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Determinants of excessive weight gain after the initiation of insulin therapy in type 2 diabetes mellitus: Retrospective inception cohort study (ZODIAC 60)

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ABSTRACT

Aims: To explore determinants of excessive weight gain after initiation of insulin therapy in type 2 diabetes mellitus (T2DM), in particular variables identified in the pre-insulin phase.

Methods: We performed a retrospective observational intervention cohort study, by means of a new user design/inception cohort concerning n = 5086 patients. We studied determinants of excessive weight gain (5 kg or more) in the first year after initiation of insulin therapy, using both visualization and logistic regression analysis with subsequent receiver operation characteristic (ROC) analyses. Potential determinants pre-, at- and post-insulin initiation were included.

Results: One out of 10 patients (10.0%) gained 5 kg weight or more. The earliest determinants of excessive weight gain were weight change (inversely) and HbA1c change in the two years prior to insulin therapy (p < 0.001). Patients that lost weight parallel with HbA1c rise in the two-years pre-insulin, showed the most pronounced weight gain. Of these patients, roughly one out of five (20.3%) gained 5 kg weight or more.

Conclusions: Clinicians and patients should be alert for excessive weight gain after initiation of insulin, in the case of weight loss prior to insulin therapy initiation, particularly with increasing and prolonged high HbA1c at (and after) insulin initiation.

1. Introduction

Initiation of insulin therapy in patients with type 2 diabetes mellitus (T2DM) can be hampered by quite some obstacles. Fear of weight gain after the initiation of insulin therapy is one of the concerns for both patients and healthcare providers. [1–2].

Several observational studies on outcomes after initiation of insulin therapy in routine clinical practice have been performed. Indeed most studies, but not all, reported weight gain after the initiation of insulin therapy. [3] Considerable variations in mean weight change were reported, both within and between studies [3–15] as well as within [7] and between [8] countries. In the first year after the initiation of insulin therapy mean reported weight gains ranged from 0.31 kg to 3.0 kg. [3,5–6,8–9,12,14] The percentage of patients gaining any amount of

weight ranged from 47.7% [3] to far over 50%. [8,12].

Few observational studies have focused on excessive weight gain, defined as ≥ 5 kg [3,8] or ≥ 7% [12] in the first year after the initiation of insulin therapy. The percentage of patients gaining excessive weight ranged from 10% to 25.6% [3,8,12] with substantial differences between countries. [8].

Knowledge of which patients are prone to gain (excessive) weight after the initiation of insulin therapy could help guide clinical decision making, including implementing early interventions to counteract weight gain. For this purpose the timing, i.e. the collecting of possibly important and preferably pre-defined determinants at, prior, of after the initiation of insulin therapy may be of importance. [3] Most studies reported a positive association of hemoglobin A1C (HbA1c) at initiation and an inverse association of body mass index (BMI) at initiation with weight gain following initiation of insulin therapy. [3].

Several studies reported on the absence of strong baseline determinants concerning weight change [6,8,12] and substantial weight gain. [16] Predictive value of models improved when variables after initiation were included. [8,16] However, in the context of preventing (excessive) weight gain, pre-defined variables prior to the decision to start insulin therapy are preferable. We previously reported that weight change in the (two) years prior to the initiation is a relatively strong and independent inverse determinant of weight change (kg) in the first year after initiation of insulin therapy in T2DM. [3].

To our knowledge, no observational studies on determinants of excessive weight gain after initiation of insulin therapy in insulin-naïve T2DM patients have been performed, which included pre-initiation parameters as well. The main aim of the present study was to investigate determinants of post-initiation excessive weight gain, in the Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) cohort.

2. Subjects, materials and methods

The writing of this paper was guided by The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement criteria. [17].

2.1. Setting

This study is part of the ZODIAC project, performed in a prospective primary care T2DM patient cohort in the Netherlands, initially initiated for benchmarking purposes in 1998. [18] Patients included in the ZODIAC cohort were diagnosed with T2DM and treated in primary care, according to national guidelines, i.e. the Dutch College of General Practitioner Guideline (Dutch: NHG-Standaard). [18–19] The ZODIAC project was approved by the Ethics Committee of Isala, Zwolle (references 03.0316 and 07.0335).

2.2. Study design

This study is the second phase of our project to study weight gain after initiation of insulin therapy in patients with T2DM, previously described in detail. [3] In summary, we used the available information in de ZODIAC database of the years 1998 – 2014, to perform a retrospective observational intervention cohort study on the effect of initiation of insulin treatment on body weight, by means of a new user design/ inception cohort.[3,20]HYPERLINK "SPS:refid::bib3_bib20".

We extracted data of the year that insulin use was first registered, and herewith defined the index time point (also referred to as T0 or baseline). Additionally, we extracted data of several years prior to index and several years after index. We identified n = 5086 patients that initiated insulin in the study period and for which body weight data at both index (T0) and one year after index (T + 1) were available. These T2DM patients formed the intention-to-treat (ITT) analysis set.

2.3. Data sources and measurement

Quality indicators on T2DM care were collected annually in primary health care practices. The core set of quality indicators included patient demographics, laboratory results, medication use, lifestyle variables and variables collected through physical examination. Clinically unlikely data points were excluded from analysis, as presented in **table S1.3**.

2.4. Outcomes and determinants

2.4.1. Outcome

Weight change in the first year after insulin initiation was calculated by subtracting consecutive years (new weight - old weight), hence a positive value indicates weight gain. Subsequently, we classified weight change in the first year post-initiation into nine ordinal groups (unequal sized and unequal spaced, as binning was not possible given the discrete weight change variable).

The primary outcome was excessive weight gain defined as 5 kg weight gain or more [8] in the first year after index, i.e. time period T0 to T + 1.

2.4.2. Determinants

Potential associates of weight gain after initiation of insulin therapy were categorized into three groups: 1) variables prior to index [T < 0], 2) variables at index [T0], and 3) variables after index [T > 0]. Based on the literature concerning weight change in kg, particularly HbA1c, weight and BMI were of interest. [3] For this second stage of our study, we also included additional measures concerning anthropometry, and estimates of renal function based on Cichosz et al (2017). [16] We explored the value of estimated glomerular filtration rate using the Cockcroft-Gault (eGFR-CG based on body weight), the Modification of Diet in Renal Disease (eGFR-MDRD), and the Chronic Kidney Disease Epidemiology Collaboration (eGFR-CKD-EPI) formulae. [21] Formulae are presented in **table S2** and a matrix scatterplot is shown by **figure S1**. Based on univariate analyses, the eGFR-CG formula was selected for further studying involving multivariable analyses.

2.5. Statistical analyses

Categorical data were presented by n (%), and discrete/ continuous variables were presented by mean (±SD) or median (Q1 – Q3) depending on the distribution.

Arithmetic means with 95% confidence intervals (95%CIs) by outcome category were plotted, and estimated means with 95%CIs obtained by linear mixed model analyses were plotted to allow longitudinal analysis. Akaike's information criterion was used to select covariance structures.

Determinants of excessive weight gain in the first year after initiation of insulin therapy were explored by means of logistic regression analysis. Comparison of baseline characteristics and univariate regression analyses were performed to identify candidate predictors. Variables with p < 0.400 by univariate analysis (**table S4**) were subsequently studied by multivariable analysis. All variables of interest were entered, and variables were one-by-one manually excluded based on the highest p-value until only statistically significant variables remained. Overall model performance was assessed using Nagelkerke's explained variation (NR^2) and discriminative value was assessed using ROC analyses. Multicollinearity was monitored using the variance inflation factor, using < 5 as criterion.

Analyses were performed using SPSS version 28 and R studio version 1.4.1717. Alpha 5% was used to indicate statistical significance.

3. Results

3.1. Participants

Patient characteristics of the ITT analysis set (n = 5086) are presented in Table 1. Mean age was 68.2 (±11.2) years and median diabetes duration was 9.0 (6.0 – 13.0) years. The sample consisted of slightly less men (46.9%), and approximately half had a BMI of 30 kg/m^2 or higher indicating obesity. Mean HbA1c at index and the year prior to index were 7.4% (58 mmol/mol) and 7.6% (59 mmol/mol),

Table 1
Patient characteristics at index.

	ITT analysis set (n = 5086)		No excessive weight gain (n = 4577)		Excessive weight gain (n = 509)		p-value *
	n	Summary statistics	n	Summary statistics	n	Summary statistics	
Demographics							
Age (years)	5085	68.2 (±11.2)	4576	68.3 (±11.2)	509	67.3 (±11.8)	0.064
Sex (men)	5086	2387 (46.9%)	4577	2144 (46.8%)	509	243 (47.7%)	0.708
Diabetes duration (years)	5013	9.9 (±5.9)	4511	10.0 (±5.9)	502	9.5 (±5.4)	0.063
		9 (6 – 13)		9 (6 – 13)		9 (6 – 12)	
Medication							
Main treatment group	5086	3628 (71.3%)	4577	3285 (71.8%)	509	343 (67.4%)	**0.039**
OGLD and insulin		1458 (28.7%)		1292 (28.2%)		166 (32.6%)	
Insulin only							
Insulin number	5086	4562 (89.7%)	4577	4106 (89.7%)	509	456 (89.6%)	0.939
1		524 (10.3%)		471 (10.3%)		53 (10.4%)	
2 or 3							
Insulin regimen	508	160 (3.1%)	4577	136 (3.0%)	509	24 (4.7%)	**0.019**
Short- and rapid-acting		1828 (35.9%)		1625 (35.5%)		203 (39.9%)	
Premixed		1633 (32.1%)		1479 (32.3%)		154 (30.3%)	
Basal		941 (18.5%)		866 (18.9%)		75 (14.7%)	
NPH		524 (10.3%)		4741 (10.3%)		53 (10.4%)	
Combination							
OGLDs number	508	1458 (28.7%)	4577	1292 (28.2%)	509	166 (32.6%)	0.118
0		2292 (45.1%)		2077 (45.4%)		215 (42.2%)	
1		1336 (26.3%)		1208 (26.4%)		128 (25.1%)	
2 or 3							
OGLD types (selection)	5086	3179 (62.5%)	4577	2872 (62.7%)	509	307 (60.3%)	0.289
Metformin		1723 (33.9%)		1568 (34.3%)		155 (30.5%)	0.093
Sulfonylureas							
Lipid lowering drugs	5086	3146 (61.9%)	4577	2849 (62.2%)	509	297 (58.3%)	0.092
Diuretics	5086	1705 (33.5%)	4577	1545 (33.8%)	509	160 (31.4%)	0.299
Physical examination							
Height (m)	4968	170.0 (±10.0)	4470	169.9 (±10.0)	498	170.9 (±9.9)	0.054
Weight (kg)	508	87.7 (±16.7)	4577	87.6 (±16.6)	509	88.8 (±18.0)	0.141
Mean		86 (76 – 97)		86 (76 – 97)		87 (76 – 99)	0.199
Median							
BMI (kg/m^2)	4978	30.3 (±5.2)	4478	30.3 (±5.1)	500	30.4 (±5.3)	0.911
Mean		29.8 (26.8 – 33.2)		29.8 (6.8 – 33.2)		29.8 (26.6 – 33.5)	0.956
Median							
BSA$_{MOSTELLER}$ (m^2)	4968	2.0 (±0.2)	4470	2.0 (±0.2)	498	2.0 (±0.2)	0.099
LBW$_{JANMAHASATIAN}$ (kg)	4978	55.7 (±11.5)	4478	55.6 (±11.4)	500	56.4 (±11.8)	0.152
SBP (mmHg)	5061	139.7 (±17.8)	4554	139.8 (±17.6)	507	138.6 (±19.6)	0.179
DBP (mmHg)	5035	77.8 (±10.3)	4531	77.8 (±10.2)	504	77.5 (±11.0)	0.526
Laboratory							
HbA1c (mmol/mol)	4968	57.7 (±10.6)	4477	57.4 (±10.3)	491	60.1 (±13.5)	**<0.001**
Mean		56.0 (51.0 – 63.0)		56.0 (51.0 – 62.0)		58.0 (51.0 – 67.0)	
Median							
Total cholesterol (mmol/L)	4877	4.4 (±1.0)	4394	4.4 (±1.0)	483	4.4 (±1.1)	0.704
HDL-cholesterol (mmol/L)	4863	1.2 (±0.4)	4383	1.2 (±0.4)	480	1.2 (±0.4)	0.202
Cholesterol/ HDL ratio (mmol/L)	4875	3.8 (±1.2)	4394	3.8 (±1.2)	481	3.8 (±1.2)	0.320
LDL-cholesterol (mmol/L)	4735	2.4 (±0.8)	4265	2.4 (±0.8)	470	2.4 (±0.9)	0.891
Triglycerides (mmol/L)	4811	1.6 (1.1 – 2.2)	4335	1.6 (1.1 – 2.2)	476	1.7 (1.2 – 2.4)	**0.030**
Renal function							
Serum creatinine (μmol/L)	4905	82.8 (±27.2)	4418	82.6 (±26.8)	487	84.7 (±30.6)	0.148
eGFR-CG.BW	4732	90.6 (±35.6)	4262	90.4 (±35.2)	470	92.7 (±39.1)	0.231
eGFR-MDRD	4801	73.5 (±22.4)	4326	73.5 (±22.1)	475	73.3 (±24.4)	0.876
eGFR-CKD.epi	4790	75.7 (±31.5)	4316	75.6 (±31.2)	474	76.0 (±34.3)	0.805
Albuminuria	1090	8 (4 – 21)	986	8 (4 – 21.3)	104	8 (4 – 18)	0.814
Albumin-to-creatinine ratio	4373	1 (0.5 – 3.0)	3950	1 (0.5 – 3.0)	423	1.1 (0.5 – 3.4)	0.057
Lifestyle							
Physical activity (adequate)	3873	1658 (42.8%)	3495	1519 (43.5%)	378	139 (36.8%)	**0.014**
Smoking	5006	1164 (23.3%)	4506	1035 (23.0%)	500	129 (25.8%)	0.163
Alcohol	3051	547 (17.9%)	2753	481 (17.5%)	298	66 (22.1%)	0.056
Treatment duration (post index)							
Insulin use duration	5086	795 (15.6%)	4577	720 (15.7%)	509	75 (14.7%)	0.607
<1 year		4291 (84.4%)		3857 (84.3%)		434 (85.3%)	
≥1 year							

*, Categorical data were tested using the Fisher's(Freeman-Halton) exact test. Continuous data were tested using the unpaired *T*-Test, except for triglycerides, albuminuria, and albumin-to-creatinine ratio which were tested using the Mann-Whitney *U* test.

respectively. Most patients (71.3%) were treated with a combination of insulin and oral glucose lowering drugs (OGLDs).

3.2. change after index and categorization

Weight change in the first year post index was normally distributed with a mean of 0.31 kg ($\pm$3.9), as shown by **figure S1**. N = 2425 patients (47.7%) gained weight, of which n = 1916 patients (37.7%) moderate (1 to < 5 kg) and n = 509 patients (10.0%, 95%CI: 9.2%–10.9%) excessive ($\geq$5 kg). N = 2661 patients (52.3%) either lost weight or showed no weight change or mild weight gain (<1 kg).

3.2.1. Patient characteristics by categories

A comparison of patient characteristics between those patients that did and did not gain an excessive amount of weight is incorporated in Table 1. Patients in the excessive weight gain group more often used insulin therapy without other glucose lowering agent(s) (p = 0.039), had a higher HbA1c at index (p < 0.001), and were less physically active (p

= 0.014). Moreover, some differences in insulin regimen were found (p = 0.019).

Patient characteristics for the nine described categories are presented in the supplementary information (**table S3**). In summary, some significant differences between categories were found, but these differences do not all seem linear. Noteworthy, the values of weight, BMI, Body Surface Area (BSA), and lean body weight (LBW) were the highest, and the percentage of patients reporting adequate physical activity was the lowest (34.5%), in those patients that lost the most weight (category 1). Furthermore, the duration of insulin use differed significantly (p = 0.001). Patients in the two categories that lost the most weight had the highest percentage short-duration of insulin use, i.e. shorter than 1 year.

3.3. Comparisons between the nine outcome categories

3.3.1. Pre-index and index comparisons

Fig. 1 shows comparisons of pre-index variables and index variables between the nine categories.
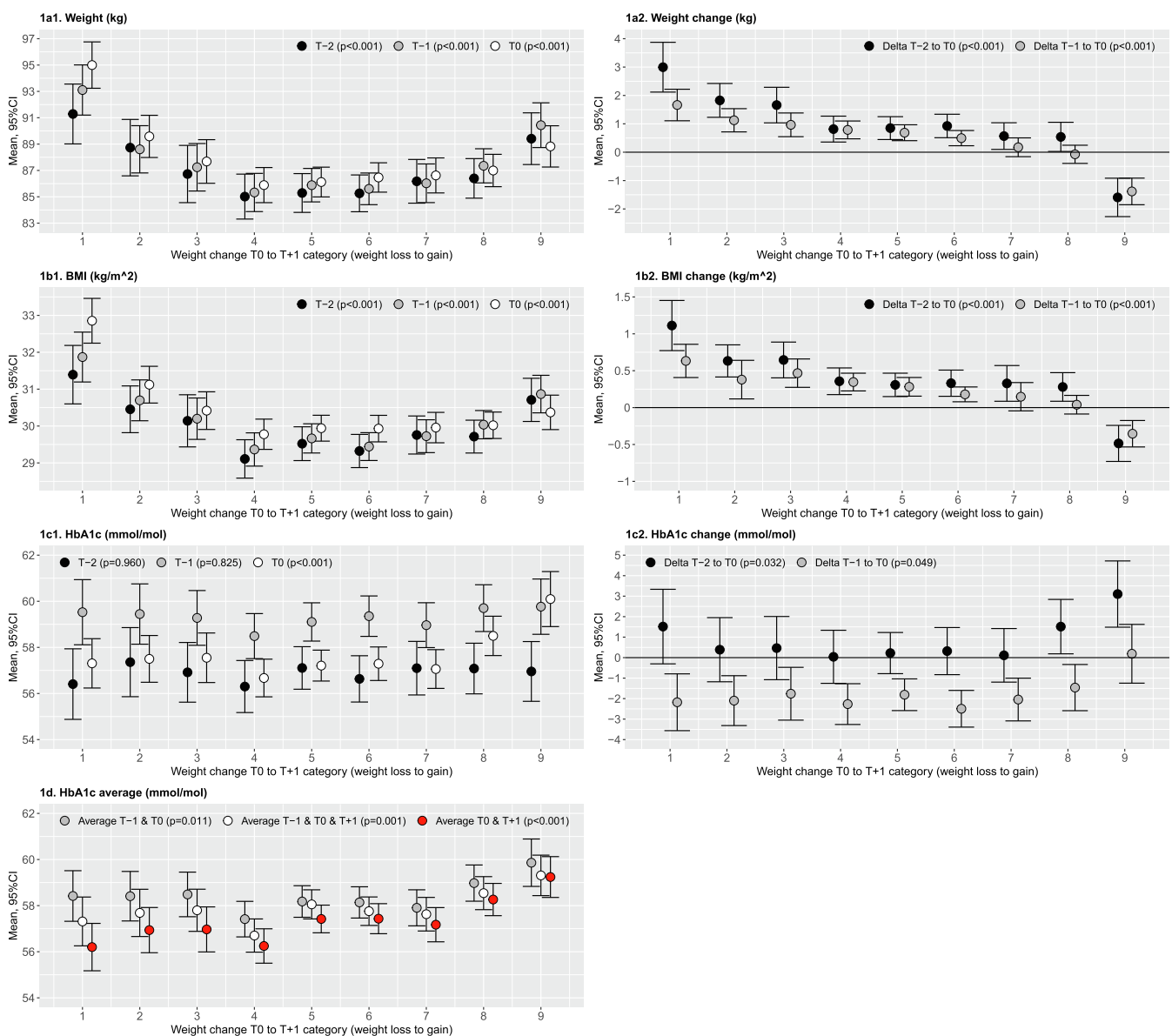
Fig. 1. Comparisons between the nine outcome categories. Data are means with 95% confidence intervals. Weight change categories: 1, <-4 kg (n = 414 [8.1%]); 2, −4 or −3 kg (n = 440 [8.7%]); 3, −2 kg (n = 379 [7.5%]); 4, −1 kg (n = 544 [10.7%]); 5, 0 kg (n = 884 [17.4%]); 6, 1 kg (n = 708 [13.9%]); 7, 2 kg (n = 567 [11.1%]); 8, 3 or 4 kg (n = 641 [12.6%]); 9, ≥5 kg (n = 509 [10.0%]). P-values were obtained by default analysis of variance (ANOVA).

3.3.1.1. Mean weight and BMI. Mean weight and BMI pre-index (T-2 and T-1) and at index (T0) differed between the nine categories (p < 0.001). Weight and BMI were the highest in the lowest and the highest categories, depicting a u-shaped quadratic association (**1a1 and 1a2**). Index values of weight and BMI in those patients that lost the most weight after index (category 1) stood out, with confidence intervals at the 95% level excluding those of all other categories, indicating statistical significance.

3.3.1.2. Mean weight change and BMI change. Mean weight change and BMI change pre-index (T-2 to T0 and T-1 to T0) differed between the nine categories (p < 0.001). Weight and BMI gain were the highest in those patients that lost the most weight after index and were lower towards higher categories, depicting a linear association (**1b1 and 1b2**). Moreover, only those patients that gained 5 kg weight or more (category 9) on average lost weight in time period T-2 to T0. Confidence intervals at the 95% level excluded all other categories, indicating statistical significance.

3.3.1.3. HbA1c and HbA1c change. There were barely any differences in pre-index mean HbA1c at T-2 and T-1 between the nine categories (**1c2**). At index, HbA1c differed between categories significantly (p < 0.001).

The category that gained 5 kg weight or more (category 9) showed the highest mean HbA1c at index, however this value was comparable to mean HbA1c at T-1 in all categories including category 9 itself. Moreover, this group showed a small average HbA1c increase in the year pre-index (**1c2**).

3.3.1.4. HbA1c averages. Averages of HbA1c concerning multiple time points were significantly different between the nine categories, with p = 0.011 for the mean concerning average HbA1c of time points T-1 and T0, p = 0.001 for means concerning average HbA1c of time points T-1, T0 and T + 1, and p < 0.001 for means concerning average HbA1c of time points T0 and T + 1 (**1d**).

3.3.2. Longitudinal comparisons

Fig. 2 shows estimated means with 95% confidence intervals of weight change, weight, BMI and HbA1c in time period T-5 to T + 5, stratified by the nine categories. This figure indicates that the estimated mean of patients that gained 5 kg weight or more remained high further in time as well. In most patients that gained an excessive amount of weight, weight in the first year after index did not only come back to pre-index level but even surpassed their weight in the two years pre-index (Fig. 2 **and figure S2**).
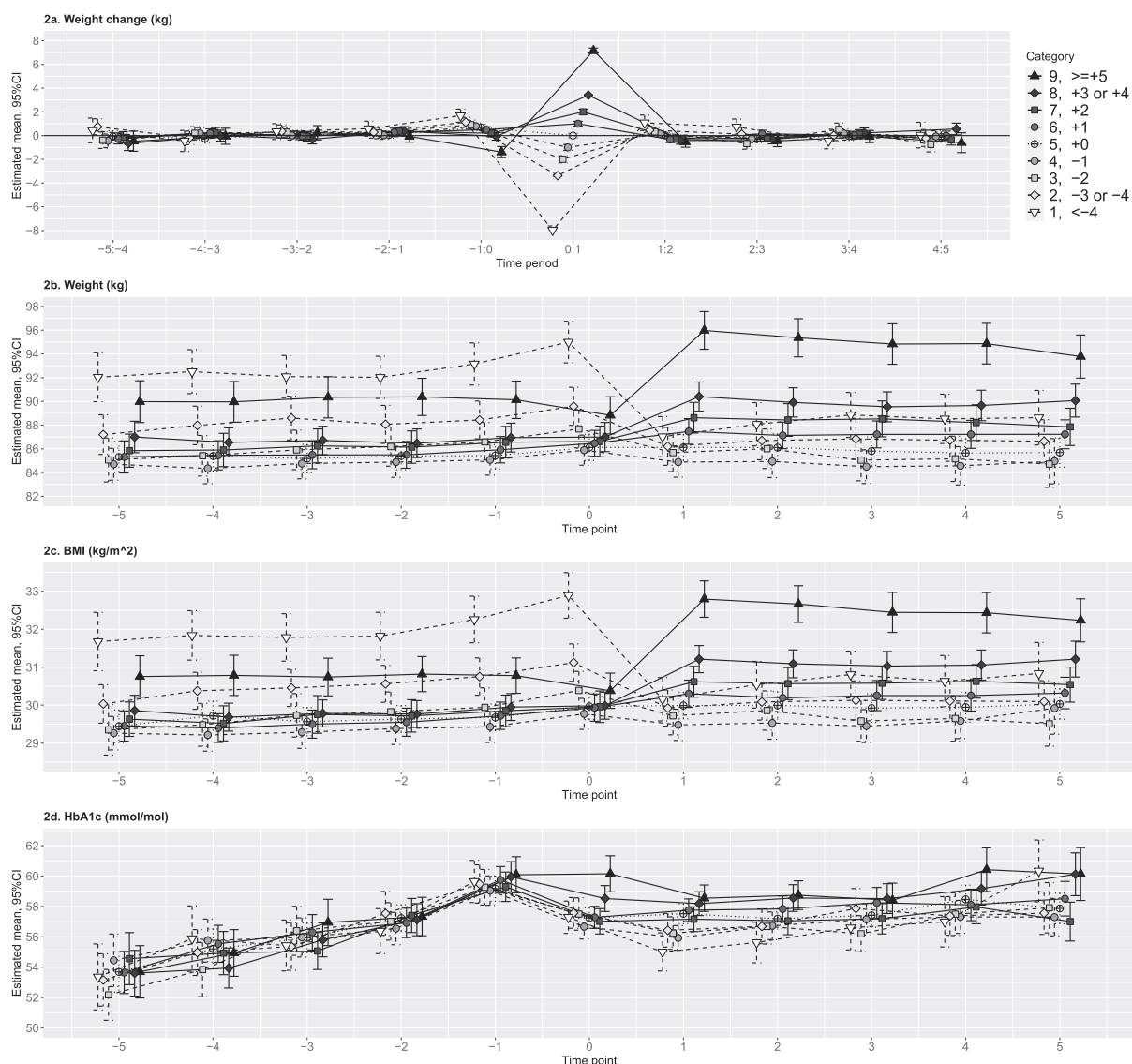

Fig. 2. Estimated means with 95% CIs of weight change, weight, BMI, and HbA1c in time period T-5 to T + 5 for the ITT analysis set, by outcome category.

3.4. Determinants of excessive weight gain

Univariate regression analyses concerning post-index excessive weight gain are shown in the supplementary appendix (**table S4**). Variables determined pre-index, in particular weight change (inverse), had the highest explained variances.

3.4.1. Associates of excessive weight gain in the first year after index

Multivariable analyses on excessive weight gain, concerning various time periods and time points, are shown by Table 3 **and table S5**. Significant AUROCs were found for all time periods and time points, but overall model performances were poor. The highest AUROCs were found when models included variables. When comparing pre-index, index, and post-index, the pre-index model showed a higher AUROC (model 3:

0.680, p < 0.001) as compared to index (model 4: 0.582, p < 0.001) and post-index (model 5: 0.656, p < 0.001). The highest AUROC was found when pre-index, index, as well as post-index variables were included in a model (model 9: 0.712, p < 0.001).

3.4.2. Earliest determinants

Pre-index weight change in the two years prior insulin was a significant inverse determinant of excessive weight gain (models 1 to 3, 6, and 8, 9) (Table 2.). The earliest determinants of post-index excessive weight gain were weight change (inversely) and HbA1c change in the two years prior to insulin therapy (model 1: AUROC = 0.668, p < 0.001).

Table 2

Multivariable logistic regression analyses followed by ROC analyses, on excessive weight gain (coded as 1) in the first year after registration of insulin therapy (T0 to T + 1), per time point and time period. Additional analyses are presented in **table S5**.

#	Models, by time points and time periods	Regression analyses					ROC analyses	
		n	B (SE)	Exp B (95% CI)	p-value	NRy^2	AUROC (95% CI)	p-value
	Pre-index T-2 including changes							
1	Weight change T-2 to T0	2879	−0.103 (0.012)	0.902 (0.881 – 0.923)	<0.001	6.4%	0.668 (0.632–0.703)	<0.001
	HbA1c change T-2 to T0		0.021 (0.005)	1.021 (1.011 – 1.031)	<0.001			
	Pre-index T-1 including changes							
2	HbA1c T-1	3764	0.024 (0.006)	1.025 (1.013–1.036)	<0.001	6.1%	0.659 (0.627–0.691)	<0.001
	Triglycerides T-1		0.148 (0.049)	1.160 (1.055–1.276)	0.002			
	Weight change T-1 to T0		−0.095 (0.012)	0.909 (0.887–0.932)	<0.001			
	HbA1c change T-1 to T0		0.030 (0.005)	1.031 (1.020–1.041)	<0.001			
	Beta-receptor blocking sympathicolytics stopped T-1 to T0		0.793 (0.254)	2.211 (1.345–3.635)	0.002			
	Pre-index T-2 en T-1 including changes							
3	Weight change T-2 to T0	2372	−0.066 (0.019)	0.937 (0.903–0.971)	<0.001	8.4%	0.680 (0.641–0.719)	<0.001
	HbA1c T-1		0.022 (0.008)	1.023 (1.007–1.038)	0.004			
	Triglycerides T-1		0.141 (0.061)	1.152 (1.022–1.297)	0.020			
	Weight change T-1 to T0		−0.067 (0.022)	0.935 (0.896–0.977)	0.003			
	HbA1c change T-1 to T0		0.030 (0.007)	1.030 (1.017–1.044)	<0.001			
	Beta-receptor blocking sympathicolytics stopped T-1 to T0		0.868 (0.310)	2.382 (1.297–4.376)	0.005			
	Index							
4	BSA$_{MOSTELLER}$ (m^2) T0	4596	−0.819 (0.363)	0.441 (0.216–0.897)	0.024	1.9%	0.582 (0.553–0.611)	<0.001
	HbA1c T0		0.021 (0.004)	1.021 (1.012–1.030)	<0.001			
	Serum creatinine T0		0.013 (0.003)	1.013 (1.007–1.020)	<0.001			
	eGFR-CG.BW T0		0.010 (0.003)	1.010 (1.004–1.016)	<0.001			
	Post-index							
5	HbA1c change T0 to T + 1	4305	−0.022 (0.005)	0.978 (0.968–0.989)	<0.001	4.5%	0.656 (0.629–0.684)	<0.001
	eGFR-CG.BW change T0 to T + 1		0.031 (0.004)	1.031 (1.023–1.039)	<0.001			
	Diuretics initiated T0 to T + 1		0.459 (0.206)	1.583 (1.057–2.372)	0.026			
	Smoking stopped T0 to T + 1		0.691 (0.212)	1.996 (1.317–3.026)	0.001			
	HbA1c T + 1		0.023 (0.005)	1.023 (1.012–1.034)	<0.001			
	Pre-index including changes AND index							
6	Weight change T-2 to T0	2467	−0.064 (0.018)	0.938 (0.906–0.971)	<0.001	8.7%	0.679 (0.640–0.718)	<0.001
	Weight change T-1 to T0		−0.074 (0.021)	0.928 (0.891–0.968)	<0.001			
	Beta-receptor blocking sympathicolytics stopped T-1 to T0		0.827 (0.300)	2.287 (1.269–4.121)	0.006			
	HbA1c T0		0.028 (0.006)	1.028 (1.016–1.041)	<0.001			
	Serum creatinine T0		0.009 (0.003)	1.010 (1.003–1.016)	0.004			
	eGFR-CG.BW T0		0.006 (0.002)	1.006 (1.001–1.011)	0.010			
	Index AND Post-index including changes							
7	BSA$_{MOSTELLER}$ (m^2) T0	4233	−1.011 (0.394)	0.364 (0.168–0.787)	0.010	5.0%	0.661 (0.633–0.689)	<0.001
	HbA1c T0		0.022 (0.005)	1.022 (1.013–1.032)	<0.001			
	Serum creatinine T0		0.011 (0.004)	1.011 (1.004–1.018)	0.003			
	eGFR-CG.BW T0		0.010 (0.003)	1.010 (1.004–1.017)	<0.001			
	eGFR-CG.BW change T0 to T + 1		0.030 (0.004)	1.031 (1.023–1.039)	<0.001			
	Diuretics initiated T0 to T + 1		0.473 (0.210)	1.604 (1.062–2.423)	0.025			
	Smoking stopped T0 to T + 1		0.575 (0.220)	1.776 (1.155–2.733)	0.009			
	Pre-index AND Index AND Post-index							
8	Weight change T-2 to T0	2390	−0.069 (0.019)	0.934 (0.900–0.969)	<0.001	11.5%	0.709 (0.672–0.745)	<0.001
	Weight change T-1 to T0		−0.062 (0.022)	0.940 (0.900–0.982)	0.006			
	Beta-receptor blocking sympathicolytics stopped T-1 to T0		0.752 (0.326)	2.121 (1.118–4.020)	0.021			
	HbA1c T0		0.031 (0.006)	1.032 (1.019–1.045)	<0.001			
	eGFR-CG.BW change T0 to T + 1		0.035 (0.005)	1.036 (1.025–1.047)	<0.001			
9	Weight change T-2 to T0	2383	−0.069 (0.019)	0.933 (0.900–0.968)	<0.001	11.6%	0.712 (0.675–0.748)	<0.001
	Weight change T-1 to T0		−0.063 (0.022)	0.939 (0.899–0.981)	0.004			
	Beta-receptor blocking sympathicolytics stopped T-1 to T0		0.758 (0.327)	2.134 (1.125–4.047)	0.020			
	Average HbA1c (T0, T + 1)		0.038 (0.008)	1.039 (1.024–1.054)	<0.001			
	eGFR-CG.BW change T0 to T + 1		0.034 (0.006)	1.035 (1.024–1.046)	<0.001			

Model 9 equals model 8, except HbA1c T0 was replaced by Average HbA1c (T0, T + 1).

3.5. Risk stratification

Table 3 shows risk stratification concerning various pre-index categories. Of all patients with available weight data T-2 to T0, patients with a combination of weight loss and HbA1c increase in the two years pre-index gained the most weight post-index. These patients on average gained 1.6 kg of weight, and the risks for weight gain and excessive weight gain were 60.8% and 20.3%, respectively.

4. Discussion

4.1. Key results

By visualization, associations of pre-insulin weight and weight change with post-initiation weight change category appeared quadratic and inverse linear, respectively.

One out of 10 patients (10%) gained 5 kg weight or more after initiation of insulin therapy. The earliest determinants of post-index excessive weight gain were weight change (inversely) and HbA1c change in the two years prior to insulin therapy (model 1: AUROC = 0.668, p < 0.001). Patients that lost weight parallel with HbA1c rise in the two-years prior to index, showed the most weight gain. Of these patients, roughly one out of five (20.3%) gained 5 kg weight or more.

4.2. Associations and characterization

Fear of weight gain might particularly be present in the more obese patients, [1–2] even though many studies - but not all - found an inverse association of pre-initiation weight/ BMI with weight change after initiation. [3,8] These findings resulted in some reassurance concerning initiation of insulin therapy in obese patients, [8] which is in contrast to general clinical believe. The quadratic association by visualization of baseline weight/ BMI (Fig. 1**b1** and Fig. 2) suggests that both hypotheses may be valid. However, as the nine outcome categories were unequal spaced and sized, types of associations (e.g. quadratic or linear) were not statistically tested.

Only pre-initiation weight change seems to be linearly and inversely associated with post-initiation weight gain. The patient group with 5 kg weight gain or more can probably best be characterized by weight loss prior to initiation of insulin therapy (Fig. 1**a2 and 1b2**), combined with persisting or increasing high HbA1c despite of initiated insulin therapy (Fig. 1**c1, 1c2, 1d, and** Table 2).

4.3. Pre-index determinants of excessive weight gain

4.3.1. Catch up weight gain

As we are the first to specifically study pre-index variables in an observational study design our pre-index results cannot directly be compared to the literature. Our results seem – at least partly – in line with the idea of "catch-up weight gain" following the initiation of insulin

Table 3
Risk stratification concerning various pre-index categories.

		Post-index T0 to T + 1				Pre-index starting point	
		N	Weight change kg (mean)	Weight gain (%)	Excessive weight gain (%)	Mean BMI	Mean HbA1c
Time period T-2 to T0						T-2	T-2
Weight change	Weight loss	1089	**1.36**	**58.5**	**17.0**	30.7	56.8
	Stable weight	341	0.52	47.5	7.6	29.4	57.1
	Weight gain	1613	−0.22	43.7	6.9	29.4	56.8
	No weight change data	2043	0.14	45.1	9.2	na	57.9
HbA1c change	HbA1c decrease	1306	0.42	48.5	9.7	29.8	62.8
	Stable HbA1c	120	**0.62**	48.3	8.3	29.7	54.3
	HbA1c increase	1547	0.42	**50.2**	**11.4**	29.9	52.1
	No HbA1c change data	2113	0.15	45.3	9.3	30.6	59.0
Combinations weight and HbA1c change	Weight loss and HbA1c decrease	476	1.12	57.4	14.3	30.6	61.7
	Weight loss and stable HbA1c	50	1.30	56.0	10.0	30.1	53.2
	Weight loss and HbA1c increase	513	**1.62**	**60.8**	**20.3**	30.7	52.6
	Stable weight and HbA1c decrease	144	0.32	41.7	6.3	28.9	61.6
	Stable weight and stable HbA1c	15	1.00	53.3	20.0	29.9	56.6
	Stable weight and HbA1c increase	160	0.58	50.6	8.1	29.5	53.2
	Weight gain and HbA1c decrease	652	−0.09	43.7	6.9	29.4	63.7
	Weight gain and stable HbA1c	50	−0.10	40.0	2.0	29.2	54.8
	Weight gain and HbA1c increase	822	−0.35	43.4	6.6	29.4	51.4
	No weight and HbA1c combination data	2204	0.16	45.4	9.4	30.7	57.8
Time period T-1 to T0						T-1	T-1
Weight change	Weight loss	1538	**1.21**	**58.0**	**15.4**	30.8	59.0
	Stable weight	698	0.02	43.8	8.2	29.7	58.8
	Weight gain	2008	−0.15	42.9	7.4	29.7	59.6
	No weight change data	842	−0.00	43.3	8.0	na	60.1
HbA1c change	HbA1c decrease	2150	0.34	**49.0**	9.8	30.0	64.1
	Stable HbA1c	366	0.32	44.5	7.9	30.5	56.0
	HbA1c increase	1685	**0.41**	48.7	**11.0**	30.1	53.9
	No HbA1c change data	885	0.05	43.7	9.5	29.7	58.9
Combinations weight and HbA1c change	Weight loss and HbA1c decrease	782	1.06	58.1	14.7	31.0	62.8
	Weight loss and stable HbA1c	122	1.29	54.9	9.0	30.3	56.1
	Weight loss and HbA1c increase	572	**1.34**	**58.2**	**17.0**	30.7	54.3
	Stable weight and HbA1c decrease	302	0.18	48.0	6.3	29.7	63.3
	Stable weight and stable HbA1c	75	−0.40	38.7	8.0	31.3	56.3
	Stable weight and HbA1c increase	280	0.04	42.1	9.3	29.4	54.6
	Weight gain and HbA1c decrease	989	−0.22	41.7	6.9	29.4	65.2
	Weight gain and stable HbA1c	151	0.00	39.7	7.3	30.4	55.7
	Weight gain and HbA1c increase	777	−0.09	44.9	7.5	29.8	53.3
	No weight and HbA1c combination data	1036	0.08	44.2	9.5	29.7	59.8
Total		**5086**	**0.31**	**47.7**	**10.0**		

therapy, [22] also referred to as "reversed weight loss". [8,23] This means that prior weight loss due to increased urinary excretion of glucose, as a consequence of poor glucose control, is turned around by initiation of insulin therapy. Larger ea. (2001) reported that maximal weight of patients came back to pre-insulin levels, after insulin therapy. One might think that catch up weight gain is not problematic as patients only gain back the weight that they previously lost. However, we found that many patients, in particular those that gained much weight post-index, even surpassed their pre-index weight (Fig. 2, **and figures S3c and S3d**). In 81.7% of the patients with 5 kg weight gain or more, weight at T + 1 surpassed pre-index weight at T-2.

4.3.2. The role of (baseline) HbA1c

Mean HbA1c in the highest weight gain category improved only slightly between T0 and T + 1 and mean HbA1c at T + 1 was still higher than in all other categories. Jansen ea. (2011) reported that although glycaemic control following insulin therapy initiation improved considerably, only 12% of early weight gain may be attributable to improved glycemic control (to HbA1c change in the first 9 months). [6] Moreover, Bramlage ea. (2017) suggested that weight gain may only be related to improved glucose control in the case of extremely high HbA1c levels. [14]

Indeed, higher HbA1c at index (Table 3.) and higher mean HbA1c at index (Fig. 1c1) were associated with excessive weight gain. However, mean T0 value was comparable to the T-1 value of all categories, which might suggest that not only the height of HbA1c is important but, even more so, the duration of high HbA1c is important. Based on the average HbA1c of T0 and T + 1 concerning the nine categories, those patients with the most weight gain do seem to have had prolonged high levels of HbA1c (Fig. 1d).

4.3.3. Other potential explanations

On the other hand, the persisting high mean HbA1c at T + 1 in the highest weight gain category does not fit the idea of catch-up weight gain well, as high blood glucose levels, and as a consequence a high HbA1c, are logically related to increased urinary excretion of glucose and subsequent weight loss. Theoretically, the combination of post-initiation persisting high mean HbA1c at T + 1 and weight gain could have been related to e.g. the presence of (fear of) hypoglycaemia resulting in extra calorie intake after starting insulin, [24] increased sedentary behavior after starting insulin, [25] and/ or possibly to other causes. [24] No data on calorie intake were available for this study. Besides less (self-reported) adequate physical activity among persons with most weight gain no clear potential explanations of excessive weight gain could be identified, based on **table S3**. Noticeable was however, the highest percentage of patients with one or more changes to their insulin regimen (14.9% in the highest weight gain category). Whether this indicates the need to quickly intensify insulin treatment due to the inability to reach adequate metabolic control with a simple insulin scheme, or whether other factors, such as the presence of latent autoimmune diabetes in adults (LADA), play a role, cannot be studied with the present database due to lack of information about such aspects.

4.4. Index determinants of excessive weight gain

Cichosz et al (2017) [16] presented a model with baseline glomerular filtration rate (GFR), daily insulin dose per kg body weight at 3 months and weight gain in the first 3 months, which reached an AUROC of 0.80. In accordance with the findings of Cichosz et al (2017), [16] we found an independent association of index eGFR-CG with excessive weight gain (p < 0.001). Information of insulin dosage and early weight response were not available for the present study which limits comparability. Furthermore, in the present study we found that BSA (inversely, with p = 0.024), HbA1c (p < 0.001), and serum creatinine (p < 0.001), and were independent associates of excessive weight gain (Table 2., model 4).

Also similar to Cichosz et al, the discriminative value increased when variables determined post-initiation were included in models. The highest AUROC was found when pre-index, index, as well as post-index variables were included in a model (Table 2., model 9: 0.712, p < 0.001).

4.5. Prevention

Importantly, weight of the patient group that gained 5 kg or more remained high after the first year as well (Fig. 2, **and figure S3a**), which highlights the importance of preventive measures to control weight gain.

It has previously been suggested that when insulin therapy is initiated relatively early, thus preventing high HbA1c levels over a prolonged period, weight gain after initiation will be limited. [8,14] In the present study, mean HbA1c at initiation was in between 7.4% (58 mmol/mol) and 7.6% (59 mmol/mol), [3] which is rather low compared to the literature. Baseline HbA1c's in other studies were 8.5% to 8.7% (69 mmol/mol to 72 mmol/mol), [16] 8.6% (70 mmol/mol), [14] 9.3% (79 mmol/mol), [12] and 9.5% (80 mmol/mol) [5] (all mean mmol/ mol) and 9.3% (78 mmol/mol), [9] and 9.9% (85 mmol/mol) [6] (all median mmol/mol). Compared to the literature, we also found a lower percentage of excessive weight gain (10.0%), [8,12] a lower percentage weight gain (47.7%), [8,12] and a lower mean weight gain (0.31 kg), in the first year after the initiation of insulin therapy in routine clinical care. [3,5–6,8–9,12,14].

Clinicians should be alerted in the case of weight loss prior to insulin therapy initiation, particularly with prolonged high HbA1c at and after initiation. Means for preventing (excessive) weight gain after initiation of insulin therapy in T2DM may include early initiation of insulin therapy, [14] lifestyle factors, [24–25] and (co–)medication.

When viewing current literature, combining insulin treatment with interventions such as intensive lifestyle modifications or more recent glucose-lowering agents, including glucagon-like peptide 1 (GLP-1) analogues and Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors, [26–27] or starting these interventions before insulin, would both be possible to either remedy excessive weight gain or even induce weight loss. Recent studies with tirzepatide [28] (a dual glucose-dependent insulinotropic peptide (GIP) and GLP-1 receptor agonist) and semaglutide [29] (a GLP1 agonist) support such an approach with regards to GLP1 analogues. These studies focused on weight loss, in itself a major contributor to increase insulin sensitivity. Semaglutide is a very effective glucose lowering therapy in patients known with T2DM. [30] Investigations with tirzepatide in T2DM are ongoing. As for SGLT2 inhibitors, no specific information yet exists with regards to the longer term effects of the combined use of SGLT2 inhibitors and insulin.

4.6. Strengths and limitations

Strengths and limitations were previously presented in detail. [3]

Strengths include the use of real-life data in the general population. Data were largely collected prior to the introduction of more recent medication known to influence weight, [3] e.g. GLP-1 analogues and to a lesser extent SGLT2 inhibitors or a combination of GLP-1 analogues and SGLT2 inhibitors, with or without insulin use, thus our results cannot be biased by this. In the near future both study data and real life data can add to the knowledge of effects of various combinations of glucose lowering agents on weight changes.

Data were collected annually, which means that the exact time of insulin initiation could not be well identified. Weight was measured to the nearest kg, which limits accuracy. No information on calorie intake, insulin dosage and frequencies of injections were available for this study. We can only speculate that insulin dosage may have been higher in those patients that gained the most weight, as insulin therapy without other glucose lowering agent(s), higher HbA1c and limited physical activity (Table 1., **and table S3**) are logically related with higher insulin

dosages. Furthermore, it needs to be kept in mind that weight change can be attributed to other factors than changes in body fat only. [23] Packianathan et al (2005) found that both body fat and body water increased after the initiation of insulin therapy.

4.7. Generalizability

The results of this study are considered generalizable to the Dutch population, at least concerning the group of patients with a Caucasian background. As the purpose of this study was to explore determinants of excessive weight gain after the initiation of insulin therapy rather than developing a prediction model, no external validation was performed.

4.8. Conclusion

Roughly 10% of patients with T2DM gained 5 kg weight in the first years after initiation of insulin therapy, which is predisposed to remain on the body thereafter, highlighting the importance of preventing early post-initiation weight gain. Clinicians and patients should be aware of risk for excessive weight gain, in the case of weight loss prior to insulin therapy initiation, particularly with increasing and prolonged high HbA1c at (and after) initiation.

Means for preventing excessive weight gain after initiation of insulin therapy in T2DM might include early initiation of insulin therapy, other (co)-medication and lifestyle interventions.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2023.110719.

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