Obesity Facts

Research Article

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Early-Onset of Obesity Model: Impact of Early-Onset Obesity on Comorbidity Risk and Life Expectancy

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Keywords
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Abstract
Introduction: Early-onset obesity increases the risk of developing comorbidities and decreases life expectancy with many variables such as age of onset, severity, and

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duration of obesity each having an individual influence. Here, we present findings from a model that aims to assess the impact of early-onset obesity. ***Methods:*** The Early-Onset Obesity Model (EOObesity Model) was built by integrating data from clinical studies with demographic information. It categorizes information into four primary groups: prevalence, morbidity risk, mortality risk, and impact of obesity duration. Type 2 diabetes, cardiovascular events (fatal and nonfatal events, cardiovascular disease, and coronary heart disease), metabolic dysfunction-associated steatotic liver disease, asthma, obstructive sleep apnea, and cancer were evaluated over a range of age and body mass index (BMI) z-scores. ***Results:*** The EOObesity Model provides a systematic approach for estimating the impact of early-onset obesity on risk of comorbidities and on life expectancy by considering individual patient weight trajectories. We test different scenarios to illustrate the potential impact of age of onset and severity of obesity on the risk of various comorbidities, on life expectancy, and on disability-adjusted life years. The model indicates that severe early-onset obesity has a high impact on life expectancy with, for example, up to 42 years of life lost if a patient has a BMI z-score of 4 by the age of 4 years. ***Discussion:*** The model and these scenarios underscore the predicted substantially detrimental effects of early-onset and prolonged obesity on life expectancy, and the increased risks of obesity-related comorbidities. They suggest that morbidity and mortality risks increase with obesity duration and severity in a nonlinear manner, thereby supporting the view that early weight-loss intervention and obesity prevention strategies may reduce long-term health risks substantially.

Plain Language Summary

Early-onset obesity, which is obesity that begins at a young age, can lead to serious health problems and shortened life expectancy. Factors such as how early obesity starts, how severe it is, and how long it lasts all influence its impact on health. To better understand these effects, we created the Early-Onset Obesity Model (EOObesity Model). The model uses data from both clinical studies and the general population to study how early obesity affects health and life expectancy. The model assesses how common early-onset obesity is, the risks of developing health problems, the chances of dying due to comorbidities, and the effects of living with obesity for a long time. The health issues examined include type 2 diabetes, heart problems, liver disease, sleep apnea, asthma, and cancer. The model shows that severe obesity starting early in life can reduce life expectancy substantially. As an example, a child with severe obesity (indicated by a body mass index [BMI] score of 4) by age 4 years could lose up to 42 years of life. The model also shows that the risk of comorbidities and early death increase with the severity and duration of obesity. In conclusion, our findings emphasize that early intervention and prevention strategies for managing obesity are important. Addressing obesity early can greatly reduce long-term health risks and improve overall quality of life.

Introduction

The worldwide obesity epidemic is associated with a concomitant increase in chronic diseases such as cardiovascular disease (CVD) and type 2 diabetes (T2D) [1, 2]. Global obesity prevalence has more than doubled since 1980, impacting over 890 million adults [3, 4]. Children are now impacted substantially in many countries, with about 160 million young people, or 8.5% of children and adolescents, living with obesity [5]. This is likely due to a complex interplay between genetic predisposition and environmental factors, including modern lifestyles encouraging increased energy intake and reduced physical activity [6]. Early-onset obesity, especially before the age of 5 years, may be a consequence of rare gene variants (monogenic or syndromic), which are often accompanied by additional phenotypic manifestations such as neurodevelopmental or endocrine disorders [7].

The prevalence of early-onset obesity in the USA and Europe is 1–2%; this is defined as a body mass index (BMI) z-score >2 or BMI >120% of the 95% percentile for sex and age, in children ≤5 years of age [8, 9]. In our model, patients with early-onset obesity are defined as children who develop obesity before the age of 5 years with the above-described obesity magnitude and with sustained obesity thereafter. This study models patients with early-onset obesity tracked longitudinally across their entire lifespan. While our model architecture can accommodate various obesity-onset patterns through its data input system, this analysis focuses on individuals with early-onset obesity to assess their lifetime comorbidity and mortality risk trajectories. The major reason for the development of this model was the limited research on how early-onset obesity impacts long-term health and mortality specifically; being overweight in childhood increases the risk of CVD, T2D, mortality, and

persistent obesity later in life [10–13]. In children, obesity may also be associated with early pubertal onset, prepubertal acceleration of linear growth velocity and advanced bone age, and impaired development of lung and cardiac architecture [14–16]. Also, approximately 60% of children and adolescents with severe obesity have more than one cardiovascular (CV) risk factor such as high blood pressure, which is the most common associated comorbidity [17]. Onset of obesity at a younger age seems to be the most important factor in determining the presence of these comorbidities [17].

Estimating the long-term impact of early-onset obesity is complex, due to a wide range of individual health factors. Here, we describe an innovative process of building a comprehensive model to qualify and quantify the impact of early-onset obesity on long-term morbidity and mortality.

The Early-Onset Obesity Model (EOObesity Model) adopts a multidisciplinary novel approach, integrating data from clinical studies with demographic information. Using multiple factors in the model allows us to evaluate the potential impact of each factor on morbidity and mortality, enabling a more comprehensive understanding of the impact of early-onset obesity. In addition, the model has been further developed to estimate disability-adjusted life years (DALYs). The model is twofold in its application: first, at the individual level, it provides customizable risk assessments to guide clinical decision-making, and second, at the population level, it helps health systems project disease burden and evaluate prevention strategies.

Methods

Methodical Approach

We have developed a novel approach that integrates prevalence and mortality data from multiple obesity-related comorbidities into unified risk matrices. Combining outcomes from multiple studies allows us to move beyond single-outcome analyses to capture the cumulative health impacts of obesity, and to quantify how weight trajectories affect total disease burden and life expectancy (LYX). To assess the consequences of early-onset obesity, we identified obesity-related factors from the literature that influence comorbidity risk and mortality. Four key factors were included in the model.

- Age of onset.
- Severity of obesity [10], mostly measured as BMI, as well as BMI z-score or percentiles in children and adolescents; the severity of obesity is related directly to an increased risk of comorbidities and mortality [18–20].
- Duration of obesity, which is an important factor in the development of comorbidities and in increased mortality risk [12, 14, 21–23]; a person who has lived with obesity for 20 years has a significantly higher risk profile than someone of the same age and weight who has lived with obesity for 10 years. Thus, living with severe obesity for a longer period of time increases the accumulation of irreversible pathophysiological alterations that cause harm and increase long-term comorbidity risk, even following weight reduction [24].
- Interaction between age and weight, which defines a person's risk of developing a certain comorbidity as well as their overall mortality risk; the natural/average comorbidity risk increases with age, and this risk increase (RI) is further compounded by obesity [24].

We separated the calculations for comorbidity and mortality risk to prevent the effect of obesity duration being double counted. Available studies report the impact of obesity duration on comorbidity development and mortality risk independently, but do not quantify the overlap between these effects. Applying duration adjustments to both comorbidity prevalence and mortality risk before combining them would result in the same underlying risk factor being compounded, since increased mortality risk from longer obesity duration likely already incorporates some of the effect mediated through increased comorbidity risk due to obesity duration. Without studies that distinguish the direct versus comorbidity-mediated effects of obesity duration on mortality, maintaining statistical independence requires adjusting each pathway separately. Therefore, we used two different approaches in the model (Fig. 1): one for LYX and one for comorbidity risk determination.

To estimate the comorbidity risk, incidence and prevalence figures are combined directly with specific comorbidity duration factors. To estimate LYX, incidence and prevalence of comorbidities are combined with mortality risks to yield an all-comorbidity mortality risk, which is modified further with specific obesity duration factors impacting total mortality risk. A sufficient number of cohort studies and their corresponding follow-up studies have quantified the impact of obesity and, specifically, obesity duration on mortality, and thus provide the model with accurate information. Our systematic approach involved constructing comprehensive risk matrices for comorbidity prevalence and mortality risk across six obesity-related conditions. This required us to make estimates for all combinations of age and weight classification. The development of these risk matrices is described in more detail in the Sources and Data Extraction section. We followed standard statistical

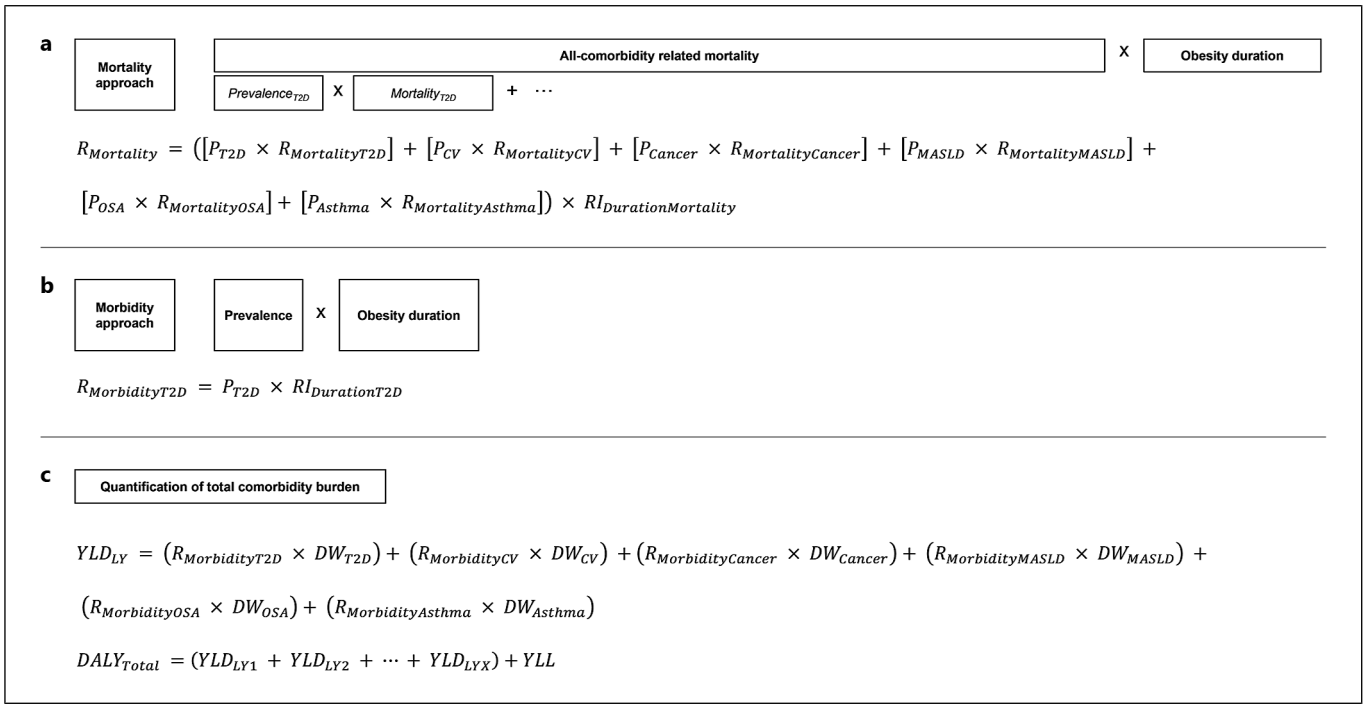

Fig. 1. a–c Methodology for modeling impact of early onset of obesity on comorbidities and mortality. Visualization of the methodological approach and equations used in the model to analyze the impact of different factors on LYX and comorbidity risk. Separate models are used for LYX and comorbidity risk to ensure accuracy, using specific evidence-based data on the impact of obesity on mortality to accurately assess mortality, while assessing comorbidity risk independently with specific data on comorbidity RIs related to obesity. CVE, cardiovascular event; DALY, disability-adjusted life year; DW, disability weight; LY, life year; LYX, life expectancy; MASLD, metabolic dysfunction-associated steatotic liver disease; OSA, obstructive sleep apnea; P, prevalence; R, risk; RI, risk increase; T2D, type 2 diabetes; YLD, years lived with disability; YLL, years life lost.

methods to validate our predictive model outputs [25–29]. As the model inputs (disease prevalence and baseline mortality risks) were derived directly from published clinical studies, the validation focused on the purely model-generated outcomes, namely, relative risk reduction (RRR) due to intentional weight loss, mortality risk estimates, and life year (LY) estimations. The coefficient of determination through the origin (R^2_0) over standard R^2 was prioritized in our validation, based on the fundamental relationship between weight loss and risk reduction. By definition, RRR due to intentional weight loss must equal zero when no weight loss occurs; this constraint means that $Y = 0$ when $X = 0$, so regression through the origin is the appropriate statistical approach. Standard regression would estimate a nonzero intercept, implying that risk reduction due to weight loss could occur without weight loss. This contradicts the definition of weight-loss-induced RRR. Regression through the origin respects this constraint while providing more efficient parameter estimates when the true intercept is known to be zero. We complemented R^2_0 with root mean square error to assess absolute accuracy, mean absolute percentage error to assess relative accuracy across different scales, and mean bias error to assess systematic over- or underestimation. The validation results (Table 1) showed that the model performed well, with R^2_0 values exceeding 0.91 for all outcomes. Mean bias error values indicated slight systematic underestimation across most outcomes. The RRR calibration plot (online suppl. Fig. S1; for all online suppl. material, see https://doi.org/10.1159/000549499) confirmed a high level of agreement between the observed and predicted values.

Model Architecture

The model consists of three main bodies: the database, which provides all the information extracted from study results; the engine, which selects case-specific information based on the two provided weight trajectories calculating comorbidity risks, LYXs, and DALYs; and an interface, through which the case data are entered, creating 2 case-specific weight trajectories, as well as

Table 1. Standard model validation metrics for relevant model outcomes

	RRR		Validation metrics			
	mean observed	mean predicted	R^2_o	RMSE	MAPE	MBE
All-comorbidity RRR[a]	−29.97%	−25.98%	0.9133	0.11	22.63%	3.98%
T2D RRR	−31.84%	−27.20%	0.9796	0.0673	14.43%	4.64%
CV RRR	−27.61%	−22.72%	0.9815	0.0685	16.01%	4.89%
MASLD RRR	−21.23%	−22.85%	0.9382	0.0614	25.87%	−1.62%
Cancer RRR	−23.47%	−20.00%	0.9978	0.0431	14.10%	3.47%
Asthma RRR	−24.85%	−27.88%	0.9329	0.0754	36.77%	−3.02%
Sleep apnea RRR	−55.10%	−36.45%	0.3277	0.2297	32.41%	14.61%
All-mortality risk[b]	51.00%	48.33%	0.9984	0.0374	7.30%	−2.67%
All LYs[c]	31.92	29.88	0.9951	3.9428	20.59%	−2.04
Total LYs	74.00	70.56	0.9960	5.5600	5.57%	−3.44
LYs lost	−4.23	−5.67	0.9704	2.0870	33.82%	−1.43
LYs gained	5.05	5.00	0.9382	1.4240	29.58%	−0.05

CV, cardiovascular; MAPE, mean absolute percentage error; MASLD, metabolic dysfunction-associated steatotic liver disease; MBE, mean bias error; R^2_o, coefficient of determination through the origin; RRR, relative risk reduction; RMSE, root mean square error; T2D, type 2 diabetes. [a]Sum of all comorbidities. [b]RI compared to normal-weight population plus RRR due to intentional weight loss. [c]Sum of total LYs, LYs lost, and LYs gained.

presenting all the model outcomes. The database contains all the information needed to model different case scenarios. A comorbidity and corresponding mortality risk matrix are given for each combination of ages between 0 and 100 years and BMI z-scores between 0 and 4. A specific duration RI is allocated depending on the year of onset of obesity, for each year of obesity duration, and BMI z-score 0–4. The resulting duration factor table was created using the hazard ratios (HRs) provided by selected studies (see Sources and Data Extraction section).

These HRs were then taken as values for the average study BMI, and the upper confidence intervals (CIs) were taken as values for the maximum BMI value. Likewise, the lower CIs represent BMI levels for obesity below the average BMI value for obesity. The remaining HRs were interpolated between the average BMI-HR and maximum BMI-HR, and between average and minimum, with no RI for BMI z-score 0.

To counteract overestimating when modifying the comorbidity risk with duration factors, we adjusted duration factors for the average obesity duration in the corresponding study cohorts. This was performed based on the assumption that in a relatively older cohort, obesity duration tends to be longer than in cohorts with younger individuals, resulting in an overestimation for the younger and an underestimation for the older patients when taking the same risk value for both age groups.

Disability stratification is given for all comorbidities; these are taken from the Global Burden of Disease Study and used for calculation of DALYs [30]. The model engine is capable of extracting data from the database and calculating comorbidity risk as well as LYX risks for all ages. Calculation of DALYs is carried out separately with the same prevalence figures. Figure 1 shows the equations applied to each year of life. The input values for these calculations are derived from the risk matrices in combination with individual weight trajectories, enabling the estimation of risk at specific ages and BMIs. The equation (a) is the mortality calculation, which determines total mortality risk by summing the products of each comorbidity's prevalence and its associated mortality risk for all six conditions, and then multiplying this sum by the obesity duration RI impact factor. We used Kaplan-Meier survival curves to estimate LYs and years of life lost based on this mortality risk. The morbidity calculation (b) determines individual comorbidity risk by multiplying baseline prevalence by the RI factor specific to the duration of obesity. The DALY calculation (c) quantifies the total disability burden (years lived with disability + years life lost) by summing the products of the morbidity risk of each comorbidity and its disability weight across all LYs and adds the years of life lost. Together, these equations enable the model to estimate the impacts of both mortality and morbidity while accounting for obesity duration.

The interface facilitates data entry, generating BMI trajectories for the engine. All information generated by the engine is visible on the interface. The interface allows input for two case-specific weight trajectories. Two timepoints are necessary to create a baseline weight trajectory: one timepoint is a specific age plus a corresponding BMI z-score. One additional timepoint is required to generate a comparison trajectory for assessing weight interventions. Up to three more timepoints can be added to improve the accuracy of the trajectory. The model assumes a BMI z-score of 0 from birth until the first timepoint is entered, then interpolates between the entered timepoints, and maintains the final z-score until the age of 100 years. This allows for year-by-year queries of age- and BMI-specific risks, with the dual-trajectory approach quantifying the impact of weight interventions on long-term health outcomes. In parallel with the data entry, LYX, DALY overview, and comorbidity risks for all ages are presented for both case scenarios via the interface.

Sources and Data Extraction

Through a systematic literature review, we identified studies assessing the prevalence and/or the mortality risk of comorbidities in relation to BMI, BMI z-score, and age, as well as studies assessing the duration of obesity in relation to the severity of obesity (online suppl. Fig. S2). We then selected studies, published from 1990 onward, that had sufficient and reliable quantification of the impact of obesity. In total, 226 studies were assessed in detail by comparing relevant study information consisting of country, cohort, mean age at baseline, observation period, sex distribution, population size, BMI values, and results. Where several studies covered similar cohorts, we applied systematic selection criteria, prioritizing those with larger sample sizes, appropriate age-BMI stratification, and methodological consistency. Of the 226 studies that were assessed in detail, 50 met our predefined inclusion criteria and were incorporated into the EOObesity Model (online suppl. Table S1).

Selected studies were required to report quantitative outcomes as prevalence or incidence percentages, or HRs, stratified by both age and BMI/BMI z-score. Studies that filled gaps in our target risk matrices were prioritized, particularly those with extreme combinations, such as young participants and those with severe obesity. For overlapping study results, we prioritized studies with larger sample sizes to ensure statistical reliability (e.g., Baker et al. [11], n = 276,835, for CV prevalence) over smaller cohorts. We maintained methodological consistency by favoring studies that used directly measured BMI rather than self-reported data.

Our systematic approach aimed to construct two comprehensive risk matrices: one for comorbidity prevalence and one for mortality risk. These were created for each of the six obesity-related comorbidities. These matrices required risk estimates for every combination of age (0–100 years) and weight classification (BMI 20–50 kg/m^2 or BMI z-score 0–4).

Studies were excluded if they lacked stratification by age or BMI/BMI z-score, if their risk estimates could not be converted to our standardized format (prevalence, incidence, or HRs), or if their populations were already represented by larger, more comprehensive cohorts. Monogenic causes of obesity were also excluded from the study given that the primary focus of such studies is to identify genetic variants and diagnostic yields rather than to document comorbidity prevalence across specific BMI ranges. For instance, in the context of reporting outcomes, such studies offer BMI thresholds for screening rather than BMI-specific risk percentages [31]. The construction of these risk matrices necessitates the availability of specific prevalence data for each BMI value across the entire age range. However, the prevailing focus of obesity research in monogenic diseases is on the reporting of phenotypic characteristics and variant frequencies, rather than the BMI-stratified prevalence quantification that is essential for populating the model matrices.

Most studies included in the EOObesity Model (online suppl. Table S1) report the weight of study participants <18 years of age in BMI z-score and that of those >18 years of age in BMI. To define the weight deviations more uniformly, the model uses weight deviation in BMI z-scores, mapping them on clinical growth charts, to create individual patient BMI trajectories.

For the pediatric population (<18 years of age), we used the Centers for Disease Control and Prevention (CDC) growth charts that provide direct BMI-for-age z-scores. For those ≥18 years of age, for whom the CDC growth references end, we developed a conversion approach to map adult BMI values to equivalent z-scores. For this conversion, we used the BMI distribution at 18 years of age as a reference point, mapping the standard adult BMI thresholds (normal weight, overweight, and obesity classes) to their corresponding percentiles and z-scores at the transition age. The BMI range studied was between 20 and 50 kg/m^2, which corresponds to a BMI z-score range of 0–4, which also covers extreme levels of obesity. The reason for this

upper limit is that most obesity impact studies have included BMI 30–40 kg/m^2, but very few studies have quantified the impact of higher levels of obesity. We have, therefore, used 50 kg/m^2 as an upper limit, assuming that patients with BMI >50 kg/m^2 have at least the same risk as patients with a BMI of 50 kg/m^2.

For morbidity incidence and prevalence, data for T2D, cardiovascular events (CVEs; fatal or nonfatal CV events), metabolic dysfunction-associated steatotic liver disease (MASLD), cancer (all cancer), asthma, and obstructive sleep apnea (OSA) were gathered for ages 0–100 years and BMI z-scores 0–4. The same data were gathered for the mortality risk information.

Information on obesity duration was gathered to assess its impact on comorbidities and mortality risk. For the impact of obesity duration on comorbidities, only data from studies describing T2D, CVEs, and cancer were available. Information on the impact of obesity duration on mortality risk between 0 and 25 years of age was available, and an RI for each additional 2 years of obesity was given [22]. The selection of these obesity-related long-term events was driven by the available literature and selected interviews with six international obesity experts.

Development of Risk Matrices

Data in relation to age and BMI extracted from the selected studies include prevalence, incidence, and mortality risk (all expressed as percentages), as well as BMI classifications and obesity duration (expressed as HRs). To create fundamental risk matrices showing comorbidity and mortality development in relation to age and weight, a value is needed for each weight classification times each age from 0 to 100 years. In instances where multiple studies reported outcomes for identical age and BMI combinations, those with the largest sample sizes whose results aligned with the median values across comparable studies were selected, whereas outliers exhibiting substantially divergent findings were excluded to minimize potential bias in the risk estimates.

The focus was on the exact age and BMI of the study cohorts. For example, prevalence information related to a specific age and BMI was extracted from one study that had investigated the risk of T2D in young adults [32]. This information was then fitted into the risk matrix described above, from which the model can extract the prevalence of T2D for this specific age in combination with a specific BMI.

If no data were available for an age group or BMI classification, the gap was closed by interpolation. For example, data were available for individuals who were 20 and 40 years of age with all corresponding BMI classifications, but there were no data for individuals who were 30 years of age. In this case, linear interpolation was used to generate data for all BMI classifications in the 30-year age group.

All prevalence figures are, therefore, related to study results and can be justified accordingly. The same approach was used to create the mortality risk matrices, with the difference being that HRs were also used to model the impact of BMI differences on mortality risk.

To calculate obesity duration only, information for the years of having obesity and the level of obesity was required. The tables were, therefore, filled with an RI HR for each year of obesity duration in relation to the degree of obesity in that year.

An irreversible risk accumulation was modeled in addition to pure RI due to duration of obesity. Information was available for T2D and CVEs, as well as for MASLD from studies assessing the effect of weight loss on comorbidity risk [14, 33].

The risk matrices developed allow access to all the information needed to generate all combinations of weight (BMI z-score 0–4), age (0–100 years), and duration of obesity (0–100 years). These combinations allow the generation of patient-specific trajectories, enabling future comorbidity risk and corresponding LYX assessments.

Irreversible Risk Accumulation Integration

One study measured the impact of weight loss on the cardiometabolic risk profile of 6,328 participants [24]. For T2D and CVEs, the risk profile of patients with weight loss resulting in return to a normal weight was higher than that of patients who never lived with obesity, indicating a risk accumulation that is nonreversible. To obtain the HRs needed for modeling, we compared those cases with the known impact of obesity duration, and, conservatively, took the difference as new HRs to model the impact of varying durations of obesity and the resulting irreversible accumulated risk in that period.

These new HRs describing the irreversible risk accumulation share of comorbidity risks over time were implemented into the modeling process of estimating the case-specific comorbidity burden. For MASLD, we derived the accumulation of irreversible risk from a meta-analysis of bariatric surgery outcomes by averaging the non-improvement rates from all the studies included in the analysis. Since the mean BMI of patients in the meta-analysis was approximately 50 kg/m^2 (corresponding to the maximum BMI value in our model), we used linear

interpolation between a BMI of 20 to 50 kg/m^2, assuming no irreversible risk at a BMI of 20 kg/m^2, with this risk increasing progressively up to a BMI of 50 kg/m^2 [33].

In addition to each model output, the model also estimates the precision of the underlying modeling in the form of a 95% CI. The CI estimation integrates the variability (standard deviation or CI) of all included study data feeding into the model. The standard error of the mean was estimated from the standard deviations and sample sizes of all input study data. Where possible, the standard error of the mean was differentiated by age and BMI. For those model outputs that are the result of combining comorbidities and mortality risks, we used standard statistical methods for adding and multiplying the CIs of the different integrated parameters to calculate the 95% CI for the final model outputs.

Results

The model suggests that earlier onset and more severe obesity increase the likelihood of developing comorbidities. For example, an individual with BMI z-score 3.5 by age 4 years without subsequent weight reduction has a 27% (95% CI: 23.5–30.5) and 44.7% (95% CI: 40.6–48.6) likelihood of developing T2D by age 25 and 35 years, respectively. The same is seen for CVEs with BMI z-score 3.5 by age 4 years without subsequent weight reduction leading to a 17.4% (95% CI: 14.7–20) and 35.4% (95% CI: 32.1–38.7) likelihood of CVEs by age 25 and 35 years, respectively.

These comorbidities drive the strong reduction in LYX associated with the development of untreated, severe, early-onset obesity. With body weight increasing linearly, LYX decreases in a nonlinear manner. In this example, obesity onset was set at age 12 years, with obesity severity at onset ranging from BMI z-score 2 to 4. LYX is 66 years (95% CI: 60–73) with BMI z-score 2 and is reduced for BMI z-scores 2.5, 3, 3.5, and 4, to 52 years (95% CI: 46–58), 45 years (95% CI: 40–52), 42 years (95% CI: 37–48), and 40 years (95% CI: 36–45), respectively (Fig. 2a). LYX, therefore, decreases rapidly at the beginning of the obesity range, but in the higher obesity ranges, corresponding to BMI z-score ≥3, incremental severity of obesity has a diminishing negative impact on LYX.

Different ages of onset, with the same severity of obesity, result in very different LYXs. As the duration of obesity increases, so does the risk of comorbidities and mortality. For example, a patient with early-onset obesity defined by BMI z-score 3.5 by age 4 years and a constant severity of obesity afterward has a LYX of 39 years (95% CI: 34–46). By comparison, a patient developing a similar severity of obesity at age 18, 30, or 45 years has a LYX of 43 years (95% CI: 40–49), 50 years (95% CI: 46–52), and 56 years (95% CI: 55–58), respectively (Fig. 2b). This suggests that earlier onset leads to shorter LYX when the severity of obesity remains constant.

The duration of obesity plays an independent role in the complex context of increased risk due to obesity. In an earlier study, it was shown that the increase in the duration of obesity increases the risk of mortality; although this effect is reduced by adjusting for potential mediators, such as newly occurring CVDs and T2D, as well as biomedical risk factors, the duration of obesity is nevertheless strongly related to an increase in mortality risk. In addition, it indicates that the impact of the duration of obesity on health outcomes varies by age; early-life obesity has a potential for risk reduction with timely intervention, whereas later life obesity is harder to reverse, with risks compounded by the cumulative physiological burden of previous obesity. The residual effects of childhood obesity, particularly on hypertension, highlight that age and duration of obesity together influence disease risk trajectories [24].

The combination of early-onset obesity and high severity of obesity has the most dramatic effect on LYX in this model (Fig. 3), due to the additive nature of risks associated with increased body weight and duration of obesity. For example, up to 42 years of life may be lost if a patient has BMI z-score 4 at the age of 4 years without subsequent weight loss (Fig. 3). The effect on DALYs is inversely proportional to the effect on LYX (Table 2) and increases with younger age of onset and with higher body weight.

CV risk is increased by early-onset obesity from a very young age, as young as 12 years, and the earlier the onset of obesity the higher the risk of CVEs remains for the person's lifetime (Fig. 4). Even late-onset obesity is associated with a significant increase in risk of CVEs with the negative impact of obesity at age 45 years approximately two-thirds that of early-onset obesity.

In contrast, cancer risk in patients with early-onset obesity remains low, with little impact of age of onset until these patients grow substantially older. Therefore, earlier onset of obesity leads to increased cancer risk in later age, as demonstrated by the curves separating after age 50 years, even though there are minor differences between very early onset (4 years of age) and young-adult onset (18 years of age). Although one study confirmed that early-onset obesity was associated with an increased risk of obesity-related cancers in adulthood, as well as death from obesity-related cancers compared with normal-weight peers, it also found a difference in risk

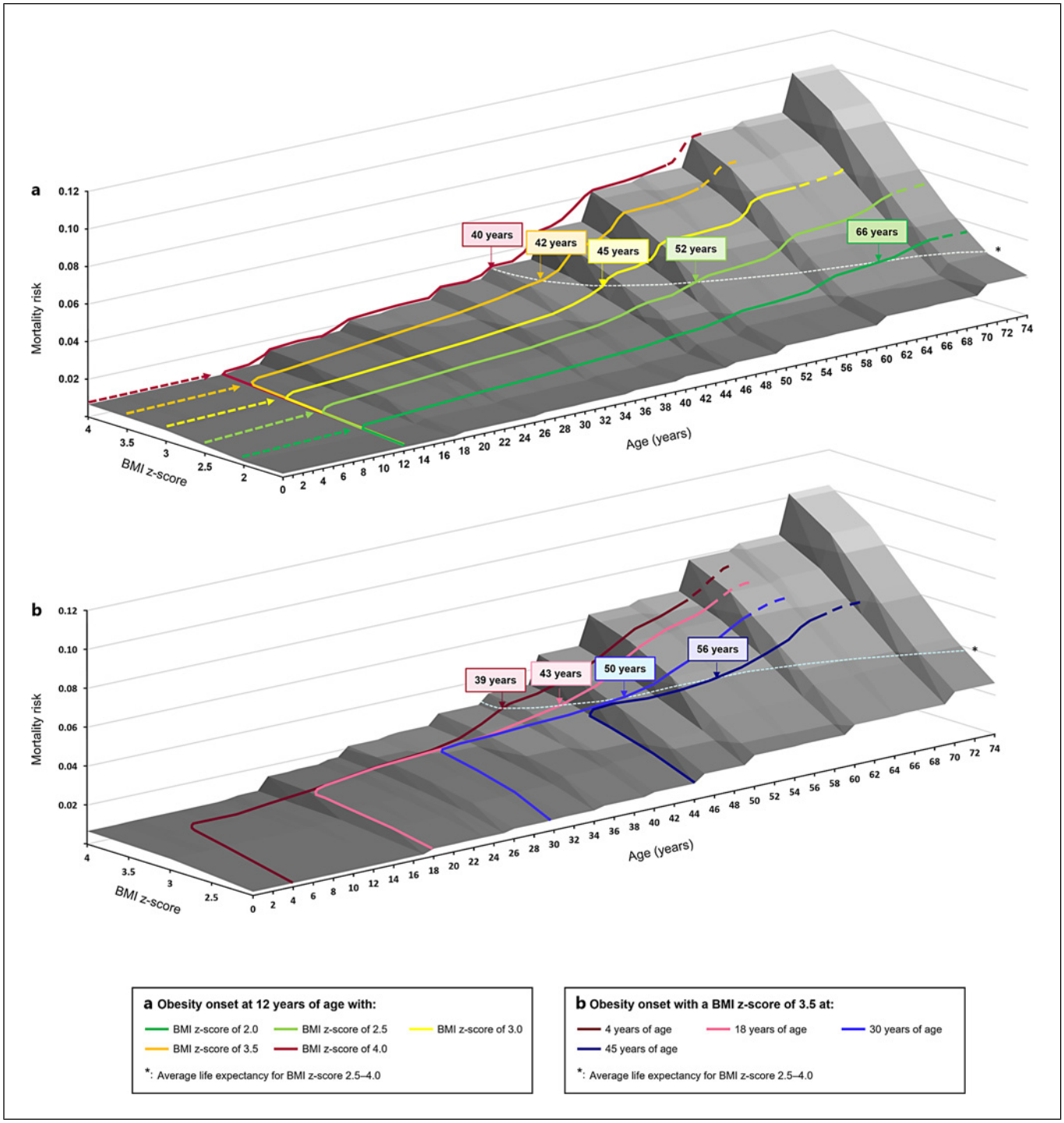

Fig. 2. a Impact of obesity severity (BMI z-score) on LYXs for a patient 12 years of age at obesity onset. Five different magnitudes of obesity at onset are mapped on a mortality risk landscape consisting of three dimensions: BMI z-score, age years, and mortality risk, to show the impact of severity of obesity in combination with duration of obesity on LYX. **b** Impact of age of onset for a patient with BMI z-score 3.5, which stays constant thereafter, on LYX. Four different ages of onset are mapped on a mortality risk landscape consisting of three dimensions: BMI z-score, age years, and mortality risk, to show the impact of age of onset and the resulting duration of obesity on LYX. All results are generated from the EOObesity Model and have been calculated using different patient trajectories. BMI, body mass index.

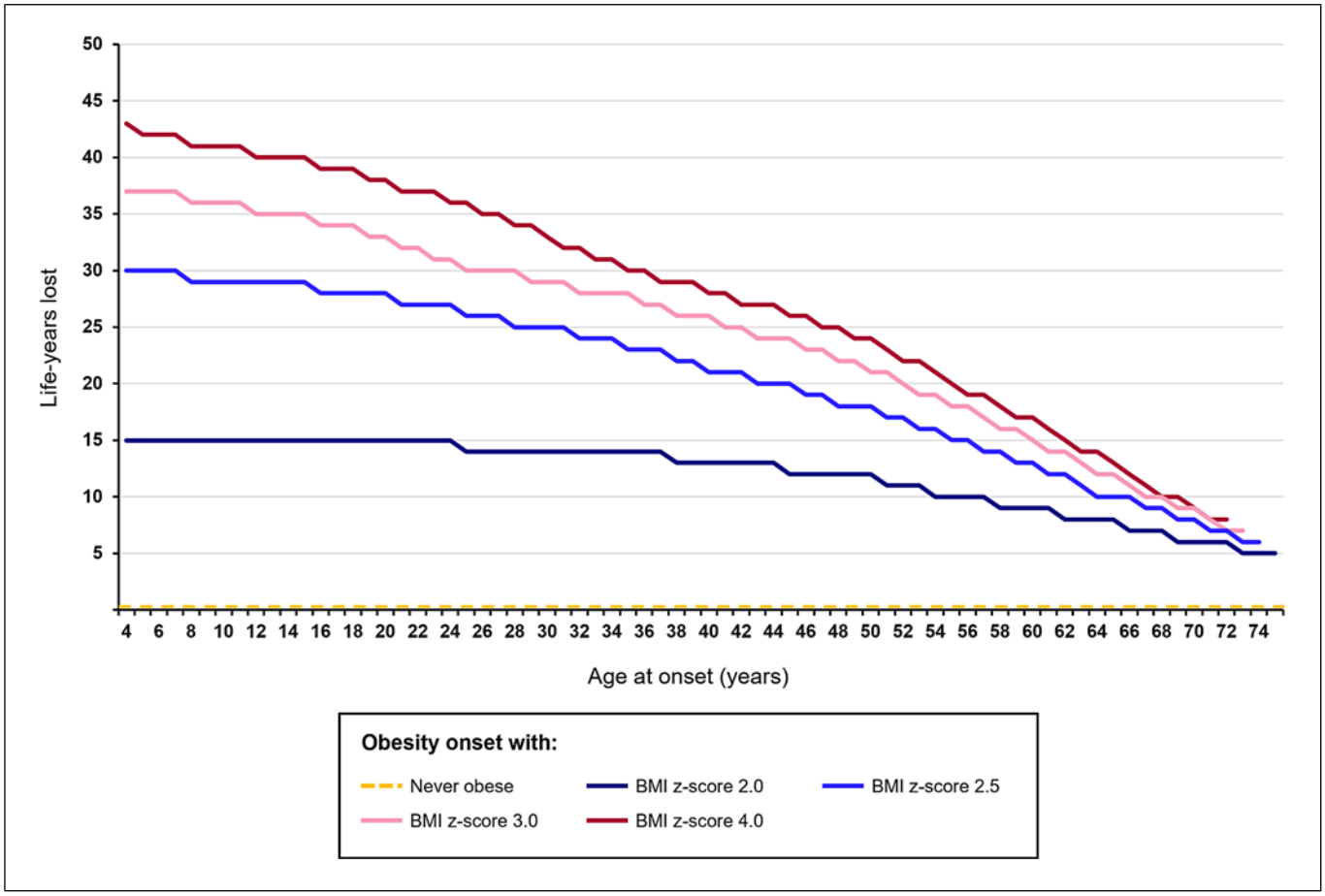

Fig. 3. LYs lost related to the age at obesity onset and severity. Four different magnitudes of obesity at onset are shown. The age of onset of obesity is shown on the x-axis, and the corresponding years of life lost are shown on the y-axis. A later onset of obesity results in fewer years of life lost and a lesser degree of obesity. The magnitude/severity of obesity remains at the same level throughout life in these modeled examples. All results are generated from the EOObesity Model and have been calculated using different patient trajectories. BMI, body mass index.

between the ages of 8 and 20. There is a stronger correlation between future cancer risk and the impact of childhood obesity than the onset of obesity in young adulthood [34].

Risk of OSA is increased substantially by very early onset obesity, but is not decreased substantially by later onset of obesity. Additional risks for cancer and OSA are provided in the online supplementary material (online suppl. Fig. S3 and S4).

Discussion

To our knowledge, this is the first model that predicts the impact of early-onset obesity on comorbidities and mortality. With all inputs based on published studies (N = 50), the model corresponds with individual outcomes reported in these studies. As part of the model development process, the impact of change in weight on comorbidities and LYs was also validated with statistical methods and expert interviews.

The model dynamics suggest the impact of early-onset obesity and severity of obesity on the development of comorbidities and on mortality risk. It shows a very high impact of severe early-onset obesity on LYX, with up to 42 years of life lost for patients reaching BMI z-score 4 by age 4 years without subsequent weight loss. Here, the number of years lost is close to half of the overall LYX. These remarkable findings are consistent with recent data not included in our model, showing that every decade of earlier onset of T2D is associated with about 3–4 years of lower LYX, and that a 50-year-old US

Table 2. DALYs calculated based on age at obesity onset (years) and BMI level

Age at obesity onset, years	DALYs				
	BMI z-score	BMI z-score	BMI z-score	BMI z-score	BMI z-score
	2	2.5	3	3.5	4
5	23.5	37.6	44.5	48.5	49.7
10	23.4	36.6	43.5	46.7	48.7
15	23.3	36.4	42.3	45.6	47.5
20	23.1	35.3	40.3	43.6	45.5
25	22.0	33.2	37.4	41.3	43.1
30	21.7	31.9	35.9	38.9	40.0
35	21.3	29.8	34.4	36.5	36.8
40	20.1	27.6	32.1	34.1	34.3
45	19.0	26.3	29.8	31.0	31.9
50	18.7	24.2	26.9	28.7	29.5
55	16.8	21.4	24.0	25.7	25.8
60	15.7	19.3	21.1	22.0	22.8
65	14.7	16.5	18.2	19.0	19.1
70	12.8	14.5	15.4	15.4	15.5

BMI, body mass index; DALY, daily-adjusted life year.

resident with T2D dies, on average, 14 years earlier when diagnosed at the age of 30 years, compared to an individual without T2D [35]. Severe early-onset obesity leads to high rates of T2D, as early as adolescence, and T2D is only one of the many contributors to loss of LYs in this model [23].

MASLD is one of these contributors, with over one-third of those with early-onset obesity developing MASLD in childhood [36, 37]. Data included in our model from a nationwide Swedish cohort show that over 20 years, the absolute risk of all-cause mortality in children and young adults with MASLD was 7.7% versus 1.1% for a matched population-based cohort without MASLD [38]. The benefit of our model is that it integrates the most important contributors to mortality, each of which already has a sizable effect, into one outcome.

The model confirms that both the magnitude and duration of obesity are critical determinants of long-term outcomes. In particular, the age at which obesity begins has a profound effect on LYX, with earlier onset leading to more years of life lost. The greatest risk comes from the combination of early-onset obesity and high BMI, with childhood obesity leading to a marked increase in the risk of CVEs from young adulthood onward. In addition, a linear increase in BMI leads to a nonlinear decrease in LYX, with a sharp decline in LYX in the early stages of obesity, which tapers off as the severity of obesity increases.

External expert validation was obtained during the development of the model and to review outcomes of patient case studies. We used the model to recreate individual patient cases and presented all the outcomes produced by the model to the clinical experts for a full review. This validation process was conducted iteratively throughout the development of the model, enabling us to adjust the model parameters and assumptions in line with the expert's real-world clinical experience. The external experts confirmed that the mortality and comorbidity risks associated with various body weight trajectories were aligned with international clinical experience. Following finalization of the model based on this expert input, we performed the aforementioned statistical validation methods to confirm and quantify the accuracy of the final model results.

The model has several limitations. First, the increase in risk due to a comorbidity being a risk factor for another comorbidity or changing the mortality risk for that of other comorbidities is not integrated into the

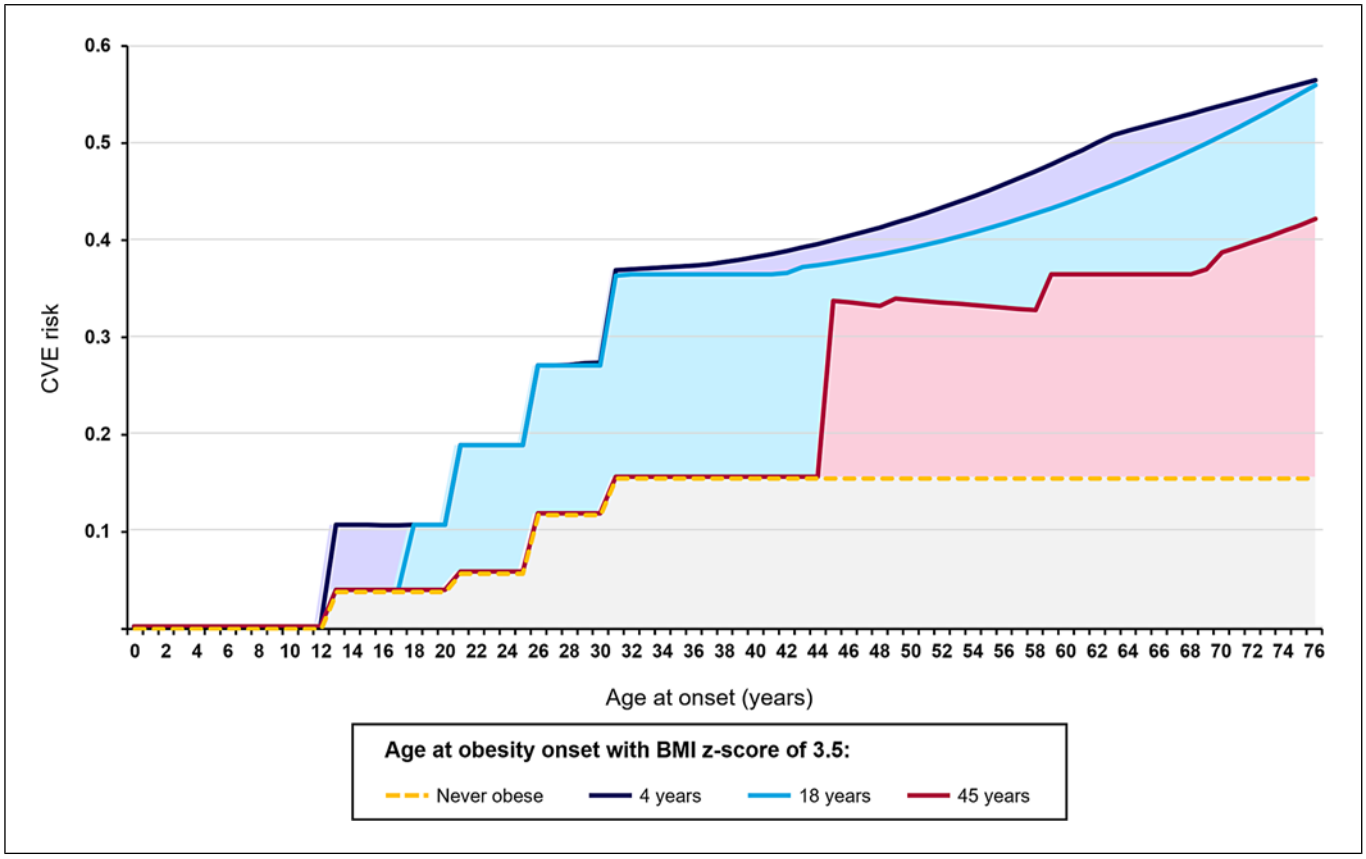

Fig. 4. Risk of a CVE related to the age at obesity onset with a BMI z-score 3.5. The increase in the risk of comorbidities for each year of age is shown for three different ages of onset of obesity, compared with an increase in the risk of never being obese over time. The AUC shows the overall lifetime risk. All results are generated from the EOObesity Model and have been calculated using different patient trajectories. AUC, area under the curve; BMI, body mass index; CVE, cardiovascular event.

model for technical reasons. The data sources used for model development often did not allow to extract the contribution of each individual comorbidity on LYX. Modeling the impact of multi-comorbidity generates a model no longer corresponding to the clinically verifiable reality because of double counting a certain number of comorbidities. In addition, combining the aforementioned duration-adjusted comorbidity risks with the comorbidity-specific mortality risks, and then further modifying the resulting all-comorbidity mortality risk with specific obesity duration mortality risk factors, would lead directly to double counting the effect of obesity duration.

Second, since the model is based on published sources from longitudinal cohorts, improved treatment of comorbidities such as T2D or CVEs could have reduced the associated mortality. In addition, waist circumference and abdominal obesity are now considered more accurate measures in assessing long-term risks [39]; however, to draw on a larger pool of study results, BMI measurement and BMI z-scores were chosen for the EOObesity Model. We acknowledge that using the BMI distribution at age 18 years as a reference point to map the standard adult BMI thresholds to their corresponding z-scores at the transition age is a methodological approximation as true z-scores are age- and sex-specific references that do not extend beyond the age of 18 years in the CDC charts. However, this standardization was necessary to create continuous risk matrices spanning all ages and to maintain mathematical consistency, while acknowledging the limitations of applying pediatric growth references to adult populations.

Also, ethnic and sex differences, familial history of comorbidities, and socioeconomic status were excluded from the modeling due to a lack of necessary data quantifying the effect of these factors on prevalence and

mortality risk figures in patients with severe obesity. The etiology of obesity and genetically determined childhood obesity were also not included in the model.

Furthermore, incorporation of lifestyle factors such as smoking status, physical activity levels, dietary patterns, and alcohol or other substance use into the risk matrices was precluded by data limitations inherent in the source studies. Although these behavioral factors are recognized as having the potential to modify obesity-related comorbidity risks, the heterogeneity in the reporting and measurement of these variables across the 226 studies that were assessed in detail precluded their systematic integration into our model input.

Early-onset obesity, in particular, is often due to the presence of obesity with a rare genetic cause, with additional metabolic or non-metabolic-associated comorbidities [7]. Some of these diseases are characterized by additional features such as increased susceptibility to infection, which increases mortality in childhood [6, 7]. Finally, the individual risk of developing comorbidities may vary from person to person. This variation may be due to differences in genetic makeup and environmental exposures. However, the model algorithm does not take this individual variability or the interaction between genes and environment into account. Unfortunately, it is not currently possible to overcome these limitations and implement these constraints into such a computational model system. Longitudinal studies, which address necessary scenarios such as development of comorbidities and LYX in cohorts with early-onset obesity or with obesity following rare diseases, e.g., those related to the leptin-melanocortin pathway, are missing. In these individuals, the EOObesity Model is likely to provide a conservative estimation of risk, based on nonselected study cohorts, and future studies are needed to develop refined estimates. Furthermore, future research could apply the model to independent datasets or population registries to provide additional external validation and improve generalizability across diverse populations and healthcare systems. Collaborative efforts to test the model against these independent cohorts could strengthen its predictive accuracy and clinical applicability even further.

Despite all the limitations mentioned, this model estimates the impact of age of onset and duration of obesity on comorbidity risk and, thereby, on LYX. As demonstrated by a long-term prospective cohort study, effective treatment of pediatric obesity can lead to a reduced risk of comorbidities, including T2D, dyslipidemia, and hypertension, with greater risk reduction observed in patients who had a better response to pediatric obesity treatment [40]. These findings emphasize the importance of effective obesity treatment strategies and interdisciplinary programs to improve access to care. Such programs could benefit people suffering with obesity, while also reducing the financial burden on national healthcare systems [41]. The model provides additional evidence that the implementation of environmental and preventative strategies to assist children in avoiding obesity could have a significant impact on their health, LYX, and quality of life [42].

In conclusion, the model suggests the major impact of early-onset obesity on comorbidities and LYX. It reinforces the importance of considering early-onset obesity as a severe chronic disease and confirms the need for early diagnosis and treatment, without waiting for comorbidities to develop, to minimize long-term negative outcomes. The model suggests that preventing obesity in young children might extend LYX and reduce disability burden. It can be used further to quantify the benefits of early weight-loss interventions in young children by directly comparing the outcomes of two possible weight trajectories for the same individual. One trajectory represents the current obesity trajectory, while the other represents the trajectory following a weight-loss intervention. The difference in the model's outcomes for both trajectories provides an indication of the potential effects of the intervention.

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Statement of Ethics

An ethics statement is not applicable because this model is based exclusively on published literature.

Conflict of Interest Statement

Urs C. H. Wiedemann is an employee of stradoo® GmbH. Erica L.T. van den Akker has no competing interests and is principal investigator in the clinical trials for genetic obesity for which the institute Erasmus MC receives funding from Rhythm Pharmaceuticals, Inc. This topic is not part of this manuscript. Thomas M. Barber has participated in advisory boards for various companies including Besins Healthcare, Novo Nordisk, and

Oviva. Karine Clément is a clinical trial investigator for Rhythm Pharmaceuticals, Inc., trials in France, BioProject, Danone Research, Integrative Phenomics, and Novo Nordisk; and has received speaker honoraria from Rhythm Pharmaceuticals, Inc. Sadaf Farooqi has consulted for a number of companies including Rhythm Pharmaceuticals, Inc., Eli Lilly, NodThera, Novo Nordisk, and Sanofi. Anthony P. Goldstone has been a consultant for Evidera, Helsinn Healthcare, Idera Pharmaceuticals, Rhythm Pharmaceuticals, Inc., Soleno Therapeutics, Tonix Pharmaceuticals, and Veda Ventures; has been an advisory board member for Millendo Therapeutics and Radius Health; has been a member of the Data Safety Monitoring Committee for Novo Nordisk; has received speaker honoraria from Novo Nordisk and Rhythm Pharmaceuticals, Inc.; and has been a Principal Investigator for clinical trials sponsored by Millendo Therapeutics, Rhythm Pharmaceuticals, Inc., and Soleno Therapeutics. Andrea M. Haqq is on advisory boards for Rhythm Pharmaceuticals, Inc., and is Principal Investigator on clinical trials for Acadia Pharmaceuticals, Eli Lilly, Novo Nordisk, and Rhythm Pharmaceuticals, Inc. Claude Marcus is on an advisory board for Novo Nordisk and Oriflame Wellness, and is shareholder and chairman of the board for Evira AB and previously advisor for Rhythm Pharmaceuticals Inc. Dénes Molnár was a member of the journal's Editorial Board at the time of submission. Luis A. Moreno has no competing interests to disclose. Evan P. Nadler has participated in advisory boards for Novo Nordisk and Rhythm Pharmaceuticals, Inc. Christine Poitou is Principal Investigator for Novo Nordisk France and is a clinical trial investigator for Rhythm Pharmaceuticals, Inc., and BioProjet. Jan Luca Schorfheide is an employee of stradoo® GmbH. Nicolas Touchot is an employee of Rhythm Pharmaceuticals, Inc. Martin Wabitsch is a clinical trial investigator for Rhythm Pharmaceuticals, Inc., and has received speaker honoraria from CHIESI Farmaceutici S.p.A., Novo Nordisk, and Rhythm pharmaceuticals, Inc. Peter Kühnen is a clinical trial investigator; was member of a Data Safety Monitoring Committee for Rhythm Pharmaceuticals, Inc., and has received a research grant from Rhythm Pharmaceuticals, Inc., and speaker honoraria from Rhythm Pharmaceuticals, Inc., Novo Nordisk, Pfizer, and Sandoz.

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Author Contributions

U.C.H.W., J.L.S., and N.T. participated in the design and creation of the model. U.C.H.W. and J.L.S. undertook the literature search, data extraction, data analysis, and validation of the model and contributed to interpretation of data and drafting of the article. All authors (U.C.H.W., E.L.T.A., T.M.B., K.C., S.F., A.P.G., A.M.H., C.M., D.M., L.A.M., E.P.N., C.P., J.L.S., N.T., M.W., P.K.) contributed to the conceptualization and critical revision of the article for important intellectual content, and gave final approval of the article.

Data Availability Statement

All data generated by the model are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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