Are we failing to capture the relationship between body mass index and cardiovascular disease and mortality in subjects with type 2 diabetes?

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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.
- Using published observational data from the Swedish National Diabetes Register (SNDR) [5] we compared the predicted incidence of fatal/nonfatal CHD (fatal/non-fatal myocardial infarction, ischaemic heart disease) and total mortality over a mean follow-up period of 5.6 years. The CDM was run using patient level data (PLD) from NHANES [6] to analyse the relationship between individual input profiles and predicted output.
- Hazard ratios (HR) from the model were compared with study HRs stratified by BMI after adjusting for baseline age, sex, duration of diabetes, BMI, smoking, HbA1c, blood pressure, use of antihypertensive and lipid-reducing drugs, and microalbuminuria.
- Results were stratified by levels of BMI: (BMI<25Kg/m^2 versus BMI >30Kg/m^2)
- 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.
- To assess the CDM's general predictive capabilities the model was first validated to UKPDS 33 [7]; ASPEN [8]; VADT [9]; ADVANCE [10]; ACCORD [11, 12]; ADDITION-Europe [13]; ASCOT [14]; CARDS [15]; UKPDS 80 [16] and DCCT [17,18].

Table 1: Summary cohort profiles used to compare endpoints predicted by the CDM with those reported in SNDR

Patient Demographics	BMI <25 kg/m2	BMI >30 kg/m2	Source
Start age	60.4 years	59.7 years	5
Duration of diabetes	10 years	8 years	5
Proportion male	0.54	0.49	5
Modifiable risk factors			
HbA1c	7.56%	7.74%	5
Systolic blood pressure	141.4 mmHg	148 mmHg	5
Total cholesterol	210 mg/dl	210 mg/dl	6
High density lipoprotein	44 mg/dl	44 mg/dl	6
BMI	23 Kg/m^2	34.1 Kg/m^2	5
Proportion smokers	0.21	0.15	5
Ethnicity			
Prop. White	0.62	0.62	6
Prop. Black	0.17	0.17	6
Prop. Hispanic	0.15	0.15	6
Prop. Native American	0.02	0.02	6
Prop. Asian/Pacific Islander	0.03	0.03	6
Baseline CVD complications			
Prop. MI	0.11	0.11	6
Prop. angina	0.11	0.11	6
Prop. PVD	0.14	0.14	6
Prop. stroke	0.09	0.09	6
Prop. HF	0.08	0.08	6
Prop. atrial filbrillation	0.01	0.01	6
Prop. LVH	0.04	0.04	6
Baseline renal complications			
Prop. MA	0.15	0.25	5
Prop. GRP	0.08	0.08	6
Prop. ESRD	0.00	0.00	6
Baseline retinopathy			
Prop. BDR	0.39	0.39	6
Prop. PDR	0.03	0.03	6
Prop. SVL	0.02	0.02	6
Baseline neuropathy			
Prop. history of amputation	0.03	0.03	6
Prop. neuropathy	0.40	0.40	6

Results

- Results from the general model validation are presented in Figure 1; with scatterplots of observed versus predicted endpoints across all validation studies stratified by year of study, trial, endpoint and diabetes type. Overall validation coefficient of determination, (R^2 = 0.89)
- Figure 3 shows the impact on predicted diabetes related endpoints obtained from the CDM in those with BMI < 25 kg/m2 compared to those with a BMI > 30 kg/m2
- Comparing subjects with BMI<25 kg/m2 (mean age 60.4 years, 53.8% male; 20.7% current smokers; duration of diabetes 9.8 years; HbA1c 7.56%; SBP 141.4mmHg and BMI 23.0 kg/m2) to those with BMI >30 kg/m2 (mean age 59.7 years, 49.0 % male; 14.7% current smokers; duration of diabetes 7.7 years; HbA1c 7.7.4%; SBP 148.0mmHg and BMI 34.1 kg/m2) produced study hazard ratios of 1.25 (1.09 - 1.44) and 1.47 (1.16-1.85) for CHD and total mortality respectively.
- Hazard ratios derived from the CDM were 1.062 (1.051-1.072) and 0.966 (0.956-0.977) for CHD and total mortality respectively; see Figure 3.

Figure 1: Scatterplot of observed versus predicted endpoints across all validation studies stratified by year of study, trial, endpoint and diabetes type. Validation coefficient of determination, (R^2 = 0.89)

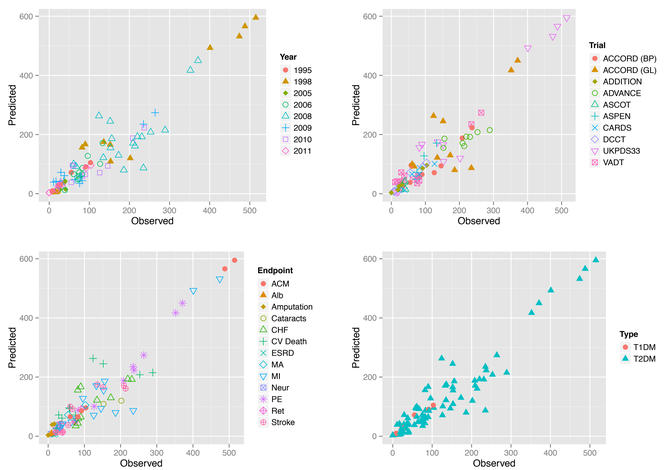


Figure 2: Predicted diabetes related endpoints obtained from the CDM in those with BMI < 25 kg/m2 compared to those with a BMI > 30 kg/m2

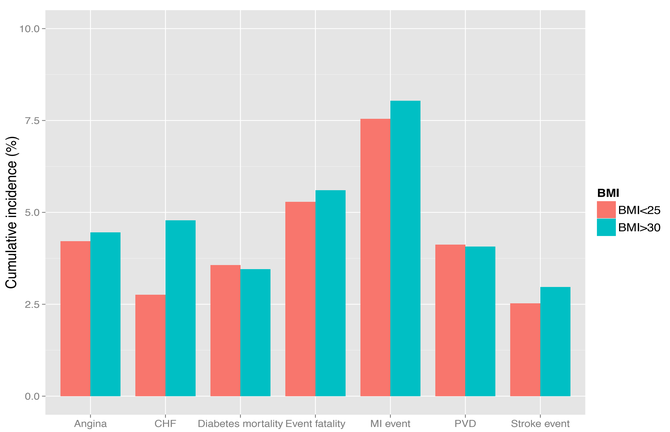
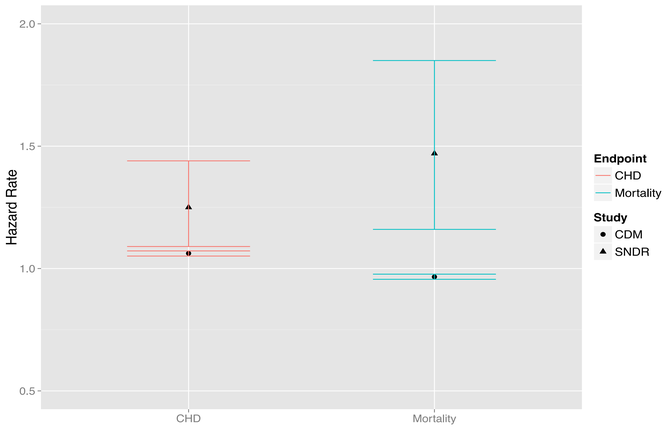


Figure 3: Comparing hazard ratios (with 95% confidence intervals) from the Swedish National Diabetes Registry with those predicted from the CDM



Conclusion

- This study demonstrates that despite using a diabetes model that has been shown to have good predictive validity to cardiovascular and mortality events reported across a large number of major T2DM outcomes studies the model significantly underestimates the relationship between increasing BMI and CHD and total mortality risk.
- There is a need for improved risk equations for use in diabetes models that adequately capture the deleterious effects of increasing body weight, particularly, if the true value of avoiding weight gain or weight loss is to be characterised.

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Acknowledgments

The CORE Diabetes Model is owned and maintained by IMS Health

Presented at the 49th Annual Meeting of the European Association for the Study of Diabetes, Barcelona, Spain, September 23-27, 2013