporters, have been shown to predispose Asian populations, including those from Japan to a higher prevalence of hyperuricaemia and gout compared with European populations.[73]

The main methodological limitation of this work relates to the sparse evidence to describe and predict obesity-related complications in Japanese/East-Asian populations.

Based on our thorough targeted search, multivariable models are currently unavailable to predict the incidence of T2D nor ACS, two major obesity-related complications, in an East-Asian population. In the absence of fully adjusted models, it was impossible to consider unobserved or unreported patient characteristics interacting with the predicted outcomes. Probabilities in our model were thus derived by combining several sources, often a baseline risk with relative risks/OR per BMI unit increase, and where possible, an age-adjustment. Combining evidence from several sources is associated with further uncertainty. For example, T2D incidences in the J-ECOH study were estimated for a relatively young population, that is, of working age, while in the KoGES dataset, the average age at baseline was 52 years. Thus, an adjustment for age was added to the predicted incidences in both studies, which resulted in the two risk functions predicting similar cumulative incidences at 10 years. However, for the time being, it is unknown whether the same age trend would be replicated at all BMI levels. T2D tended to be underpredicted in cohorts with obesity and overpredicted in those with normal and preobesity weight; these results are deemed fair considering all uncertainties. The lack of an age-adjustment parameter may have caused some of the mispredictions in cancer, TKR and hyperuricaemia endpoints. The high uncertainty associated with the observed outcomes in people with obesity (BMI>30 kg/m^2) and TKR in the source study may further explain the discrepancies noted on this endpoint.

A proper risk equation was available to predict the incidence of stroke, though not based on a Japanese population but on Chinese data, namely the China HNS. To address this, predictions in the COM were calibrated to reflect the distribution of haemorrhagic-to-ischaemic strokes from a Japanese study.[38] Further CV event rates were calibrated using proportions (ACS:stroke and MI:UA) sourced from studies in Japan.[40 41] CV events and all-cause mortality tended to be mildly underpredicted.

A fully adjusted model was also available to estimate OSA prevalence.[50] The validation was limited since the source study did not provide raw prevalence rates by BMI levels. A systematic literature review in Asian individuals[74] showed significant differences in OSA prevalence rates between studies in Japan, ranging from 3.7% to 97.3%, with these differences attributed to differences in age and BMI of the studied populations. These two factors were retained as independent predictors in the Park *et al* model, along with sex, T2D and hypertension.

With only two multivariable models identified, our study was limited by the lack of an Asian equivalent to the Framingham cohort. Involving Japanese/East-Asian populations in longitudinal, large-scale cohort studies evaluating obesity-related complications and relevant risk factors is critical to support future international research and health equity.

Another limitation is that changes over time in prediction variables are generally not reported in the source studies. Such is the case of glycaemic levels which are expected to influence the prediction of T2D, and more so in people with overweight and obesity. It is also uncertain how current changes in BMI may revert or delay the evolution of NAFLD, and how the rates of late-stage liver complications including decompensated cirrhosis, cancer and transplant, will be affected. Using the COM for Japan, the 10-year predicted rates of NAFLD complications were relatively low and changed little with changes in BMI, suggesting a conservative approach. Such uncertainty could be partly addressed via probabilistic sensitivity analyses within the COM.

Some complications listed by the JASSO were examined in the literature but were not included in the COM due to insufficient or inconclusive data regarding the existence of an association between obesity and an increased risk of, for example, the spectrum of menstrual disorders, severe CKD or end-stage renal failure. There were no Japanese or East-Asian studies to inform the link between endometriosis and BMI. Looking at international publications, a meta-analysis by Liu and Zhang[75] reported a protective effect of obesity with regard to endometriosis: overall, the RR for endometriosis was 0.67 with each 5 kg/m^2 increase in BMI. In three Asian studies from Iran, the reduction of endometriosis risk was even stronger: RR 0.55 (95% CI 0.46 to 0.65) per 5 kg/m^2 increase. A Korean study also

reported a protective effect: women with advanced-stage endometriosis had lower BMIs than those with minimal or mild disease.[76] Considering the current evidence, this complication was not included in the Japanese COM.

Finally, and as a general limitation of this work, it was not possible to include other measures of adiposity, aside from BMI, such as abdominal circumference, waist-to-hip ratio and abdominal circumference-to-height ratio, which may better predict CVD and CV mortality,[77 78] due to currently insufficient data on their association with the herein considered clinical endpoint, and more empirical evidence around this will be needed to allow incorporation of such measures into the COM. Collecting a broader range of adiposity indicators in future studies of obesity-related complications would greatly enhance the assessment of health and economic impact of obesity across geographical locations and ethnicities.

In conclusion, this study is relevant for obesity-related research in anticipating future events and analysing the impact of therapeutic interventions on the occurrence of complications as well as on their health and economic outcomes in Japan. This model may also be more readily adapted to other East-Asian countries compared with the Western model, although this may require further adjustments and validation.

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Contributors IT was responsible for the methodology and reviewing and editing the manuscript. JB-K was responsible for conceptualisation, methodology and reviewing and editing the manuscript. LG was responsible for the methodology, formal analysis and investigation, preparation of the original draft and reviewing and editing the manuscript. A-VO was responsible for the methodology, formal analysis and investigation, preparation of the original draft and reviewing and editing the manuscript. ML was responsible for conceptualisation, methodology, preparation and writing of the original draft, reviewing and editing the manuscript and supervision. ML was responsible for the overall content as guarantor.

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