Do existing risk equations fail to adequately account for the relationship between body mass index and mortality in subjects with type 2 diabetes?

PDB55

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Objectives

- There is a substantial body of epidemiological evidence relating body-mass index (BMI) to increased risk of cardiovascular disease and all-cause mortality (ACM) in subjects with type-2 diabetes mellitus (T2DM)[1,2].
- Cardiovascular (CV) and mortality risk equations typically incorporate the effects of elevated BMI via the inter-relationship between modifiable CV risk factors (such as cholesterol and systolic blood pressure) and BMI; this approach may underestimate true mortality risk.
- Accurate prediction of the long-term health consequences associated with the management of T2DM is crucial if the value of new health technologies that promote weight loss are to be fully captured.
- Therefore, the objective of this study was to assess by how much existing risk equations underestimate the risk of mortality as a function of increasing levels of BMI.

Methods

- This study used the IMS Core Diabetes Model (CDM) [3,4], a lifetime simulation model designed to assess the health outcomes and economic consequences of interventions in T1DM or T2DM, to evaluate the degree to which the association between all cause mortality and BMI is captured by the CV and mortality risk equations included within the model.
- The CDM was applied to project the lifetime history of 1858 individual patient level data (PLD) profiles from NHANES. Life expectancy (LE) and Quality Adjusted Life Expectancy (QALE) was assessed for each individual patient profile and results were subsequently stratified by different levels of BMI.
- The NHANES patient level data extract was obtained over the period of 1999 to 2008, consisting of T2DM subjects treated with oral therapy only.
- UKPDS based risk equations [5] were used to determine CV risk and the risk of death following the first event of MI, CHF, stroke, amputation or renal failure, and the long-term elevation of risk of death following the occurrence of one or more of these complications. Non-diabetes related mortality risk was applied based on WHO life tables.
- The association between BMI, LE and QALE was explored using two distinct approaches:

  1. The risk of CV incidence and related death was projected through the original and unmodified UKPDS equations; [referred to as 'UKPDS'].
  2. The long-term risk of death following a history of relevant complications and non diabetes specific death risk scores were subsequently adjusted for BMI. A hazard ratio of 1.29 per 5Kg higher BMI > 25 Kg/m^2 was assumed, based on data from a published prospective analysis of 900,000 adults [2]. BMI correlated risk factors such as HbA1c, SBP and lipid ratio were set to have no effect in the applied CV risk equations such that mortality difference was predominantly determined by BMI change; [referred to as 'BMI adjust'].

- LE and QALE were discounted at 3.0%.
- For both approaches, the association between BMI, LE and QALE was assessed through multiple linear regression analysis of simulation output using R [6].

Table 1: Summary statistics of NHANES population used in the patient-level analysis

	All	Normal 18.5-24.99 kg/m2	Overweight 25-29.99 kg/m2	Obese I 30-34.99 kg/m2	Obese II 35+ kg/m2
N (%)	1853	464 (24.18)	487 (26.58)	568 (31.00)	334 (18.23)
Age[Yrs] (SD)	63.62 (12.10)	67.07 (11.69)	65.42 (11.73)	62.02 (11.92)	58.70 (11.38)
Male [Proportion] (N)	0.53 (989)	0.56 (262)	0.49 (290)	0.51 (292)	0.43 (145)
Smoker [Proportion] (N)	0.16 (300)	0.20 (91)	0.15 (71)	0.17 (96)	0.13 (42)
Duration DM [Yrs] (SD)	9.56 (8.51)	11.14 (9.60)	9.46 (8.14)	8.61 (7.63)	8.99 (8.48)
SBP [mm Hg] (SD)	134.92 (21.99)	137.39 (24.23)	135.91 (22.05)	132.60 (20.29)	133.81 (21.08)
Total cholesterol [mg/dl] (SD)	189.79 (48.67)	196.37 (57.54)	195.11 (46.64)	196.56 (48.32)	189.79 (48.67)
HDL cholesterol [mg/dl] (SD)	43.30 (13.83)	51.58 (15.77)	47.59 (12.98)	46.01 (12.57)	46.30 (12.69)
HbA1c [%] (SD)	7.39 (1.79)	7.49 (2.01)	7.38 (1.81)	7.41 (1.67)	7.26 (1.66)
Body mass index [kg/m2] (SD)	30.57 (6.27)	23.67 (1.73)	28.01 (1.16)	32.51 (1.68)	40.76 (4.35)

Figure 1: Discounted life expectancy predicted by the CDM and stratified by age and level of obesity

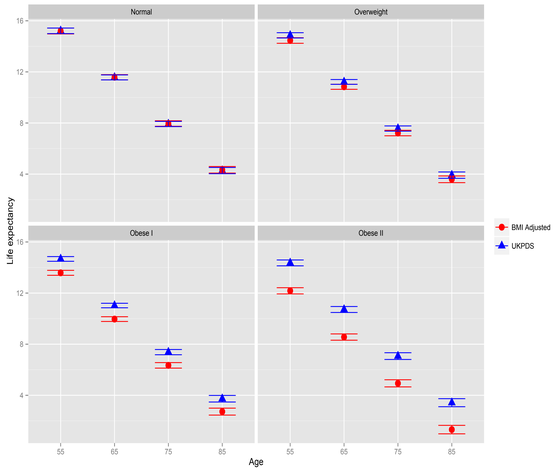
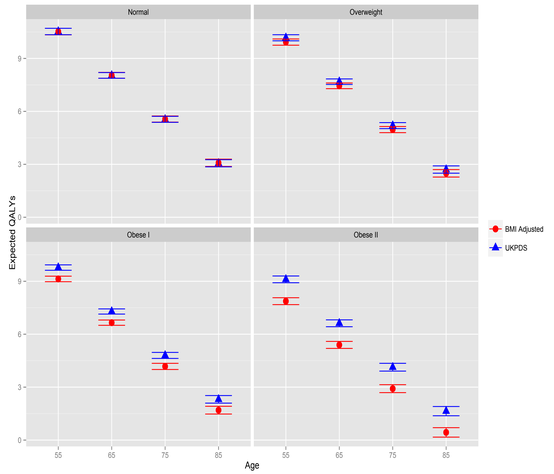


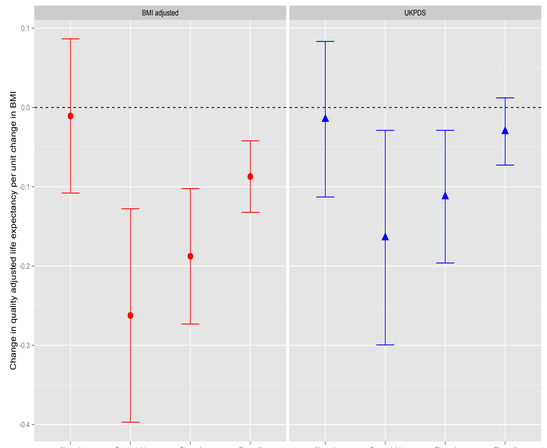
Figure 2: Discounted quality adjusted life years expected derived via the CDM and stratified by age and level of obesity



Results

- Results were obtained for 1,853 subjects with mean age 63.6 years, 53% male; 16% current smokers; duration of diabetes 9.5 years; HbA1c 7.4%; SBP 135mmHg; total cholesterol 195mg/dl and BMI 30.6kg/m2. Table 1 reports summary statistics by BMI category.
- The relationship between discounted LE (Figure 1), discounted quality adjusted life expectancy (Figure 2) and age stratified by obesity shows a considerable degree of discordance between the two scenarios modelled.
- Using UKPDS mortality risk the predicted mean discounted LE was 11.8 years with each unit increase in BMI associated with a 0.05 years less life expectancy. Using BMI cause specific mortality decreased mean discounted LE to 10.85 years; with each unit increase in BMI linearly associated with a 0.17 years reduction in LE.
- Using UKPDS mortality risk the predicted QALE was 7.81 years (95% CI: 7.68 to 7.94) while using the BMI adjusted mortality discounted QALE was 7.34 years (95% CI: 7.20 to 7.47). Figure 3 reports change in discounted QALE as a function of units changes in BMI stratified by BMI category

Figure 3: Change in discounted quality adjusted life years per unit change in BMI for the 'BMI adjust' and 'UKPDS' scenarios stratified by BMI category



Conclusion

- The management of weight, either by avoiding therapy related or natural history weight gain, and promotion of weight loss is an important component of diabetes management.
- In obese patients, conventional modifiable CV risk factors, such as SBP and cholesterol, may not fully capture the association between weight change and CV and all-cause mortality risk.
- Failure to adequately incorporate the deleterious effect of increasing levels of BMI on risk of mortality may substantially distort the health economic assessment of type 2 diabetes specific therapies; particularly those associated with the avoidance of weight gain or weight loss.

References

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Acknowledgments

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