Relationship Between a Single Measurement at Baseline of Body Mass Index, Glycated Hemoglobin and the Risk of Mortality and Cardiovascular Morbidity in Type 2 Diabetes Mellitus

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Abstract

Objective

This study aims to evaluate the relation between a single measurement at baseline of body mass index (BMI), glycated hemoglobin (HbA1c) and subsequent clinical outcomes in patients with type 2 diabetes mellitus (T2DM).

Method

Patients with T2DM were recruited from an outpatient diabetes clinic in a single large teaching hospital in Kingston upon Hull, UK. At baseline, demographics and HbA1c were recorded. Patients were categorized by BMI: normal weight (18.5-24.9 kg/m2), overweight (25-29.9 kg/m2) and obese (>30 kg/m2). Multivariable Cox regression models that included demographic, risk factors and comorbidities were separately constructed for all-cause, cardiovascular, cancer and sepsis related mortality, using four groups of HbA1c (<6%, 6.0-6.9%, 7.0-7.9% and >8%)

Results

In total, 6220 patients with T2DM (median age 62 years, 54 % male) were followed for a median of 10.6 years. HbA1c levels >8.0% were associated with increased risk of all-cause mortality and cardiovascular death. However, this increased risk was not consistent across the weight categories and reached statistical significance only in overweight patients (BMI 25-29.9 kg/m^2).

Conclusions

In a large cohort of patients with T2DM elevated HbA1c levels at baseline do not consistently predict increased risk of all-cause and cardiovascular mortality across the different BMI categories.

Introduction

Type 2 diabetes mellitus (T2DM) and obesity are major causes of morbidity and mortality worldwide.[1] Obesity is a major risk factor for both diabetes and cardiovascular disease.[2,3]

The percentage of hemoglobin that is glycated in the blood (HbA1c) is routinely used in the diagnosis and monitoring of patients with diabetes. Large epidemiological studies in patients with T2DM suggest that having either a high or a low HbA1c is associated with increased all-cause mortality compared with HbA1c in the middle of the range.[4,5] A number of factors are known to affect HbA1c levels, mainly time since diagnosis of diabetes, cholesterol levels and age.[6,7]

The association between HbA1c and body weight is less clear and mainly affected by the interaction of different hypoglycemic treatment which can reduce HbA1c levels and cause either weight loss or gain.[8] Whether the relationship body weight and HbA1c affects clinical prognostic outcomes is unclear. To our knowledge this association has never been fully explored, but only investigated in the context of interaction analysis between HbA1c and BMI to predict all-cause mortality.[5,9] In particular, Van Munster et al demonstrated a significant interaction between HbA1c and BMI toward risk of mortality in a cohort of T2DM patients. [9]Similarly, Li et al in a subgroup analysis of their study demonstrated that higher HbA1c levels were associated with increased risk of mortality in obese diabetic patients.[5]

The aim of our study was to assess the relationship between a single measurement at baseline of glycated hemoglobin (HbA1c), body mass index (BMI) and the risk of all-cause mortality, causal mortality and hospitalization for cardiovascular outcomes in patients with T2DM.

Methods

Study Population

Patients with a diagnosis of T2DM who attended the outpatient clinic service for diabetes in Kingston upon Hull, UK, were enrolled in a registry between 1995 and 2005. The secondary diabetes service in Kingston upon Hull provided most of the care that is usually provided by primary care service elsewhere, particularly during the years analysed for this cohort. In particular, the catchment area for the diabetic service covered about 230,000 people, of whom an estimated 6% have been diagnosed with T2DM[10].

Data were collected by medical and nursing staff and entered into a specifically designed electronic database [Angoss (Westman Medical Software, Manchester, UK)]. More than 99% of patients at the first visit had no known history of cardiovascular disease (CVD) (ischaemic heart disease, cerebrovascular, heart failure or peripheral vascular disease). Data on age, time since diagnosis of diabetes, smoking history, height, weight, and blood pressure were collected at the initial visit. Information on comorbidity (cancer, chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD)) was collected at baseline.

Patients were divided by BMI category as recommended by the World Health Organization (WHO): underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2) and obese (>30 kg/m^2).[11] The cohort was followed for clinical events until December 2011.

Ethics

The study protocol along with all other study documentation was approved by the research ethics committee (reference number 13/SW/0168).

Study Outcomes

The primary outcome of the analysis was all-cause mortality. A national register informed the hospital of the death of any patient previously under the hospital's care regardless of whether the patient had left the region. In addition to all-cause mortality, the cause of death was obtained from the Office of National Statistics. We divided deaths as being due to: cardiovascular; cancer; sepsis (intended as a general term of infective illness). The secondary outcome was cardiovascular hospitalizations, divided into: acute coronary syndrome (ACS); heart failure (HF); and cerebrovascular accident (CVA). Information on hospitalizations, coded using the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM), and mortality was collected through the Patient Information Service of the Hull and East Yorkshire Hospitals National Health Service Trust, the sole hospital provider of emergency medical services in the region.

Statistical analysis

Results are presented as medians and interquartile ranges (IQR). Kruskal-Wallis tests for nonparametric data and chi square tests were used to compare continuous and dichotomous data, respectively, between BMI categories.

Multivariable Cox regression models were constructed for all-cause mortality and cardiovascular events (ACS, CVA, or HF) using four groups of HbA1c (<6%, 6.0-6.9% (reference group), 7.0-7.9% and >8%). The models were adjusted for age, sex, time since diagnosis of diabetes, smoking history, systolic blood pressure and comorbidities that could have affected the body weight like COPD, cancer and CKD. If a patient had more than one admission for a given cause, only the first admission was included in the analysis. Each model was constructed for each BMI category. We excluded underweight patients (BMI <18.5), as their sample size was small (only 44 patients). To check the consistency of the results we

performed a sensitivity analysis by assessing the outcomes in reverse by constructing each model for categories of HbA1c.

All analyses were presented as hazard ratios (HR) with 95% confidence intervals (95% CI). A two-tailed P value less than 0.05 was considered statistically significant. Adjustment for multiple tests was made using the Benjamini-Hochberg procedure.

All analyses were performed using STATA 11.0 (Stata Corp. College Station, TX, USA) and SPSS, 23.0 (IBM Corp. Chicago, IL, USA).

Data and Resource Availability

The data supporting the findings of this study are available from our institution as aggregate data, as restrictions apply to the availability to confidentiality agreements. Under certain circumstances, data are available from the authors upon reasonable request and with permission of the National Health Service relevant institutions.

Results

The cohort (Table 1) included 6,220 patients (54% men) who had a median age of 62 (IQR 42 - 82) and were followed up for a median of 10.6 years (IQR 4.6-16.6). Only 44 patients (0.7%) were classed as underweight, 1,354 (21.8%) patients were normal weight, 2,316 patients (37.2%) were overweight and 2,505 (40.3%) patients were obese.

Of 2,187 patients (35.2%) who died during follow-up, 946 (15.2%) died from cardiovascular causes, 423 (6.8%) from cancer, 527 (8.5%) were sepsis-related deaths and 291 (4.7%) died from other causes (including pulmonary embolism and uncategorized causes). In addition, there were 1,305 patients hospitalized for a cardiovascular event: 535 for ACS (8.6%), 356 for HF (5.7%) and 414 for CVA (6.7%).

Irrespective of BMI category, a baseline single measurement of HbA1c >8.0 was associated with increased risk of all-cause and cardiovascular mortality (HR 1.17, 95% CI: 1.04-1.32, p=0.008) (Figure 1). However, HbA1c was not shown to significantly predict cardiovascular hospitalization (Figure 2).

For patients with a normal BMI, an increased baseline single measurement of HbA1c was not associated with all-cause, cause-specific mortality (Figure 1) or hospitalization for ACS, HF or stroke (Figure 2).

For patients who were overweight, a baseline single measurement of HbA1c <6.0 was associated with an increase in all-cause mortality (HR: 1.35, 95% CI: 1.02-1.79, p = 0.03), which might have been driven by an increase in sepsis-related death (HR: 1.80, 95% CI: 1.04-3.14, p = 0.04). HbA1c >8.0 was associated with a borderline-significant increase in cardiovascular death (HR: 1.32, 95% CI: 1.00-1.77, p = 0.05). HbA1c was not associated with

an increase in cancer-related deaths (Figure 1). There was no significant association between HbA1c and rate of ACS, HF or stroke (Figure 2).

Similarly to patients with normal weight, for obese patients, there was no significant association between HbA1c and any of the clinical outcomes (Figures 1 and 2).

The multiple-test procedure for type I error control gave an adjusted $p < 0.001$ to be possibly considered statistically significant. Therefore, we cannot exclude that in view of multiple testing the statistical significant results of these studies are the result of type I error.

Finally, as sensitivity analysis we assessed the outcomes in reverse by constructing each model for categories of HbA1c. This did not show a substantial difference in the results (Supplemental Tables and Supplemental Figure 1)

Discussion

In a large cohort of patients with T2DM, enrolled consecutively at their first-attendance at a diabetes clinic, increasing HbA1c levels were not consistently associated with increased risk of all-cause mortality and cardiovascular death. A single baseline measurement of HbA1c >8.0% was associated with increased mortality only in overweight patients (BMI 25-29.9 kg/m^2). In the other weight categories (normal and obese) a trend of increased all cause and cardiovascular mortality was observed with a HbA1c >8.0%, although this did not reach statistical significance

In our study, single baseline measurement of HbA1c did not significantly predict cardiovascular hospitalizations, although there was a trend of higher HbA1c levels and risk of CVA and HF hospitalizations.

It is well acknowledged that higher levels of HbA1c are associated with increased mortality in diabetic patients, as we have confirmed in our study. [5,9,12] Previous studies have investigated BMI as an interacting factor with HbA1c toward prognostic outcomes.[5,9] Compared to these studies, ours is the first study that systematically investigated the prognostic value of HbA1c according to different weight categories for different causes of death and adjusting for comorbidities that could have affected the BMI.

In view of these differences in study design, our results are not directly comparable with the available literature, however some consistency in the results can be observed with Li et al. In particular, in their subgroup analysis of a study in which they investigated the association of HbA1c with all-cause mortality in a T2DM population, they reported an increased mortality with an HbA1c >9.0% in obese patients ($BMI \geq 30 kg/m^2$).[5]
Our results are consistent with those from Van Munster et al. Similarly, they investigated the relationship of HbA1c with cardiovascular events and mortality in a cohort of patients with T2DM. Similarly, they did not find a significant association between higher levels of HbA1c

and cardiovascular events or all-cause mortality, although they reported an interaction with BMI as continuous variable.[9] Compared to our study, Van Munster et al had a smaller sample size (1753 patients) and did not have the possibility to include comorbidities in their statistical analysis.[9]

Higher HbA1c is associated with an increased risk of macrovascular and microvascular complications in patients with diabetes,[13–15] and so a relation between HbA1c and mortality might be expected. We found such an association in the overweight subset of patients (BMI 25-29.9 kg/m^2). Whereas, only a trend towards increased risk of all-cause and cardiovascular mortality with HbA1c level >8% was observed in normal and obese patients. It could possible that with a bigger sample size statistical significance could have been reached. Interestingly, intermediate levels of glycemic control like HbA1c 7-7.9% were not associated with increased risk of cardiovascular hospitalizations, cardiovascular or all-cause mortality in any of the BMI categories.

A recent systematic review reported that raised HbA1c is associated with an increase in cancer mortality,[16] in particular pancreatic, colorectal, respiratory and gynecological cancers. In our study, HbA1c levels were not associated with cancer-related mortality (Figure 1), in the overall population and across the weight categories.

In our study, the association between HbA1c <6.0 and increased risk of death amongst patients who were overweight was possibly driven by sepsis. In a study of patients with T2DM and sepsis, higher HbA1c at admission was associated with increased hospital mortality, but this was a very different population from ours. In our study, the link between low HbA1c and

increased mortality might reflect frailty, which increases the risk of sepsis and impairs recovery from illness.[17]

Limitations

There is a risk of type II error as some of the subgroups were small. Some true associations between HbA1c and clinical outcome may thus have been missed due to low statistical power.

We included patients only recruited before 2006 and the management of diabetes has subsequently changed substantially, which might have an impact on outcome. Particularly in the UK, in 1996 sulphonylureas were the main treatment. However, by 2005 the use of this drug class had decreased substantially, and there had been an increase of treatment with metformin and glitazone.[18]

Patients will have had different time since diagnosis of T2DM prior to referral, which may have affected both HbA1c and weight. We did not have information on medications, cholesterol levels, education or ethnicity, although our population is almost exclusively of European decent. We do not have information on hospitalizations outside the Hull and East Yorkshire Hospital Trust, but the rate of emigration from the area amongst adults is low.

We used only measurements made at the time of referral. Treatment and the evolution of disease will have altered risk factors, weight and HbA1c, which may have disrupted the relationship with initial measurements.

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PC and OB are the guarantors of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

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Figure legends

Figure 1 - Adjusted Cox Regression analysis of HbA1c and all-cause mortality, cardiovascular mortality, cancer mortality and sepsis mortality. Model adjusted for age, sex, time since diagnosi of diabetes, smoking history, systolic blood pressure and comorbidities that could have affected the body weight like COPD, cancer and CKD. *Abbreviations*: BMI, Body Mass Index; CI, Confidence Interval; HR, Hazard Ratio; N, number

Figure 2 - Adjusted Cox Regression analysis of HbA1c and hospitalization for ACS, CVA and HF. Model adjusted for age, sex, time since diagnosis of diabetes, smoking history, systolic blood pressure and comorbidities that could have affected the body weight like COPD, cancer and CKD. *Abbreviations*: ACS, Acute Coronary Syndrome; BMI, Body Mass Index; CI, Confidence Interval; CVA, Cerebrovascular Accident; HF, Heart Failure; HR, Hazard Ratio; N, number

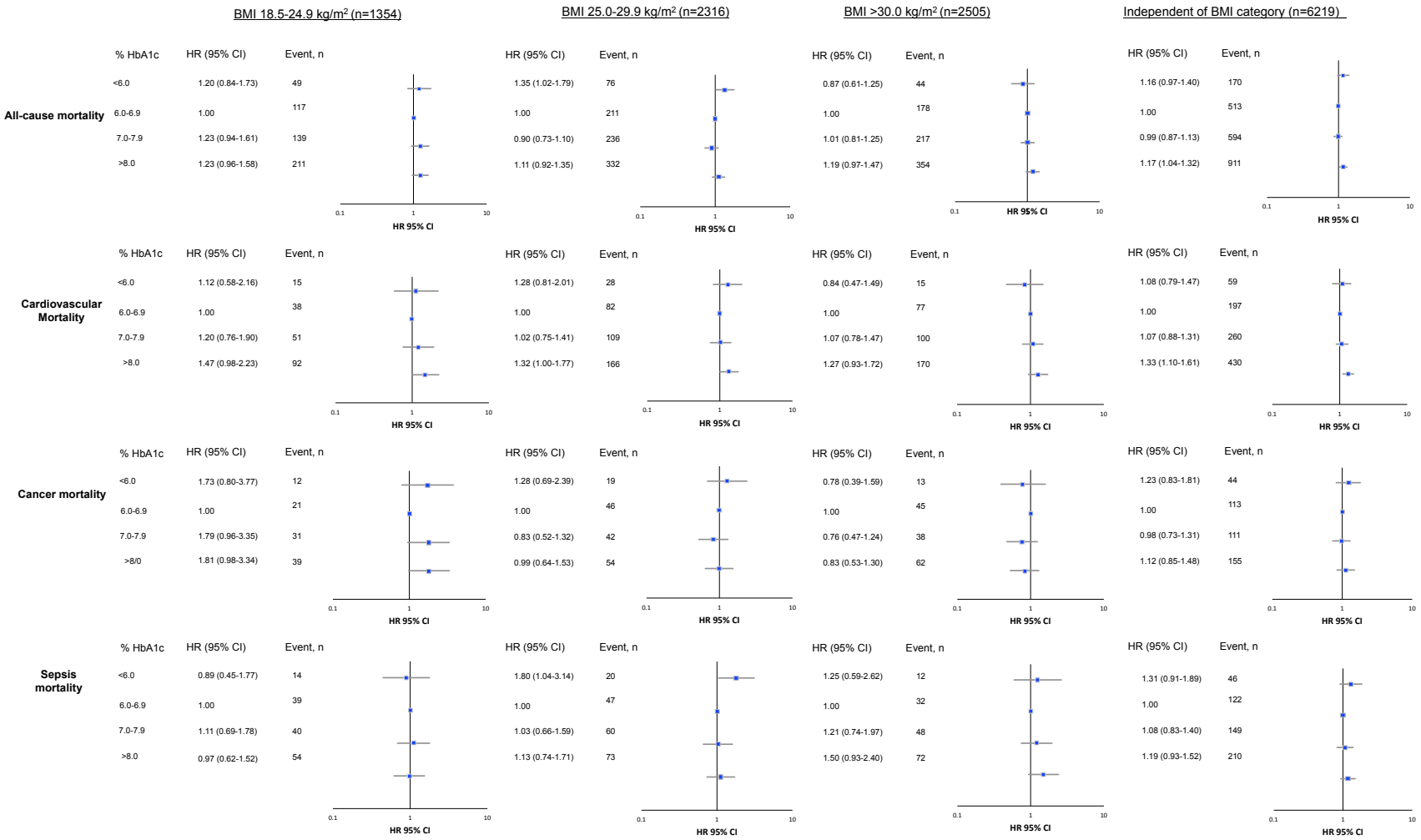
Supplemental Figure 1 - Adjusted Cox Regression analysis of BMI categories divided by HbA1c groups and all-cause mortality, cardiovascular mortality, cancer mortality and sepsis mortality. Model adjusted for age, sex, time since diagnosis of diabetes, smoking history, systolic blood pressure and comorbidities that could have affected the body weight like COPD, cancer and CKD. *Abbreviations*: BMI, Body Mass Index; CI, Confidence Interval; HR, Hazard Ratio; N, number

Table 1 – Baseline characteristics of study population. Where not already stated results are shown as median (interquartile range)

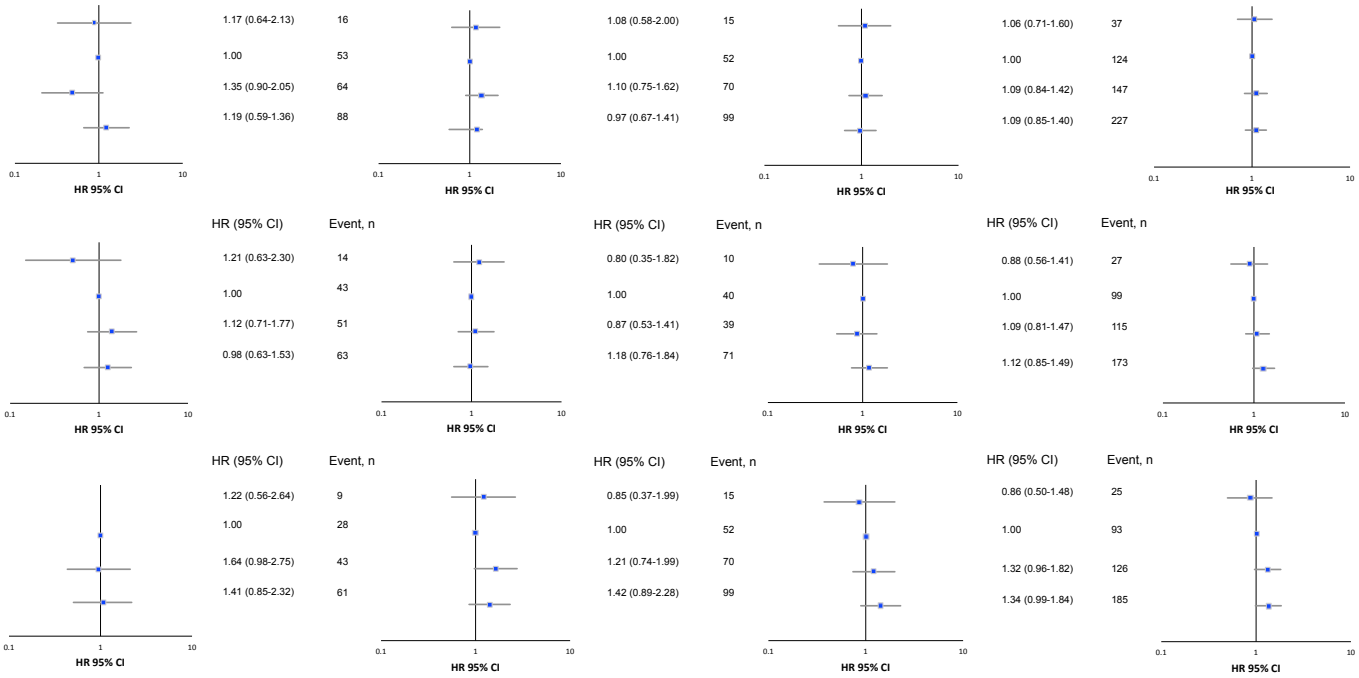
Supplemental Tables - Assessment of outcomes divided by HBa1c categories.

Variable	Total population	BMI				P value
		<18.5	18.5-24.9	25-29.9	>30	
Total (n)	6220	44	1354	2316	2505	<0.001
Age (years)	62.0 (20)	56.0 (37.0)	64.0 (28.0)	64.0 (17.0)	60.0 (17)	<0.001
Men (%)	54.1	48.8	52.2	62.4d	47.6	<0.001
Time since diagnosis of diabetes (years)	2.0 (7.0)	1.5 (5.3)	4.0 (11.0)	2.0 (7.0)	1.0 (4.0)	<0.001
Follow up duration (years)	10.6 (6.0)	8.3 (10.3)	11.6 (7.1)	11.1 (6.2)	10.8 (5.4)	0.009
Height (m)	1.67 (0.15)	1.64 (0.16)	1.67 (0.15)	1.69 (0.14)	1.65 (0.16)	<0.001
Weight (kg)	81.0 (23.4)	48.0 (10.0)	64.2 (12.8)	78.0 (13.3)	95.1 (19.3)	<0.001
BMI	28.7 (7.3)	17.6 (0.9)	23.2 (2.4)	27.6 (2.4)	34.0 (5.7)	<0.001
SBP (mmHg)	142.0 (29.0)	126.0 (34.5)	136.0 (34.0)	142.2 (28.0)	141.0 (28.0)	<0.001
Smoking (%)	15.3	36.3	18.5	14.3	16.3	<0.001
Cancer (%)	14.6	9.1	12.3	15.5	15.2	0.033
CKD (%)	8.2	6.8	6.5	9.9	7.5	0.001
COPD (%)	7.8	15.9	4.9	7.0	8.7	<0.001

Table 1 – Baseline characteristics of study population. Where not already state results are shown as median (interquartile range)


BMI 18.5-24.9 kg/m² (n=1354)
BMI 25.0-29.9 kg/m² (n=2316)
BMI >30.0 kg/m² (n=2505)
Independent of BMI category (n=6219)
All-cause mortality
Cardiovascular Mortality
Cancer mortality
Sepsis mortality
% HbA1c
HR (95% CI)
Event, n
<6.0
6.0-6.9
7.0-7.9
>8.0
>8/0
1.20 (0.84-1.73)
1.00
1.23 (0.94-1.61)
1.23 (0.96-1.58)
49
117
139
211
1.35 (1.02-1.79)
1.00
0.90 (0.73-1.10)
1.11 (0.92-1.35)
76
211
236
332
0.87 (0.61-1.25)
1.00
1.01 (0.81-1.25)
1.19 (0.97-1.47)
44
178
217
354
1.16 (0.97-1.40)
1.00
0.99 (0.87-1.13)
1.17 (1.04-1.32)
170
513
594
911
1.12 (0.58-2.16)
1.00
1.20 (0.76-1.90)
1.47 (0.98-2.23)
15
38
51
92
1.28 (0.81-2.01)
1.00
1.02 (0.75-1.41)
1.32 (1.00-1.77)
28
82
109
166
0.84 (0.47-1.49)
1.00
1.07 (0.78-1.47)
1.27 (0.93-1.72)
15
77
100
170
1.08 (0.79-1.47)
1.00
1.07 (0.88-1.31)
1.33 (1.10-1.61)
59
197
260
430
1.73 (0.80-3.77)
1.00
1.79 (0.96-3.35)
1.81 (0.98-3.34)
12
21
31
39
1.28 (0.69-2.39)
1.00
0.83 (0.52-1.32)
0.99 (0.64-1.53)
19
46
42
54
0.78 (0.39-1.59)
1.00
0.76 (0.47-1.24)
0.83 (0.53-1.30)
13
45
38
62
1.23 (0.83-1.81)
1.00
0.98 (0.73-1.31)
1.12 (0.85-1.48)
44
113
111
155
0.89 (0.45-1.77)
1.00
1.11 (0.69-1.78)
0.97 (0.62-1.52)
14
39
40
54
1.80 (1.04-3.14)
1.00
1.03 (0.66-1.59)
1.13 (0.74-1.71)
20
47
60
73
1.25 (0.59-2.62)
1.00
1.21 (0.74-1.97)
1.50 (0.93-2.40)
12
32
48
72
1.31 (0.91-1.89)
1.00
1.08 (0.83-1.40)
1.19 (0.93-1.52)
46
122
149
210
0.1
1
10
HR 95% CI

	BMI 18.5-24.9 kg/m² (n=1354)			BMI 25.0-29.9 kg/m² (n=2316)			BMI >30.0 kg/m² (n=2505)			Independent of BMI category (n=6219)		
	% HbA1c	HR (95% CI)	Event, n	HR (95% CI)	Event, n		HR (95% CI)	Event, n		HR (95% CI)	Event, n	
ACS	<6.0	0.88 (0.32-2.43)	6	1.17 (0.64-2.13)	16		1.08 (0.58-2.00)	15		1.06 (0.71-1.60)	37	
	6.0-6.9	1.00	19	1.00	53		1.00	52		1.00	124	
	7.0-7.9	0.48 (0.21-1.11)	13	1.35 (0.90-2.05)	64		1.10 (0.75-1.62)	70		1.09 (0.84-1.42)	147	
	>8.0	1.22 (0.66-2.28)	40	1.19 (0.59-1.36)	88		0.97 (0.67-1.41)	99		1.09 (0.85-1.40)	227	
CVA	% HbA1c	HR (95% CI)	Event, n	HR (95% CI)	Event, n		HR (95% CI)	Event, n		HR (95% CI)	Event, n	
	<6.0	0.51 (0.15-1.77)	3	1.21 (0.63-2.30)	14		0.80 (0.35-1.82)	10		0.88 (0.56-1.41)	27	
	6.0-6.9	1.00	16	1.00	43		1.00	40		1.00	99	
	7.0-7.9	1.41 (0.75-2.67)	25	1.12 (0.71-1.77)	51		0.87 (0.53-1.41)	39		1.09 (0.81-1.47)	115	
	>8.0	1.26 (0.68-2.32)	39	0.98 (0.63-1.53)	63		1.18 (0.76-1.84)	71		1.12 (0.85-1.49)	173	
HF	% HbA1c	HR (95% CI)	Event, n	HR (95% CI)	Event, n		HR (95% CI)	Event, n		HR (95% CI)	Event, n	
	<6.0	Insufficient number of events	1	1.22 (0.56-2.64)	9		0.85 (0.37-1.99)	15		0.86 (0.50-1.48)	25	
	6.0-6.9	1.00	13	1.00	28		1.00	52		1.00	93	
	7.0-7.9	0.95 (0.43-2.09)	13	1.64 (0.98-2.75)	43		1.21 (0.74-1.99)	70		1.32 (0.96-1.82)	126	
	>8.0	1.06 (0.51-2.19)	25	1.41 (0.85-2.32)	61		1.42 (0.89-2.28)	99		1.34 (0.99-1.84)	185	



HbA1c <6.0%

HbA1c 6.0-6.9%

HbA1c 7-7.9%

HbA1c >8.0%

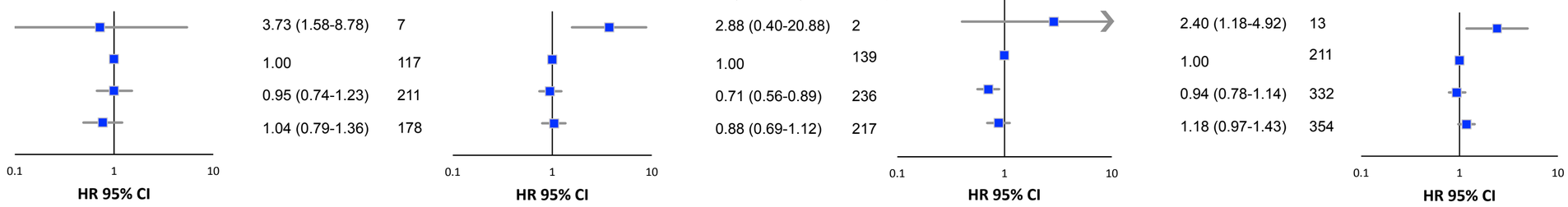
All-cause mortality

BMI	HR (95% CI)	Event, n
<18.5	0.72 (0.10-5.45)	1
18.5-24.9	1.00	49
25.0-29.9	1.00 (0.67-1.51)	76
>30.0	0.77 (0.49-1.21)	44

HR (95% CI)	Event, n
3.73 (1.58-8.78)	7
1.00	117
0.95 (0.74-1.23)	211
1.04 (0.79-1.36)	178

HR (95% CI)	Event, n
2.88 (0.40-20.88)	2
1.00	139
0.71 (0.56-0.89)	236
0.88 (0.69-1.12)	217

HR (95% CI)	Event, n
2.40 (1.18-4.92)	13
1.00	211
0.94 (0.78-1.14)	332
1.18 (0.97-1.43)	354



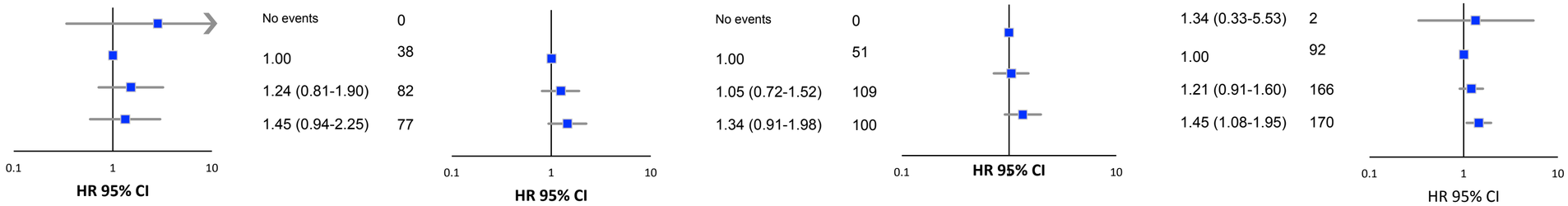
Cardiovascular Mortality

BMI	HR (95% CI)	Event, n
<18.5	2.84 (0.34-24.0)	1
18.5-24.9	1.00	15
25.0-29.9	1.52 (0.72-3.21)	28
>30.0	1.33 (0.59-3.00)	15

HR (95% CI)	Event, n
No events	0
1.00	38
1.24 (0.81-1.90)	82
1.45 (0.94-2.25)	77

HR (95% CI)	Event, n
No events	0
1.00	51
1.05 (0.72-1.52)	109
1.34 (0.91-1.98)	100

HR (95% CI)	Event, n
1.34 (0.33-5.53)	2
1.00	92
1.21 (0.91-1.60)	166
1.45 (1.08-1.95)	170



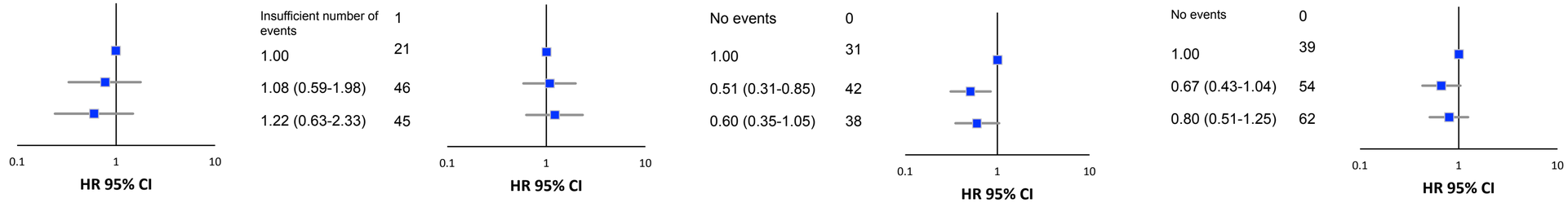
Cancer mortality

BMI	HR (95% CI)	Event, n
<18.5	No events	0
18.5-24.9	1.00	12
25.0-29.9	0.77 (0.33-1.77)	19
>30.0	0.60 (0.24-1.48)	13

HR (95% CI)	Event, n
Insufficient number of events	1
1.00	21
1.08 (0.59-1.98)	46
1.22 (0.63-2.33)	45

HR (95% CI)	Event, n
No events	0
1.00	31
0.51 (0.31-0.85)	42
0.60 (0.35-1.05)	38

HR (95% CI)	Event, n
No events	0
1.00	39
0.67 (0.43-1.04)	54
0.80 (0.51-1.25)	62



Sepsis mortality

BMI	HR (95% CI)	Event, n
<18.5	No events	0
18.5-24.9	1.00	14
25.0-29.9	1.06 (0.47-2.39)	20
>30.0	0.82 (0.33-2.03)	12

HR (95% CI)	Event, n
7.27 (2.30-23.04)	4
1.00	39
0.57 (0.35-0.93)	47
0.59 (0.35-1.02)	32

HR (95% CI)	Event, n
Insufficient number of events	1
1.00	40
0.55 (0.35-0.85)	60
0.64 (0.40-1.03)	48

HR (95% CI)	Event, n
7.41 (3.06-17.90)	11
1.00	54
0.78 (0.53-1.14)	73
1.02 (0.69-1.53)	72