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# Association between insulin-induced weight change and CVD mortality: Evidence from a retrospective cohort study of 18,814 patients in UK Primary Care

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**Novelty statement:**

- Despite the well-recognised correlation between weight gain and cardiovascular (CV) disease, as well as Insulin-induced weight gain, there is little direct evidence relating to the impact of insulin-induced weight gain on CV outcomes.
- This study robustly investigates the impact of insulin-induced weight gain on the 5-year risk of CV outcome and mortality
- Weight loss >5kg in insulin users was associated with up to 31% higher risk of a three-point composite of mortality, non-fatal acute myocardial infarction (MI) and non-fatal stroke.
- We observed that although insulin treatment was indeed associated with weight gain, this did not translate to adverse CV outcomes and mortality in patients with T2D and so provides reassurance on the cardiovascular safety of insulin-induced weight gain in these patients.

**Abstract:**

**Background:** This study aims to explore the association of insulin-induced weight (wt) gain on CV outcomes and mortality amongst patients with T2D following insulin initiation using real-world data

**Methods:** A retrospective cohort study was performed in 18,814 adults with insulin-treated T2D derived from the UK Health Improvement Network (THIN) database. Based on the average weight change of 5kg, one year post-insulin initiation, patients were grouped into 5 categories (>5kg wt loss; 1.0-5.0kg wt loss; no wt change; 1.0-5.0kg wt gain; and >5.0kg wt gain) and followed-up for 5 yrs. Cox proportional hazard models and Kaplan-Meier estimators were fitted to estimate the hazards of a three-point composite of non-fatal myocardial infarction, stroke and all-cause mortality between the categories.

**Results:** The median age was 62.8 (IQR: 52.3–71.8) years, HbA1c: 8.6% (IQR: 7.4–9.8) and mean BMI: 31.8(6.5) kg/$m^2$. The 5-year probability of survival differed significantly within the wt-change categories (log-rank test p-value=0.0005). A total of 1963 composite events occurred. Compared to the weight-neutral group, the risk of composite events was 31% greater in the >5kg wt-loss group (aHR: 1.31; 95%CI: 1.02, 1.68), the same in the 1.0-5.0kg wt-gain category; but non-significantly increased in the 1.0-5.0kg wt-loss (15%); and >5.0kg wt-gain (13%) categories respectively. In the obese subgroup, this risk was 50% (aHR: 1.50, 95%CI: 1.08 – 2.08) more in the >5kg weight-loss group, compared to the weight-neutral group.

**Conclusion:** Insulin-induced weight-gain did not translate to adverse CV outcomes and mortality in patients with T2D. This data provides reassurance on the cardiovascular safety of insulin-induced wt gain in patients with T2D

**Introduction:**

Insulin therapy commonly results in weight gain in patients with type 2 diabetes (T2D).[1] In the United Kingdom Prospective Diabetes Study (UKPDS), patients in the intensive intervention cohort gained in excess of 5 kg during the 10-year follow-up period, with most of this gain occurring in the first 12 months.[2] In routine clinical practice, however, we have previously shown that the effectiveness of insulin therapy to lower HbA1c levels however is variable and associated with patients' baseline weight.[3,4] This is because insulin-induced weight gain results in an increase in the amount of insulin required to control hyperglycaemia [5,6], at the expense of further weight gain, possible poor treatment compliance and increased insulin resistance.

Despite the well-recognised correlation between weight gain and cardiovascular (CV) disease, there is little direct evidence relating to the impact of insulin-induced weight-gain on CV outcomes. However, there is compelling indirect evidence that weight-gain does adversely affect CV risk. In the Nurses' Health Study, weight gain of >2kg following a diagnosis of diabetes was associated with a 16% increased risk of CV heart disease.[7] The ACCORD study designed to investigate whether an aggressive therapeutic strategy to achieve tight glucose target (HbA1c <6.5%) would reduce CV events surprisingly resulted in an increased mortality in the intensively treated group.[8] The mean BMI of patients in the study was 32.2kg/$m^2$ and weight-gain by more than 10kg occurred in 27.8% of the intensively treated patients compared with 14.1% in the standard therapy. While a causal relationship between weight gain and adverse CV outcomes cannot be assumed, retrospective studies have shown that people with diabetes who actively lose weight improve not only their risk profile [9–11] but also survival rate. The aim of the present study therefore was to explore the association of insulin-induced weight (wt) gain on CV outcomes and mortality in patients with T2D following insulin initiation using evidence from real-world data.

**Methods:**

***Study Design and Data Source:***

A retrospective cohort study was conducted with data obtained from the UK Primary Care via The Health Improvement Network (THIN) database. This database hosts the UK computerised anonymised longitudinal Primary Care records which have data systematically entered in a non-interventional manner by Primary Care physicians. In addition, it contains details of over 10.5 million patients (of this, 4.8 million are currently active) derived from 532 General Practices within the UK. It contains information on patients' demography, lifestyle characteristics, diagnoses, hospital admissions, laboratory results, prescriptions, referrals, immunisations, clinical measures and Townsend deprivation scores. Several studies have validated and shown it to be demographically representative of the UK population in terms of demography, disease prevalence and mortality. [12,13] We have also used it previously to evaluate diabetes-related outcomes in routine clinical practice. [14,15,16] Ethical approval was obtained from the South-East Research Ethics Committee.

***Study Population:***

All adult T2D insulin users, aged 18 and above were eligible for inclusion. Furthermore, these patients must have initiated insulin therapy between January 2007 and 2014 irrespective of previous or concurrent use of other glucose-lowering therapies (GLTs). Patients with history of CV diseases prior to insulin initiation were excluded from the study. Additionally, to minimise the prevalent user bias, patients with diagnoses of CV diseases (non-fatal MI and stroke) on insulin initiation or up to 180 days after were also excluded; while patients with type 1 diabetes were not eligible for inclusion in the study. Figure 1 is a flow chart illustrating how the study cohort was derived.

***Exposure and Outcome:***

We defined the exposure as change in weight, one year post-insulin initiation. Change in weight was measured by the difference between the baseline weight (at insulin initiation) and the weight after one year, measured in kilogram. There was no consideration on the specific type or mode of administration of insulin. We classified the change in weight after one year of initiating insulin into five categories based on the average weight change of 5kg within this period as reported by previous studies. [2] Change in weight was classified into the following categories: >5kg wt loss; 1.0-5.0kg wt loss; no wt change; 1.0-5.0kg wt gain; and >5.0kg wt gain. Participants were followed up for 5years to the earliest of the occurrence of any of the defined composite outcome, loss to follow-up (transfer out of practice), discontinuation of insulin therapy, or at the end of the study after 5 years .

The study outcome was time to a three-point composite of all-cause mortality, non-fatal myocardial infarction (MI) and non-fatal stroke. Appropriate READ CODES were used to identify and extract these outcomes from the THIN database.

***Covariates:***

Baseline variables were selected *a priori* based on clinical significance. These were extracted within the time period extending 90 days before and after initiation of insulin. These covariates included baseline demographic parameters as age, sex, socioeconomic deprivation and smoking status. In addition, clinical measures as body weight, body mass index (BMI) and blood pressure (systolic and diastolic); biochemical parameters as baseline HbA1c, creatinine level, total cholesterol levels, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides were included. Other important covariates as the use of other medications as statins, aspirin, antihypertensive drugs, and oral antidiabetic drugs; comorbidities; the duration

of diabetes, duration of insulin use; and the duration of treatment of diabetes were also explored and included.

***Statistical Analyses:***

Baseline variables were summarised within these categories of weight-change using mean values and standard deviation (SD) for continuous variables; and frequencies (%) for categorical variables. The differences between these baseline categories were analysed using Pearson's Chi square tests or linear regression and summarized in a table. Missing data among the exposure variable (weight) and other baseline covariates in the dataset were generally accounted for using multiple imputations with the chained equation (MICE) model.

The primary analysis was time to a three-point composite outcome of non-fatal MI, non-fatal stroke and all-cause mortality. Crude and adjusted Kaplan–Meier estimates of survival functions were obtained for the categories of weight-change with log-rank test comparing the equality of the survival curves between them. From these survival functions, the absolute reduction in the probability of an event occurring within a 5-year follow-up was determined.

We fitted a Cox proportional regression model to estimate the marginal hazard ratios and quantify the adjusted hazard of an event occurring in all the quintile groups compared to the third (no weight change) group. Covariates which had significant association in our univariate analysis at a p value $\leq 0.05$ were included and adjusted for in the final model. Violations of the proportional hazards assumptions were confirmed through Schoenfeld residuals test.

***Subgroup/Sensitivity Analyses:***

Additional sensitivity analyses were carried out to evaluate the robustness of our data. We examined the assumption of no unmeasured covariate by examining if any unmeasured covariate would influence the measure of effect. Also, we compared results of the study

outcome between the datasets with missing data and the imputed data. This is to assess the reliability of these outcomes and any possible impact any missing data might have on them. Additionally, the exposure was reclassified as quintiles of weight-change and the outcomes were compared with our results. Subgroup analyses were performed on patients with BMI > 30kg/$m^2$ to estimate the impact of weight changes on adverse composite outcomes in the obese population.

Point estimates with 95% confidence intervals (CI) at the conventional statistical significance level of 0.05 were used in the regression models. All analyses were conducted using Stata software, version 14. [17] The study was reported using the STROBE criteria for reporting observational studies.

**Results:**

***Cases and Total Follow up:***

A total of 18,814 adult T2D patients, identified in the UK Primary care electronic records via THIN database, fulfilled our inclusion criteria. In Figure 1, a flow diagram illustrates how this cohort was derived. This population was distributed thus: >5kg wt loss (21.9%); 1.0-5.0kg wt loss (28.2%); no wt change (5.2%); 1.0-5.0kg wt gain (20.5%); and >5.0kg wt gain (24.3%). The mean follow up duration was 3.7±2.9 years which represents a total follow-up period of 65,435.704 person-years.

***Patients' Characteristics:***

The overall mean age was 61.5 (SD: 13.6) years with a mean HbA1c of 8.7% (SD: 1.8) and higher proportion (53.2%) of males. The 1.0 - 5.0kg group was younger, while the weight neutral group had lower HbA1c. The overall mean weight was 91.3kg but the group who lost more than 5kg had a greater weight of 96.6kg. Summarily, significant differences were observed between the categories in socio-economic status ($p = 0.05$), alcohol intake ($p = 0.048$) and use of lipid-lowering agents ($p=0.0001$). Table 1 summarises the baseline characteristics of the study cohort by the categories of change in weight one year after the initiation of insulin. The proportions of recorded data observed to be missing for weight were 15.8% and 36.5% at baseline and after one year were respectively. These were noted to be missing at random.

***Crude Event Rates:***

Although the probability of survival was similar (99%) between the weight categories at one year, there was a general decrease at five years in all the weight-change categories. This ranged from 83% in the group who lost > 5kg, to 88% in the weight neutral group (log-rank test p-

value =0.0005). Figure 2 shows a Kaplan-Meier plot of survival probability for the composite outcomes within the weight-change categories

Overall, there were 1,963 composite events of all-cause mortality, non-fatal stroke and non-fatal acute MI; with a crude incidence rate of 30 per 1,000 person-years (95%CI: 28.8 – 31.5). These were distributed thus within the weight change categories: Those with >5kg weight loss: 498 events (36 per 1000pyrs); 1 to 5kg weight loss: 544events (29 per 1000pyrs); no change in weight: 87 events (26 per 1000pyrs); 1 to 5kg weight gain: 360events (26 per 1000pyrs); and >5kg weight gain: 474 events (30 per 1000pyrs). These events are summarised in Table 2.

***Risk of Composite CV Outcomes:***

The Hazard of the three-point composite outcome of non-fatal AMI, non-fatal stroke and all-cause mortality was compared to the no weight change group (Table 2). The unadjusted hazard for the composite outcome was 41% higher (HR: 1.41, 95%CI: 1.23 – 1.77) in patients who lost greater than 5kg weight year post-insulin initiation compared to the weigh-neutral group. However, this risk was 15%, 3% and 19% non-significantly higher in the 1.0 – 5.0kg weight loss; 1.0 - 5.0kg weight gain and >5.0kg weigh-gain groups respectively in the unadjusted model..

Following adjustment for significant baseline variables as age, duration of diabetes, diastolic and systolic blood pressures, height, weight, albumin, glomerular filtration rate, gender, smoking status, alcohol status, lipid profile, socio-economic status (measured by Townsend deprivation scores), use of other glucose-lowering medications and antihypertensives; and other comorbidities (as heart failure and peripheral artery disease); the hazard slightly reduced to 31% (aHR: 1.31, 95%CI: 1.02 – 1.68) in patients who lost greater than 5kg compared to the

weight-neutral group. Similarly, the hazard was non-significantly reduced to 13% (95%CI: 0.93 – 1.15) in those who gained > 5kg of weight but was the same (aHR: 1.15, 95%CI: 0.90 – 1.47) in those who lost 1 to 5kg and unity (aHR: 1.00, 95%CI: 0.78 – 1.30) in those who gained 1 to 5kg, compared to the weight-neutral group.

The proportional hazards assumptions of the cox-regression analysis were tested by adding by comparing the cumulative hazard plots groups on the exposure group, including an interaction term of the predictor and log time and also by using Schoenfeld residuals test. We observed no violations as both were found to be non-significant and satisfied the proportional hazard assumption.

***Sensitivity and Subgroup Analyses:***

***Obese subgroup:*** In the obese (BMI of 30kg/$m^2$ and above) population subgroup, 1201 composite events occurred, giving a crude incidence rate of 29/1,000 person-years (95%CI: 28 - 31). The distribution of the events and their incidence rates by the weight change groups are shown in Table 2. Compared to the weight-neutral group, the adjusted risk of composite CV risk and all-cause mortality event was 50% (aHR: 1.50, 95%CI: 1.08 – 2.08) more in the obese population group who lost greater than 5kg at one year post-insulin initiation compared to the weight-neutral group. Similarly, a non-significant increase of 27%, 14% and 29% in this risk was, however, reported in the 1 to 5kg weight-loss, 1 to 5kg weight-gain and >5kg weight-gain groups as shown in Table 2.

***Risk of mortality, non-fatal MI and non-fatal stroke***: The events, and hazards of the components of the three-point composite event are shown in Table 3. Patients who lost greater than 5 kg one-year post-insulin initiation showed increased risk of mortality of 27% (95%CI:

1.01 – 1.89, but no statistically significant difference in risk was found for non-fatal MI although it showed a 5-fold increased risk (aHR: 5.06, 95%CI:0.68 – 37.67).Also, the risk of non-fatal stroke was non-significantly increased by 15% (aHR: 1.15, 95%CI: 0.77 – 1.71) compared to the no weight-neutral category. Summarily, other weight categories in all the composite components showed non-significant greater risks compared to the weight-neutral group as shown in Table 3.

Sensitivity analyses comparing the hazards of the composite events between the weight-change categories ranked in quintiles, showed similar pattern in the risk of the three-point composite event. Similarly, we obtained similar results and trend in risk of the composite outcome and individual components of the 3-point composite outcome when we compared the incomplete and imputed datasets. This affirmed that the imputation robustly addressed the missing data.

**Discussion:**

This observational study, derived from a large longitudinal real world data provides reassurance that weight-gain associated with insulin treatment is not associated with adverse CV outcomes. Conversely, patients who demonstrated significant weight loss with insulin treatment appear to have a more adverse CV outcomes compared to that observed in patients who maintained or increase their body weight. This observation persists when sub-analysed for patients who are obese (BMI 30kg/$m^2$) at baseline and when adjusted for various confounding factors.

Our findings are further supported by consistency of the outcomes in patients from the entire cohort, and in the subgroup and sensitivity analyses. The level of HbA1c and CV risk profile (e.g. lipid, blood pressure) were clinically similar across all weight change categories. Although we did not assess the impact of HbA1c change and weight change across different baseline weight categories, a previous study using a US-based electronic medical record reported a reduction in HbA1c was associated with progressively less weight gain as baseline BMI rose. [18] The inference from that study that the lesser weight gain seen in obese patients was due to the use of less intensive insulin therapy may also apply to this cohort.

Although it seems logical that weight gained in people with diabetes, a disease with a high incidence of CV risk, would increase CV events, there is in fact little direct evidence to support this. Robust large scale clinical trials such as UKPDS [2], ADVANCE [19] and ACCORD [8] study did not stratify their CV outcomes by weight-loss or weight-gain, for any given level of glycaemic control. Even though the ACCORD study reported excess mortality (and more weight gain) in the intensively treated group, a causal link cannot be inferred. Of note however, was in a post hoc analysis of that same study, patients who were inadequately controlled at baseline and received intensive glucose lowering strategy but still had suboptimal glucose

control (HbA1c >7% (>53 mmol/mol)) experienced higher mortality rate [20]. Thus, patient-factors associated with persistently high HbA1c, despite intensive treatment, appear to be the most important determinant of increased mortality risks. To this end, insulin-induced weight gain in our study was seen to be associated with a reduction in HbA1c, while those who lost weight were associated with a deterioration or unchanged HbA1c levels (Figure 3).

Three possible explanations could be inferred from this observation. Firstly, a rise in HbA1c levels may dilute any favourable impact of weight reduction and lead to an increase in CV events. In support of this, there is evidence that intensive control of blood glucose levels in patients with T2D reduces the long-term risk of adverse CV events.[21,22] These benefits may take many years to become apparent but in view of the association between patients' HbA1c level, and risk of developing long-term vascular complications, current clinical guidelines recommend aggressive treatment escalations among patients with T2D to achieve low HbA1c targets.[23,24,25] Conversely, patients may however find the demands of intensive glycaemic control difficult to manage resulting in psychological stress, frustration and non-adherence especially if hypoglycaemia occurs.[26] A second, perhaps more likely explanation is the presence of other comorbidities (e.g. cancers, gastrointestinal disorders, other endocrine/metabolic disorders, etc.) which are associated with weight loss in the group who lost weight in excess of 5kg. These could have possibly driven the adverse outcomes seen in this group. Thirdly, insulin-induce weight gain could suggest patients' compliance to insulin treatment intensification and thus a surrogate marker of compliance to holistic care and treatment. Nevertheless, we contend that there is indirect evidence that failure to achieve HbA1c reduction, irrespective of the evidence for this, should be used as a trigger to intensify cardiovascular risk reduction strategies.

Our study findings are in keeping with the outcome of another real world study in Australia which showed that insulin-induced weight-gain was not associated with adverse changes in cardiovascular risk factors after one year of insulin initiation. [27] Conversely, our data are in contrast to the findings in type 1 diabetes. In a sub-analysis of the DCCT study, Purnell et al. stratified data from the intensively treated DCCT cohort by quartiles of weight gain. [28] Comparing the first quartile (where BMI remained stable) with the fourth (where BMI increased by 7 kg/m2), after a mean follow-up of 6.1 years, patients in the fourth quartile were associated with significant negative changes in all CV risk parameters. While a causal relationship between weight gain and adverse CV outcomes again cannot be assumed, other studies have reported that people with diabetes who actively lose weight improve not only their risk profile but also their longevity.[29,30] These studies however did not focus on patients with T2D receiving insulin therapy. In this context, while weight-gain has to be viewed as an undesirable side effect of insulin therapy, it appears to be associated with adverse CV outcome in patients with type 1 diabetes.

Our analyses were subject to a number of limitations that are inherent to observational studies. Firstly, we cannot be certain that the patients were fully compliant with their medication. Also, some factors like lifestyle and dietary intervention and records of comorbidities as cancers and metabolic disorders (which were not so robustly included in our data) may influence our findings. We were also not able to obtain the longitudinal insulin doses, an important predictor of insulin-induced weight gain. [31,32] Since our aim was to look at status of weight-change due to insulin initiation per se on CV outcomes, we would argue that this should not influence the robustness of our findings. Although we could not account for potential residual confounders such as compliance, indications for intensification treatments, markers of β-cell deterioration and frequency of hypoglycaemia, we were able to account for differences in the

observed covariates and used robust analytical techniques to control confounding that may bias the results of the estimated treatment effects.

In conclusion, we observed that in the group which experienced weight gain following insulin treatment, insulin-induced weight gain+ was however not associated with adverse CV outcomes as indirectly suggested in previous clinical trials. These findings should provide important reassurance among patients with T2DM who gained weight following insulin treatment in routine clinical practice

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**Legend:**

**Figure 1** – Flow diagram illustrating the selection of the study cohort

**Figure 2** – Kaplan-Meier Curve showing the probability of survival between the weight-change categories within the follow-up period. Log-rank test p-value = 0.0005.

**Figure 3** – Relationship between change in weight and glycaemic control.
This figure illustrates the association between glycaemic control (measured by the difference between baseline HbA1c and level after one year of insulin initiation) and change in weight after one year of initiation of insulin in naïve insulin users. For a unit increase in weight at one year post-insulin initiation, there was a marginal but significant reduction in HbA1c (r: -0.005%, 95%CI: -0.007 to -0.002%; p-value: 0.001).

**Table 1** - Baseline characteristics of study cohort by categories of weight change.

**Table 2** – Events, Incidence Rate and Hazards of Composite Outcome by Weight-Change Categories

**Table 3** - Events, Incidence Rate and Hazards of the Components of the Three-point Composite Outcome by Weight-Change Categories

Table 1

Tables

Table 1:

| Weight Change | Lost > 5kg (n = 4116) | Lost 1.0 to 5.0kg (n = 5311) | No Change (n = 970) | Gained 1.0 to 5.0kg (n =3852) | Gained > 5.0kg (n = 4565) | Total (n = 18,814) |
|---|---|---|---|---|---|---|
| **Demographics** | | | | | | |
| Age (yrs). Mean (SD) | 61.8 (14.0) | 61.3 (13.5) | 61.8 (13.6) | 60.8 (13.6) | 62.1 (13.5) | 61.5 (13.6) |
| Gender. No. (%) | | | | | | |
| Male | 2150 (52) | 2807 (53) | 503 (52) | 2046 (53) | 2508 (55) | 10,014 (53.2) |
| Female | 1966 (48) | 2504 (47) | 467 (48) | 1806 (47) | 2057 (45) | 8800 (46.8) |
| Smoking Status. No (%) | | | | | | |
| Non-smoker | 2006 (49) | 2607 (49) | 464 (48) | 1893 (49) | 2208 (48) | 9178 (48.8) |
| Ex-smoker | 1497 (36) | 1924 (36) | 355 (37) | 1402 (36) | 1754 (38) | 6,932 (36.8) |
| Current | 613 (15) | 780 (15) | 151 (16) | 557 (14) | 603 (13) | 2704 (14.4) |
| Alcohol Status. No (%) | | | | | | |
| Never | 1635 (40) | 1960 (37) | 338 (35) | 1401 (36) | 1725 (38) | 1202 (6.4) |
| Ex-drinker | 249 (6) | 328 (6) | 70 (7) | 253 (7) | 302 (7) | 7059 (32.5) |
| Current | 2232 (54) | 3023 (57) | 562 (58) | 2198 (57) | 2538 (56) | 10,553 (56.1) |
| Deprivation. No (%) | | | | | | |
| Least deprived | 814 (21) | 1042 (21) | 204 (22) | 732 (20) | 888 (20) | 3680 (19.7) |
| Second quintile | 784 (20) | 1016 (20) | 187 (20) | 751 (20) | 863 (20) | 3601 (19.1) |
| Third quintile | 846 (22) | 1088 (21) | 193 (21) | 740 (20) | 963 (22) | 3830 (20.4) |
| Fourth quintile | 822 (21) | 1116 (22) | 202 (22) | 818 (22) | 937 (21) | 3895 (20.7) |
| Most deprived | 655 (17) | 816 (16) | 140 (15) | 634 (17) | 711 (16) | 2956 (16.5) |
| **Clinical Parameters. Mean (SD)** | | | | | | |
| HbA1c (%) | 8.6 (1.8) | 8.7 (1.8) | 8.6 (1.8) | 8.7 (1.8) | 8.7 (1.9) | 8.7 (1.8) |
| BMI (kg/m$^2$) | 34.7 (6.8) | 32.9 (6.6) | 32.3 (6.4) | 31.9 (6.7) | 30.6 (6.8) | 32.5 (6.9) |
| Diabetes duration (yrs) | 4.5 (4.8) | 4.1 (4.9) | 4.3 (4.6) | 4.1 (4.8) | 4.6 (5.1) | 4.3 (4.9) |
| Time on insulin (yrs) | 4.1 (6.2) | 3.8 (6.4) | 4.3 (6.4) | 3.7 (6.2) | 4.0 (6.6) | 3.9 (6.4) |
| Height (m) | 1.7 (0.1) | 1.7 (0.1) | 1.7 (0.1) | 1.7 (0.1) | 1.7 (0.1) | 1.7 (0.1) |
| Weight (kg) | 96.6 (18.3) | 92.1 (18.2) | 90.3 (17.8) | 89.8 (18.4) | 87.0 (18.8) | 91.3 (18.7) |
| DBP (mmHg) | 76.2 (10.8) | 75.8 (10.9) | 75.9 (10.7) | 75.8 (10.9) | 76.1 (10.8) | 76.0 (10.8) |
| SBP (mmHg) | 138.7 (23.1) | 136.6 (22.9) | 135.7 (21.6) | 135.7 (22.7) | 134.5 (23.5) | 136.3 (23.0) |
| Albumin (g/L) | 4.0 (0.4) | 4.1 (0.4) | 4.1 (0.4) | 4.1 (0.4) | 4.1 (0.4) | 4.0 (0.4) |
| ACR (mg/mol) | 5.8 (8.5) | 5.8 (8.6) | 6.1 (8.4) | 5.7 (8.4) | 5.8 (8.4) | 5.8 (8.5) |
| eGFR (mls/min/1.73m$^2$) | 61.7 (21.3) | 63.0 (21.2) | 62.4 (21.4) | 63.6 (20.8) | 63.6 (21.3) | 62.9 (21.2) |

| | | | | | | |
|---|---|---|---|---|---|---|
| TC. (mmol/L) | 4.6 (1.3) | 4.5 (1.3) | 4.5 (1.2) | 4.5 (1.3) | 4.5 (1.3) | 4.5 (1.3) |
| Triglyceride (mmol/L) | 2.1 (1.3) | 2.1 (1.2) | 2.0 (1.1) | 2.0 (1.2) | 2.1 (1.2) | 2.0 (1.2) |
| LDL (mmol/L) | 2.4 (1.1) | 2.4 (1.1) | 2.3 (1.0) | 2.4 (1.1) | 2.3 (1.1) | 2.4 (1.1) |
| HDL (mmol/L) | 1.2 (0.4) | 1.2 (0.4) | 1.2 (0.4) | 1.2 (0.5) | 1.2 (0.5) | 1.2 (0.4) |
| BMI Categories | | | | | | |
| Normal | 319 (8) | 580 (11) | 128 (13) | 569 (15) | 948 (21) | 2544 (13.5) |
| Overweight | 717 (17) | 1296 (24) | 241 (25) | 990 (26) | 1233 (27) | 4477 (23.8) |
| Obese | 3080 (75) | 3435 (65) | 601 (62) | 2293 (60) | 2384 (52) | 11,793 (62.7) |
| **Use of Medications** | | | | | | |
| Aspirin | 3940 (98) | 5079 (97) | 923 (99) | 3710 (99) | 4395 (98) | 18047 (98) |
| LLT | 3541 (90) | 4621 (91) | 840 (91) | 3368 (91) | 3972 (90) | 16342 (90.5) |
| Antihypertensives | 3565 (90) | 4630 (91) | 844 (91) | 3370 (91) | 4022 (91) | 10830 (87.7) |
| **Comorbidities** | | | | | | |
| Hypoglycaemia | 725 (18) | 902 (17) | 177 (18) | 686 (18) | 790 (17) | 3280 (17) |
| Heart Failure | 568 (14) | 712 (13) | 138 (14) | 518 (13) | 663 (15) | 2599 (13.9) |
| PAD | 522 (13) | 688 (13) | 130 (13) | 511 (13) | 660 (14) | 2511 (13.4) |
| Other CHD | 1226 (30) | 1615 (30) | 276 (28) | 1144 (30) | 1420 (31) | 5681 (30.2) |

*Diabetes duration is time from first diagnosis of diabetes to date of intensification with insulin (index date).*
*Comorbidities: other recorded medical disorders.*
*ACR, albumin creatinine ratio; BMI, body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, Haemoglobin A1c; HDL, high-density lipoprotein; INS, insulin; LDL, low-density lipoprotein; LLT, lipid-lowering therapy; PAD, peripheral arterial disease; SBP, systolic blood pressure; TC, total cholesterol.*

Table 2:

| Weight Change | Lost > 5kg | Lost 1.0 to 5.0kg | No Change | Gained 1.0 to 5.0kg | Gained > 5.0kg | Total |
|---|---|---|---|---|---|---|
| | (n = 4116) | (n = 5311) | (n = 970) | (n =3852) | (n = 4565) | (n = 18,814) |
| **Study Population** | | | | | | |
| **Composite Outcome**[a] | 498 | 544 | 87 | 360 | 474 | 1963 |
| **Incidence rate (per 1000pyrs)** | 35.7 | 29.4 | 25.5 | 26.3 | 30.3 | 30.1 |
| **(95% CI)** | (32.7 – 39.0) | (27.0 – 32.0) | (20.7 – 31.5) | (23.7 – 29.2) | (27.7 – 33.1) | (28.8 – 31.5) |
| **Adjusted Hazard Ratio**[b] | 1.31 | 1.15 | 1 (ref) | 1.00 | 1.13 | - |
| **(95% CI)** | (1.02 – 1.68) | (0.90 – 1.47) | - | (0.78 – 1.30) | (0.93 – 1.15) | - |
| **p-value** | 0.032 | 0.263 | - | 0.975 | 0.344 | - |
| **Obese subgroup (BMI ≥ 30kg/m$^2$)** | | | | | | |
| **Composite Outcome**[a] | 362 | 335 | 49 | 209 | 246 | 1201 |
| **Incidence rate (per 1000pyrs)** | 34.5 | 27.7 | 23.3 | 25.5 | 29.8 | 29.2 |
| **(95% CI)** | (31.2 – 38.3) | (24.9 – 30.9) | (17.6 – 30.8) | (22.2 – 29.1) | (26.3 – 33.8) | (26.3 – 33.8) |
| **Adjusted Hazard Ratio**[b] | 1.50 | 1.27 | 1 (ref) | 1.14 | 1.29 | - |
| **(95% CI)** | (1.80 – 2.08) | (0.91– 1.76) | - | (0.81 – 1.60) | (0.92 – 1.81) | - |
| **p-value** | 0.014 | 0.159 | - | 0.455 | 0.136 | - |

[a] *Composite outcome includes all-cause mortality, non-fatal acute myocardial infarction (AMI) and non-fatal stroke.*
[b] *Adjusted for age, diabetes duration diastolic and systolic blood pressure, height, weight, albumin, glomerular filtration rate, gender, smoking status, alcohol status, lipid profile, Townsend Deprivation score, number of glucose-lowering therapies, Lipid-lowering therapies, antihypertensives, heart failure and peripheral artery disease.*

Table 3

| Weight Change | Lost > 5kg | Lost 1.0 to 5.0kg | No Change | Gained 1.0 to 5.0kg | Gained > 5.0kg | Total |
|---|---|---|---|---|---|---|
| | (n = 4116) | (n = 5311) | (n = 970) | (n =3852) | (n = 4565) | (n = 18,814) |
| **Mortality** | | | | | | |
| Total Events | 312 | 320 | 51 | 208 | 260 | 1151 |
| Incidence rate (per 1000) | 19.9 | 15.3 | 13.2 | 13.5 | 14.6 | 15.6 |
| (95% CI) | (17.8 – 22.2) | (13.7 – 17.1) | (10.0 – 17.4) | (11.8 – 15.5) | (12.9 – 16.5) | (14.8 – 16.6) |
| Adjusted Hazard Ratio[a] | 1.37 | 1.14 | 1 (ref) | 0.99 | 1.01 | - |
| (95% CI) | (1.01 – 1.89) | (0.83 – 1.57) | - | (0.71 – 1.38) | (0.72 – 1.39) | - |
| p-value | 0.051 | 0.421 | - | 0.947 | 0.986 | - |
| **Non-fatal Myocardial Infarction** | | | | | | |
| Total Events | 25 | 25 | 2 | 28 | 36 | 116 |
| Incidence rate (per 1000) | 1.6 | 1.2 | 0.5 | 1.9 | 2.1 | 1.6 |
| (95% CI) | (1.1 – 2.4) | (0.8 – 1.8) | (0.1 – 2.1) | (1.3 – 2.7) | (1.5 – 2.9) | (1.3 – 1.9) |
| Adjusted Hazard Ratio[a] | 5.06 | 4.26 | 1 (ref) | 5.42 | 7.71 | - |
| (95% CI) | (0.68 – 37.67) | (0.58 – 31.57) | - | (0.73 – 40.33) | (1.06 – 56.34) | - |
| p-value | 0.113 | 0.156 | - | 0.099 | 0.044 | - |
| **Non-fatal Stroke** | | | | | | |
| Total Events | 161 | 199 | 34 | 124 | 178 | 696 |
| Incidence rate (per 1000) | 11.3 | 10.4 | 9.7 | 8.8 | 11.0 | 10.3 |
| (95% CI) | (9.6 – 13.1) | (9.1 – 12.0) | (6.9 – 13.6) | (7.4 – 10.5) | (9.5 – 12.7) | (9.6 – 10.3) |
| Adjusted Hazard Ratio[a] | 1.15 | 1.10 | 1 (ref) | 0.95 | 1.12 | - |
| (95% CI) | (0.77 – 1.71) | (0.74 – 1.63) | - | (0.63 – 1.43) | (0.75 – 1.65) | - |
| p-value | 0.509 | 0.627 | - | 0.810 | 0.579 | - |

[a]*Adjusted for age, diabetes duration diastolic and systolic blood pressure, height, weight, albumin, glomerular filtration rate, gender, smoking status, alcohol status, lipid profile, Townsend Deprivation score, number of glucose-lowering therapies, Lipid-lowering therapies, antihypertensives, heart failure and peripheral artery disease.*