Changes in body mass index following newly diagnosed type 2 diabetes and risk of cardiovascular mortality: A cohort study of 8486 primary-care patients

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Abstract

Aims. – Elevated body mass index (BMI) is associated with an increased risk of type 2 diabetes and cardiovascular disease (CVD). This study explored the association between BMI changes in the first 18 months of newly diagnosed type 2 diabetes and the risk of long-term CVD mortality.

Methods. – A total of 8486 patients with newly diagnosed type 2 diabetes and no previous history of CVD or cancer were identified from 84 primary-care centres in Sweden. During the first year after diagnosis, patients were grouped according to BMI change: ‘increase’, or \( \geq +1 \) BMI unit; ‘unchanged’, or between +1 and –1 BMI unit; and ‘decrease’, or \( \leq -1 \) BMI unit. Associations between BMI change and CVD mortality, defined as death from stroke, myocardial infarction or sudden death, were estimated using adjusted Cox proportional hazards models (NCT 01121315).

Results. – Baseline mean age was 60.0 years and mean BMI was 30.2 kg/m². Patients were followed for up to 9 years (median: 4.6 years). During the first 18 months, 53.4% had no change in their BMI, while 32.2% decreased and 14.4% increased. Compared with patients with unchanged BMI, those with an increased BMI had higher risks of CVD mortality (hazard ratio: 1.63, 95% CI: 1.11–2.39) and all-cause mortality (1.33, 1.01–1.76). BMI decreases had no association with these risks compared with unchanged BMI: 1.06 (0.76–1.48) and 1.06 (0.85–1.33), respectively.

Conclusion. – Increased BMI within the first 18 months of type 2 diabetes diagnosis was associated with an increased long-term risk of CVD mortality. However, BMI decrease did not lower the long-term risk of mortality.

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Keywords: Epidemiology; Type 2 diabetes; Weight control; Cardiovascular disease mortality

Résumé

Impact des modifications de l’IMC après le diagnostic de diabète de type 2 sur le risque à long terme de mortalité cardiovasculaire chez 8486 patients en soins primaires.

Objectifs. – Un indice élevé de masse corporelle (IMC) est associé à un risque accru de diabète de type 2 et de maladies cardiovasculaires (CV). Nous avons étudié l’association entre l’évolution de l’IMC au cours des 18 mois après le diagnostic du diabète de type 2 et le risque de mortalité CV à long terme.

Méthodes. – Un total de 8486 patients diabétiques de type 2 nouvellement diagnostiqués et sans antécédent de cancer ou de maladies CV issus de 84 centres de soins primaires en Suède ont été étudiés. Au cours de la première année après le diagnostic, les patients ont été regroupés en fonction de l’évolution de l’IMC (augmentation \( \geq 1 \) unité d’IMC; « inchangé » entre +1 et –1 unité d’IMC; « diminution » \( \leq -1 \) diminution unité d’IMC). Les associations entre l’IMC et la mortalité CV, définie comme le décès par accident vasculaire cérébral, infarctus du myocarde ou mort subite, ajustées ont été estimées par des modèles de Cox à risques proportionnels.

Résultats. – L’âge moyen à l’inclusion était de 60,0 ans et l’IMC moyen de 30,2 kg/m². Les patients ont été suivis pendant neuf ans (médiane de 4,6 ans). Pendant les 18 premiers mois, 53,4% n’ont pas changé leur IMC, 32,2% ont eu une diminution, et 14,4% une augmentation. Par rapport aux patients avec un IMC inchangé, le groupe présentant une augmentation de l’IMC avait un risque plus élevé de mortalité CV (HR: 1,63)
1. Introduction

Weight control or the attainment of optimal body weight is a recommended treatment goal in type 2 diabetes patients based on the subsequent beneficial effects on cardiovascular disease (CVD) risk factors [1–3]. The suggested CVD risk reduction with weight loss has been supported by one small observational study of diabetes patients and by extrapolated data from non-diabetic populations [4]. Bariatric surgery for severe obesity with sustained and substantial weight losses of 14–25% over several years has also shown significantly reduced risk of mortality compared with untreated patients [5]. However, the Look AHEAD (Action For Health in Diabetics) trial was prematurely terminated in 2012 because it failed to demonstrate any associations between CVD risk and sustained moderate weight loss in diabetic patients using prospective lifestyle interventions [6]. The clinical effect of weight loss on CVD in the context of routine lifestyle changes in general diabetes care has previously been debated and remains unsettled in the light of recent results [6,7]. Weight gain has been reported to be associated with increased CVD risk in diabetic patients; however, clinical interpretation is difficult due to the secondary nature of the results and the methods used for weight-change calculations [8,9]. Indeed, the importance of weight changes in type 2 diabetes patients on fixed outcomes is currently unclear, thereby supporting the need for new studies addressing this issue.

The objective of the present study was to investigate the association between weight change and risk of CVD mortality in a large primary-care-based sample of patients with newly diagnosed diabetes in a real-world setting.

2. Methods

The study was based on the Retrospective Epidemiological Study to Investigate Outcome and Mortality with Glucose-lowering Drug Treatment in Primary Care (ROSE) study [10]. In 2010, patients’ data were extracted from 84 primary-care centres in Sweden, using the Pyrgus Customized Extraction Program (CXP) [11], to constitute a representative sample of both publicly and privately owned primary-care centres (61% and 39%, respectively) [12,13]. The 84 centres selected made up approximately 8% of the total number of primary-care centres in Sweden. All data were extracted for the 58,326 patients diagnosed with type 2 diabetes between 1999 and 2009. The diagnosis was identified by the registered diagnostic code and/or prescription of any blood glucose-lowering drug [10]. The International Statistical Classification of Diseases and Related Health Problems (ICD) is used to classify diagnoses in both hospital and primary care in Sweden, and codes 250 (ICD 9) and E10–E14 (ICD 10) were used to identify type 2 diabetes. The Anatomical Therapeutic Chemical (ATC) classification system code A10 was used to identify the prescription of glucose-lowering drugs.

Patients were excluded from the study cohort if they had a previous history of prevalent diabetes from 1987 up to the data-extraction date, or were aged either less than 35 years or more than 79 years, or newly diagnosed with diabetes after 2008. Patients aged less than 35 were excluded to lower the risk of type 1 diabetes patients in the main data extraction from the ROSE study. The exclusion of patients aged more than 79 years was decided upon because they were considered to have little benefit from weight loss and low risk of weight gain. In addition, subjects were excluded if they had a history of CVD, active cancer or missing data on BMI at baseline and within 18 months of the diabetes diagnosis (Supplementary patient flow chart, Fig. S1). Patients were also excluded from analyses if they developed CVD or cancer during the time between the two BMI measurements.

BMI was mainly chosen because it reflects body composition (underweight, normal weight, overweight or obese), which determines the risk of different weight changes [14]. Changes in weight were assessed by calculating BMI changes within the first 18 months of being newly diagnosed with diabetes. Baseline BMI was defined as the closest registration found in the interval from 15 months before to 45 days after the time of newly diagnosed diabetes. The second BMI was sought in the interval from 46 days to 18 months after newly diagnosed diabetes, using only the last registration if several readings were found. BMI change was calculated by subtracting the baseline BMI from the second BMI, after which the patients were divided into three BMI groups: increased, or more than or equal to +1 BMI unit; unchanged, or +1 to –1 BMI unit; and decreased, or less than or equal to –1 BMI unit. The mean interval duration between the index and second BMI in the increased, unchanged and decreased groups was 1.1, 1.0 and 1.0 year, respectively.

2.1. Outcome and covariates

Follow-up time started after the second BMI measurement, and all patients were followed until death or the last date for extracting data from registers. The primary endpoint CVD mortality included all primary causes of death diagnosed with ICD-10 codes I00–I99. Non-fatal CVD comprised myocardial infarction (ICD-9 code 410; ICD-10 code I21), unstable angina (ICD-9 411; ICD-10 I20.0), heart failure (ICD-9 428; ICD-10 I11.0, I50), atrial fibrillation (ICD-9 427; ICD-10 I48), hemorrhagic and embolic stroke (ICD-9 430–438; ICD-10 I60,
I61, I63.0–I63.5, I63.8–I63.9, I64), transient ischaemic attack (ICD-10 G45) and peripheral artery disease (ICD-9 440, 441, 444; ICD-10 I70–I79). ICD codes were retrieved by linking the patients’ personal identification numbers to data from validated national hospitalization and cause-of-death registries [15]. Data on educational levels and marital status were extracted from Statistics Sweden databases.

Baseline covariates were calculated as the means of the last three measures within 15 months before and 14 days after the date of diabetes diagnosis. Descriptions of temporal covariate changes were subsequently updated in the follow-up period by calculating the means of all measures within the subsequent time period from day 15 to day 365. For each 12-month period thereafter, the means of all measures within the time interval were calculated.

2.2. Statistical methods

Differences in baseline data between groups (using unchanged BMI as the reference group) were tested by Student’s t test and Pearson’s chi-square test according to the type of data. P values for continuous data were two-tailed, and differences between groups were considered significant if P < 0.05. CVD mortality risks were estimated using Cox regression models selected to adjust for risk of CVD: model A = age, gender, BMI at baseline and previous angina pectoris; and model B = model A plus education, marital status and use of glucose-lowering drugs. Directed acyclic graphs were used to minimize the risk of bias and identify the primary adjustment model, which led to model B [16]. Formal statistical interactions between baseline BMI and BMI change, and between treatment group and BMI change, were performed using a logistic likelihood test comparing the original and adjusted model B.

2.3. Sensitivity analyses

To study the effects of baseline BMI, patients with BMI ≥ 30 kg/m² were excluded. The cohort was also divided into four groups according to baseline BMI quartiles, with survival analyses performed within each group. The effect of different time intervals between baseline and second BMI was studied in separate analyses by excluding all patients with < 120-day intervals and adjusting for the time difference. The effect of time from baseline BMI to date of diabetes diagnosis was assessed by including only patients with BMI registrations close to the diagnosis date (within −30 to +15 days).

A previous diagnosis of type 2 diabetes might have been missed because patients had moved from one primary-care centre not included for data extraction and had no hospital registration in Sweden. To minimize the risk of previous and undetected diagnoses, two separate analyses were performed by excluding patients with a primary-care history < 15 months and those taking insulin treatment at baseline.

To study the effects of an unmeasured binary confounder such as smoking on CVD mortality risk, the prevalence differences between the increased and unchanged BMI groups were calculated [17]. The hazard ratio (HR) for smoking was set at 2 with a smoking prevalence of 15% in the unchanged BMI group, based on the reported characteristics of Swedish type 2 diabetes patients, which were set at 15% [9,18,19]. R statistics package software, version 2.13.1, was used for all analyses.

3. Results

Baseline mean age was 60.0 years (range 35–79 years) and mean BMI was 30.2 kg/m² (range 16.7–58.5 kg/m²). Mean overall time between baseline and second BMI registration dates was 383 days (range 46–545, SD 121 days). Patients were followed for up to 9 years, with a median follow-up time of 4.6 years and 38,300 patient-years. Slightly more than half the patients had an unchanged BMI (53.4%), and more patients had a decrease (32.2%) than increase (14.4%) in BMI (Table 1). During follow-up, the incidence rates (per 1000 patient-years) of CVD mortality were 8.59 (6.35–11.38), 5.98 (4.97–7.14) and 5.74 (4.48–7.26) in the increased, unchanged and decreased BMI groups, respectively. Very few patients (4.1%) had less than 120 days between baseline and second BMI measurements. Patients with increased BMI were younger, with higher levels of education, lower HbA1c, higher high-density lipoprotein (HDL), lower creatinine levels, higher estimated glomerular filtration rate (GFR) and less angina pectoris compared with the unchanged BMI group (Table 1). Patients who decreased their BMI were more often women, and had higher education levels, higher baseline BMI, higher levels of triglycerides, higher blood pressure, lower creatinine levels and lower incidence of angina compared with the unchanged BMI group. A history of angina was less prevalent in both the increased and decreased groups than in the unchanged group.

During follow-up, both the increased and decreased BMI groups maintained higher BMIs compared with the unchanged group, and the increased group had the highest readings (Supplementary follow-up data, Fig. S2). The overall BMI trend was a slight decrease in BMI during follow-up in all groups. A trend towards higher levels of HDL cholesterol and lower levels of triglycerides was observed in the decreased BMI group compared with the increased group during follow-up.

3.1. Glucose-lowering drugs

Approximately one-third of patients were taking some kind of glucose-lowering drug at the time of diabetes diagnosis (Supplementary baseline data, Table S1). During the first year, more patients received treatment with glucose-lowering drugs in the increased BMI group than in the other two groups. Fewer patients were using metformin in the increased group and more patients were taking it in the decreased group compared with the unchanged group. The average daily starting dose of metformin was ~1000 mg and the overall use of metformin during follow-up was similar for all three groups (Supplementary follow-up data, Fig. S3).

More patients were taking sulphonylurea and insulin in the increased BMI group and fewer in the decreased group compared with the unchanged group (Supplementary baseline data, Table S1). The use of sulphonylurea and insulin was also higher during
Table 1
Characteristics of 8486 patients with newly diagnosed diabetes.

<table>
<thead>
<tr>
<th></th>
<th>Increased BMI (n = 1238)</th>
<th>Unchanged BMI (n = 4523)</th>
<th>Decreased BMI (n = 2725)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>57.9 (10.2)***</td>
<td>59.7 (10.1)</td>
<td>59.0 (10.3)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>720 (58.2)</td>
<td>2671 (59.1)</td>
<td>1279 (46.9)***</td>
</tr>
<tr>
<td>First BMI, kg/m²</td>
<td>30.1 (5.8)</td>
<td>30.2 (5.1)</td>
<td>32.7 (5.8)***</td>
</tr>
<tr>
<td>Second BMI, kg/m²</td>
<td>32.2 (6.0)***</td>
<td>30.1 (5.1)</td>
<td>30.2 (5.5)</td>
</tr>
<tr>
<td>BMI change, kg/m²</td>
<td>2.1 (1.5)***</td>
<td>-0.1 (0.6)</td>
<td>-2.5 (1.7)***</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>6.55 (0.80)***</td>
<td>6.73 (0.81)</td>
<td>6.94 (0.83)</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.64 (1.19)</td>
<td>5.62 (1.13)</td>
<td>5.68 (1.22)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>3.45 (0.96)</td>
<td>3.47 (0.91)</td>
<td>3.50 (0.97)</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>1.47 (0.88)*</td>
<td>1.40 (0.78)</td>
<td>1.36 (0.77)</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>145.4 (18.6)</td>
<td>140.8 (17.9)</td>
<td>147.4 (17.9)*</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>83.8 (9.4)</td>
<td>83.4 (9.4)</td>
<td>84.7 (9.3)***</td>
</tr>
<tr>
<td>Creatinine, mmol/L</td>
<td>78.0 (18.3)*</td>
<td>79.6 (17.1)</td>
<td>78.3 (19.0)**</td>
</tr>
<tr>
<td>Estimated GFR, mL/min</td>
<td>85.8 (17.5)**</td>
<td>83.4 (16.8)</td>
<td>83.0 (17.4)</td>
</tr>
<tr>
<td>Angina pectoris, n (%)</td>
<td>40 (3.2)**</td>
<td>236 (5.2)</td>
<td>104 (3.8)**</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>32 (2.6)</td>
<td>80 (1.8)</td>
<td>64 (2.3)</td>
</tr>
<tr>
<td>Higher education, n (%)</td>
<td>769 (64.1)**</td>
<td>2650 (59.6)</td>
<td>1691 (63.1)**</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married, n (%)</td>
<td>636 (51.7)*****</td>
<td>2637 (58.4)</td>
<td>1498 (55.1)*</td>
</tr>
<tr>
<td>Divorced, n (%)</td>
<td>232 (18.9)</td>
<td>765 (17.0)</td>
<td>496 (18.2)</td>
</tr>
<tr>
<td>Unmarried, n (%)</td>
<td>264 (21.5)**</td>
<td>748 (16.8)</td>
<td>504 (18.5)</td>
</tr>
<tr>
<td>Widow/widower, n (%)</td>
<td>97 (7.9)</td>
<td>363 (8.0)</td>
<td>222 (8.2)</td>
</tr>
</tbody>
</table>

BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; BP: blood pressure; GFR: glomerular filtration rate; COPD: chronic obstructive pulmonary disease.

Numbers in parentheses are standard deviations (SD).

* Secondary school, college or other graduate degree.

† P < 0.05 versus unchanged BMI.

** P < 0.01 versus unchanged BMI.

*** P < 0.001 versus unchanged BMI.

The use of statins, antihypertensives and low-dose ASA was similar in all groups during follow-up (Supplementary follow-up data, Fig. S3), and no differences were noted in cholesterol and blood pressure levels across all three groups (Supplementary follow-up data, Fig. S2).

3.3. BMI changes associated with CVD and all-cause mortality

The risks of CVD and all-cause mortality were 83% (HR: 1.83, 95% CI: 1.29–2.58) and 48% (HR: 1.48, 95% CI: 1.16–1.90) higher in the patients with increased BMI compared with unchanged BMI, respectively (Table 2), whereas mortality risk did not differ in the decreased BMI group compared with the unchanged group. In model B, patients with increased BMI had significantly higher risks of CVD and all-cause mortality than patients with unchanged BMI at 63% (HR: 1.63, 95% CI 1.11–2.39) and 34% (HR: 1.34, 95% CI 1.01–1.76), respectively.

follow-up in the increased BMI group and lower in the decreased BMI group during the follow-up period than in the unchanged BMI group (Supplementary follow-up data, Fig. S3).

Also, as shown in Supplementary follow-up data, Fig. S2, from the time of being newly diagnosed with diabetes, HbA1c levels decreased substantially in the decreased BMI group and remained low compared with the other two groups during follow-up. The general trend in all three groups was, however, a slight increase in HbA1c levels during the follow-up period.

3.2. CVD prevention drugs

Fewer patients in the increased BMI group were treated with acetylsalicylic acid (ASA) and antihypertensives than in the unchanged group (Supplementary baseline data, Table S1). The decreased BMI group had a slightly lower use of ASA and similar use of antihypertensives compared with the unchanged group. However, there was greater use of thiazide diuretics in the decreased BMI group than in the two other groups. The
Introducing adjustments for age in the survival model changed estimates of CVD and all-cause mortality the most. The adjusted increased cumulative risk of CVD mortality in the increased BMI group was evident and statistically verifiable from 3 years onwards (Fig. 1).

### 3.4. Sensitivity analyses

In the subgroup of 4,458 patients (52.5%) with BMI ≥ 30 kg/m², the incidence rates of CVD mortality were 7.87 (4.83–12.17), 5.61 (4.23–7.32) and 5.84 (4.30–7.76) in the increased, unchanged and decreased BMI groups, respectively. Compared with the unchanged BMI group, the corresponding risks of CVD mortality were 1.73 (95% CI: 0.98–3.07) and 1.12 (95% CI: 0.73–1.72) in the increased and decreased BMI groups, respectively. In the subgroups according to baseline BMI quartiles 1 to 4, CVD mortality risk was 1.73 (95% CI: 0.92–3.24), 1.20 (95% CI: 0.49–2.99), 2.12 (95% CI: 0.96–4.66) and 1.33 (95% CI: 0.52–3.39), respectively, compared with the unchanged BMI group.

For 8,135 patients (95.9%), the time between baseline and second BMI measurements was at least 120 days, and the risk of CVD mortality was 1.52 (95% CI: 1.02–2.27) and 1.05 (95% CI: 0.75–1.48) in the increased and decreased BMI groups, respectively. The main results did not change with additional adjustments for time between baseline and second BMI: 1.62 (95% CI: 1.10–2.39). When using only the BMIs registered from 30 days before to 14 days after the date of diabetes diagnosis, the corresponding risks of CVD mortality were 1.66 (95% CI: 1.04–2.65) and 1.15 (95% CI: 0.78–1.68) in the increased and decreased BMI groups, respectively.

On analyzing the 7,169 patients (84.5%) with a treatment history >15 months at their respective primary-care centres, the associations were slightly stronger than in the primary analysis sample, with HRs of 1.74 (95% CI: 1.16–2.61) for CVD mortality and 1.30 (95% CI: 0.96–1.74) for all-cause mortality in the increased BMI group versus the unchanged BMI group. Excluding patients using insulin at baseline or within the first year of diagnosis did not change risk estimates for CVD and all-cause mortality in the increased BMI group versus the unchanged group: 1.68 (95% CI: 1.12–2.52) versus 1.29 (95% CI: 0.96–1.74), respectively.

On applying all adjusted covariates at the time of the second BMI, the risk of CVD mortality did not change significantly compared with the main results (1.57, 95% CI: 1.04–2.37 versus 1.63, 95% CI: 1.11–2.39). Compared with all other covariates, BMI influenced the results the most.

On assessing the effect of smoking, it was calculated that 15% and 10% higher smoking prevalences in the increased and unchanged BMI groups changed CVD mortality risk to 1.44 (95% CI: 0.98–2.11) and 1.50 (95% CI: 1.02–2.20), respectively.

On introducing the product of (BMI change * baseline BMI) and (BMI change * glucose-lowering drug [sulphonylurea or
metformin]) in the Cox model, no interaction was detected; P values were 0.59 and 0.22, respectively.

4. Discussion

The present study demonstrates that slightly more than half of patients (53.4%) maintain their BMI with no changes during the first 18 months after type 2 diabetes diagnosis. The least common observation was an increased BMI (14.4%) by more than 1 BMI unit (~3.6 kg), and this group had a 63% greater risk of CVD mortality compared with patients with unchanged BMI. Interestingly, no risk reduction was detected in the 32.2% of patients whose BMI decreased by more than 1 BMI unit compared with those whose BMI remained unchanged. These findings were robust and remained virtually unchanged after adjusting for several important risk factors. Furthermore, on replacing the CVD mortality with the all-cause mortality endpoint, the results were still similar, albeit slightly weaker.

Very few studies have addressed the relationship between weight change, closely associated with BMI, and incidence of CVD in diabetes patients. Drawing from the Swedish National Diabetes Register, Eeg-Olofsson et al. [9] reported an increased risk of non-fatal and fatal CVD with increasing weight in 4916 patients with prevalent diabetes (24,144 person-years). In that study, the assessment of weight change was a secondary objective and the method used differed substantially from ours by calculating the BMI difference up to a CVD event or the study end. On comparing patients with very high increases (median +3.8 BMI units) versus moderate weight increases (median +1 BMI unit), the former group was associated with a 1.54-fold increased risk of CVD compared with the latter. As in our present study, those authors observed no association between weight reduction and CVD risk. However, despite considerable differences in methods and materials, the two studies both have similar findings of an increased CVD risk with increasing BMI in patients with type 2 diabetes.

Weight loss may be unintentional, such as that caused by poorly controlled diabetes or other advanced disease, or intentional, such as with lifestyle modifications. Weight increase may be due to failure of lifestyle modifications or effects of pharmacological treatment. Undesirable weight gain is related to glucose-lowering drugs that directly or indirectly increase levels of insulin, including insulin itself [20–22] and insulin secretagogues (sulphonylureas) [23–26]. In our present study, a larger proportion of patients in the increased BMI group were already using sulphonylurea and insulin, and more patients added these drugs during follow-up (Supplementary follow-up data, Fig. S3), thus partially explaining the increase in BMI in this group (Supplementary follow-up data, Fig. S2). The proportion of patients taking metformin was significantly lower in the increased BMI group and higher in the decreased BMI group both at baseline and during follow-up. These substantial differences might also partly explain the weight changes, supported by the notion of metformin’s weight-reducing effects [27–31].

Baseline characteristics of the increased BMI group (higher insulin use and lower HbA1c) could indicate a greater probability of beta-cell failure than in the unchanged BMI group. The pathophysiology that accompanies newly diagnosed diabetes changes clinical management, thereby introducing an unknown confounding effect. However, on excluding all non-obese patients (BMI < 30 kg/m²) and those treated with insulin, thereby lowering the probability of pancreatic insufficiency, the risk of CVD mortality changed only slightly. The associations between BMI increase and CVD mortality risk were also estimated according to baseline BMI categories (quartiles). HRs remained numerically similar, but lost their statistical significance, and no trends were visible. These sensitivity analyses address some of the confounding properties of different pathways and support the main results of our study.

As with other studies [6,32–35], our study failed to demonstrate any CVD risk-altering effects with weight reduction, despite showing positive long-lasting effects on BMI, HbA1c, HDL and triglycerides (Supplementary data, Fig. S2). Recently, the Look AHEAD trial was stopped by the study’s data and safety monitoring board when it became evident that, although the intensive lifestyle interventions to reduce weight in obese type 2 diabetes patients did no harm, they also did not lower the risk of CVD events either [6]. However, the Look AHEAD findings have yet to be published, making any interpretation difficult at this time.

Other studies have reported lower risks of clinical events with weight loss. The Swedish Obese Subjects (SOS) study reported reduced mortality with substantial and sustained weight loss (14–25%) after gastric surgery [5]. Intentional weight loss was associated with reduced CVD risk in an observational study based on patient-reported weight changes [36]. In a CVD population with or without diabetes, early weight loss (over 6 weeks) of just over 2 kg lowered the risk of CVD mortality over the subsequent 5-year follow-up [37]. This suggests that, despite large differences in patients’ characteristics and study design, the results may yet support beneficial effects with substantial or moderate weight loss in specified subgroups of diabetes patients, such as those with established CVD.

The proportion of patients with unintentional weight loss caused by poorly controlled blood glucose levels may have been higher in the decreased BMI group (who were heavier, with higher HbA1c levels and less use of glucose-lowering drugs) than in the unchanged BMI group. Interestingly, the slightly increased use of diuretics (thiazides) in the decreased BMI group might partially explain the unintentional weight loss while at the same time indicating low-intensity antihypertensive treatment. Such reasons for unintentional weight loss could somewhat compromise CVD risk estimates for the decreased BMI group. However, it cannot be ruled out that our findings may hold true for BMI decreases, supported by recent results from the prospective Look AHEAD trial [6].

The time between BMI measurements may have influenced our results, especially considering that these were records from real-life clinical settings. By introducing the criterion of at least 120 days between baseline and second BMI measurements, and adjusting for time between the two measurements, the results did not change significantly and, thus, support our
primary results. The choice of adjusting for either the index or second BMI also had no effect on our main results, thereby bolstering the view that BMI changes can affect future CVD risk.

4.1. Strengths and limitations

The strengths of the present study include the selection of patients with newly diagnosed diabetes and large numbers of patients with long-term follow-ups in real-life clinical settings through the use of nationwide healthcare registries. However, data on beta-cell function, diet, waist circumference, physical activity and smoking were not adequately recorded in these registries. In type 2 diabetes patients, neither smoking history nor current smoking at baseline has been associated with weight gain or weight loss, respectively [14,38]. These results would argue for potentially fewer smokers in the increased BMI group and more smokers in the decreased BMI group compared with the unchanged BMI group. There is also the greater possibility of higher numbers of successful smoking cessation in the increased BMI group, given that stopping smoking is generally associated with a weight increase of 4–5 kg in 80% of patients over a 12-month period [39]. However, smoking interventions in a real-world setting among diabetes patients have had rather disappointing results, ranging from 7% in Sweden to 2.3% in Spain [40,41]. This reasoning therefore suggests the possibility of a higher prevalence of smokers in the unchanged and/or decreased BMI groups. However, the generally low prevalence of smokers and low success rates of smoking cessation also point to less of an impact of smoking behavior on CVD risk in the increased BMI group. In addition, the estimated 10–15% difference in smoking prevalence applied to blunt the main results between the increased and unchanged BMI groups seems unlikely in a country with an overall 15% smoking prevalence. Moreover, the directed acyclic graphs used to create optimal models for minimizing bias did not identify smoking as a crucial confounder, which may be explained by the smoking-associated risk being accounted for by other covariates extracted from the otherwise detailed database [16].

Furthermore, if the increased BMI group had a higher CVD risk profile at baseline, any differences would have been apparent earlier in the follow-up. Yet, the risk difference in CVD mortality only became evident 3 years after the BMI changes, thus supporting similar risk profiles at baseline but with different rates of disease progression.

5. Conclusion

Weight gain in patients with newly diagnosed type 2 diabetes may be more hazardous than previously recognized, and efforts should be made to prevent weight increases in diabetes patients. However, weight loss did not lower the long-term risk of either CVD or all-cause mortality. Nevertheless, the results of this retrospective study need to be confirmed in prospective studies before any definitive conclusions can be drawn.

Disclosure of interest

J.B. holds a full-time position at AstraZeneca as an epidemiologist. J.S., P.N., C.J.O., B.S. and G.J. have received compensation for the work on this report from AstraZeneca.

Contributions: J.B. researched data, contributed to the discussion, and wrote, reviewed and edited the manuscript. B.S. had full access to the data and performed statistical analyses. J.S., C.J.O., P.N., B.S. and G.J. researched data, contributed to the discussion, reviewed and edited the manuscript. J.B. is the guarantor of this work and, as such, takes responsibility for the integrity of the data and accuracy of the data analysis.

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Appendix A. Supplementary data

Supplementary materials (Figs. S1–S3 and Table S1) associated with this article can be found at http://www.sciencedirect.com at http://dx.doi.org/10.1016/j.diabet.2013.05.004.

References


