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ORIGINAL ARTICLE

WILEY

Association of weight loss and weight loss maintenance following diabetes diagnosis by screening and incidence of cardiovascular disease and all-cause mortality: An observational analysis of the ADDITION-Europe trial

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Abstract

Aims: Short-term weight loss may lead to remission of type 2 diabetes but the effect of maintained weight loss on cardiovascular disease (CVD) is unknown. We quantified the associations between changes in weight 5 years following a diagnosis of diabetes, and incident CVD events and mortality up to 10 years after diagnosis.

Materials and methods: Observational analysis of the ADDITION-Europe trial of 2730 adults with screen-detected type 2 diabetes from the UK, Denmark and the Netherlands. We defined weight change based on the maintenance at 5 years of weight loss achieved during the year after diabetes diagnosis, and as 5-year overall change in weight. Incident CVD events (n = 229) and all-cause mortality (n = 225) from 5 to 10 years follow-up were ascertained from medical records.

Results: Gaining >2% weight during the year after diabetes diagnosis was associated with higher hazard of all-cause mortality versus maintaining weight [hazard ratio (95% confidence interval): 3.18 (1.30-7.82)]. Losing ≥5% weight 1 year after diagnosis was also associated with mortality, whether or not weight loss was maintained at 5 years: 2.47 (0.99-6.21) and 2.72 (1.17-6.30), respectively. Losing ≥10% weight over 5 years was associated with mortality among those with body mass index <30 kg/m² [4.62 (1.87-11.42)]. Associations with CVD incidence were inconclusive.

Conclusions: Both weight loss and weight gain after screen-detected diabetes diagnosis were associated with higher mortality, but not CVD events, particularly among participants without obesity. The clinical implications of weight loss following a diagnosis of diabetes probably depend on its magnitude and timing, and may differ by body mass index status. Personalization of weight loss advice and support may be warranted.

KEYWORDS

cardiovascular disease, diabetes complications, type 2 diabetes, weight control

1 | INTRODUCTION

Weight management is recognized as critical in controlling cardio-metabolic risk factors; however, there is little evidence about the long-term effects of weight loss on diabetes complications. Prospective observational studies have suggested that short-term weight loss may lead to remission of diabetes and reduction in 10-year incidence of cardiovascular disease (CVD) events among people with type 2 diabetes,¹ particularly if weight loss occurs soon after diagnosis.² Weight loss occurring soon after diabetes diagnosis may be representative of intentional weight loss, motivated by the recent diagnosis. However, other research has shown null or inverse associations between weight loss and CVD among people with diabetes.^{3–5} Long-term weight loss or weight loss later in the course of diabetes, particularly among older adults, may not be protective against complications, as this may be indicative of unintentional weight loss due to illness or frailty, which is more common among people with diabetes.⁶

The effects of intentional weight loss achieved through behavioural intervention programmes on CVD remain unclear. The Action for Health in Diabetes (Look AHEAD) trial of an intensive lifestyle intervention among adults with overweight or obesity and type 2 diabetes was stopped after 9 years of follow-up, as the intervention did not demonstrate a reduction in CVD events.⁷ The lack of effect on long-term outcomes may be due to heterogeneity in intervention effects⁸ or the fact that behaviour-based weight management programmes, while effective for short-term weight loss,^{9,10} are typically followed by weight regain.^{11–13}

Despite weight regain, weight loss early in the course of the disease may still yield long-term reductions in cardio-metabolic risk.^{14,15} For example, in Look AHEAD, participants who had the largest 1-year weight loss but fully regained weight, had larger improvements in glycaemic control at 4 years than participants with no initial weight loss;¹⁶ this suggests a potential legacy effect of large initial weight loss on glucose metabolism. However, the extent to which weight loss regain and weight loss maintenance are associated with incidence of CVD events has not been assessed. In light of recent results from the Diabetes Remission Clinical Trial (DiRECT) showing that substantial weight loss leads to sustained remission of type 2 diabetes,¹⁷ there is need for evidence on the long-term effects of weight loss among people with diabetes.

We aimed to assess whether maintenance of weight loss following diabetes diagnosis by screening, and longer-term changes in weight, are associated with incidence of CVD events and all-cause mortality among participants in the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care (ADDITION-Europe).

2 | METHODS

This study includes adults with screen-detected type 2 diabetes from 343 general practices in Denmark, the Netherlands, Cambridge (UK) and Leicester (UK) enrolled in the ADDITION-Europe trial. Details on the enrolment and data collection procedures have been

reported previously¹⁸ and additional information is available on the study website (<http://www.addition.au.dk/>). Adults aged 40–69 years registered at participating general practices were invited to attend a stepwise diabetes screening programme from 2001 to 2006. Criteria for invitation to the screening programmes varied across the centres, as follows: a diabetes risk score based on medical records (Cambridge), self-administered questionnaires (Denmark and the Netherlands), or invitation to attend screening with no previous diabetes risk assessment (Leicester). During the screening programme, 3057 people were diagnosed with type 2 diabetes based on World Health Organization criteria¹⁹ and 3055 of them consented to participate in the ADDITION-Europe trial.¹⁸ Practices were cluster-randomized to either multifactorial treatment (n = 167 practices) or routine care (n = 176 practices).¹⁸ Briefly, physicians at the practices randomized to multifactorial treatment were invited to attend academic sessions where they were encouraged to consider prescribing medication for the control of glycaemia, blood pressure and blood lipids early on. The patients at these practices were also given educational materials on diabetes management. Physicians at practices in the routine care arm were encouraged to follow standard care procedures according to the national recommendations in each country.¹⁸ As most study participants were overweight or obese at the time of diabetes diagnosis, as part of standard care they would have routinely received weight management advice; however, no specific behavioural interventions were administered as part of the trial. While treatment targets across the study centres were generally similar, we addressed potential confounding by differences in standard care across the centres by adjusting for study centre in all analyses. The present study is an observational analysis pooling participants from the two trial arms.

Weight and waist circumference were measured at the time of diabetes screening, 1 year later (centres in the UK and Netherlands) and at 5 years (at all study centres) by trained staff. Body weight was measured in light clothing, according to standard operating procedures as described previously.¹⁸ Waist circumference was estimated as the average of two measurements taken with a tape measure halfway between the lowest point of the rib cage and the anterior superior iliac crests. During the baseline, 1-year and 5-year visits, participants completed questionnaires regarding demographics, lifestyle and medication use, among other health-related factors. The EuroQol three-level index score (EQ-5D), which assesses health in the domains of mobility, self-care, usual activities, pain/discomfort and anxiety/depression, was also administered at baseline. Incidence of CVD events and all-cause mortality was ascertained from national registers and medical records for the 10-year period following diabetes diagnosis.

2.1 | Exposure definition

Change in weight between baseline, 1 and 5 years was defined in two ways to assess separately the maintenance of 1-year weight loss and overall 5-year weight change.

2.1.1 | Weight change at 1 year

At study centres in the UK and the Netherlands, changes in weight from baseline to 1 year were determined by subtracting the weight at baseline from the weight at 1 year. Among those with $\geq 5\%$ weight loss at 1 year, maintenance of this weight loss at 5 years was defined by the amount of weight regained, where $\geq 50\%$ regain at 5 years distinguished weight maintenance from weight regain. Categories of weight changes at 1 year were defined as follows: $>2\%$ weight gain; $\leq 2\%$ gain or $<2\%$ loss (no change); 2% - 5% loss; $\geq 5\%$ loss with regain at 5 years; $\geq 5\%$ loss with maintenance at 5 years.

2.1.2 | Weight change at 5 years

Five-year weight change was determined by subtracting the weight measured at baseline from the weight measured at 5 years. Percentage weight change was then categorized as follows: $>5\%$ gain, $>2\%$ to $\leq 5\%$ gain; $\leq 2\%$ gain or $<2\%$ loss (maintained weight); $\geq 2\%$ to $<5\%$ loss; $\geq 5\%$ to $<10\%$ loss; $\geq 10\%$ loss.

We also considered changes in waist circumference as a measure of central adiposity. Five-year changes in waist circumference were determined by subtracting waist circumference at baseline from waist circumference at 5 years. Change in waist circumference was categorized based on quintile cut-points of the distribution.

2.2 | Outcome definition

The outcomes were a composite CVD endpoint and all-cause mortality occurring from years 5 to 10 of follow-up (mean duration of follow-up 5.0 years). The composite CVD endpoint includes non-fatal myocardial infarction, non-fatal stroke, fatal CVD events, non-traumatic amputation, peripheral vascular revascularization and invasive cardiovascular revascularization. Information on outcome events was ascertained from national registers, medical records, electrocardiographs, hospital discharge summaries and death certificates, among other sources, and each event was independently adjudicated.¹⁸

As weight change was assessed during the 5 years following diabetes diagnosis, the follow-up period for incident CVD events began after the 5-year study visit (Figure 1). For individuals with a CVD event occurring during the period when weight was measured (within the first 5 years after diabetes diagnosis), the first subsequent event occurring after the 5-year study visit was counted. Participants who did not attend a 5-year study visit ($n = 327$) were excluded from the analyses.

Among the 2730 people included in the study, there were 229 incident CVD events and 249 deaths during the 5-year follow-up period. Among the participants with incident CVD events, 44 reported having had a history of myocardial infarction or stroke before their diabetes diagnosis. We excluded 24 individuals who died within 1 year after the weight change was assessed (i.e. in the sixth year after the diabetes diagnosis) to reduce the chance that weight loss

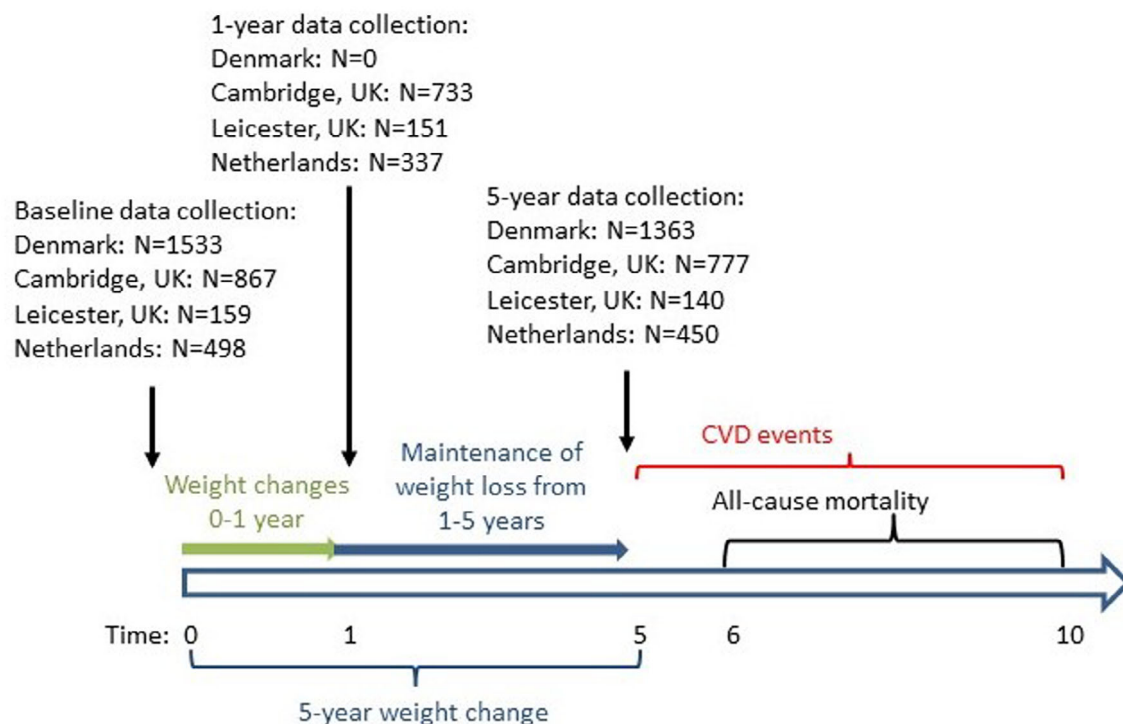


FIGURE 1 Timeline of assessment of weight at 0 (baseline), 1 and 5 years, and incident cardiovascular disease and all-cause mortality from 5 to 10 years. ADDITION-Europe 2002-2014. Among those with $\geq 5\%$ weight loss at 1 year, maintenance of this weight loss at 5 years was defined by the amount of weight regained, where $\geq 50\%$ regain at 5 years distinguished weight maintenance from weight regain. Five-year weight change was defined as the difference in weight at baseline (year 0) and 5 years

may be due to underlying disease. Therefore, in total, 229 CVD events and 225 deaths were included.

2.3 | Statistical analyses

We used Cox proportional hazards regression models to estimate associations between weight change categories and 5-year incidence of CVD and all-cause mortality. The time scale was time since the 5-year final study visit. In analyses in which mortality was the outcome of interest, time at risk began 6 years after diabetes diagnosis because deaths during the year following the 5-year study visit were not counted (Figure 1). Models were adjusted for trial arm, study centre and confounders identified a priori using a causal diagram²⁰: sex (male, female); age at diabetes diagnosis (continuous); weight at baseline (continuous); smoking status at baseline (current, former, never); CVD event within 5 years following diabetes diagnosis (yes, no); antihypertensive medication use before diabetes diagnosis (yes, no); lipid-lowering medication use before diabetes diagnosis (yes, no); changes in each of antihypertensive, lipid-lowering and glucose-lowering medication use between baseline and 5 years (initiated medication use, stopped medication use, no change); and age left full-time education (<16 years, ≥16 years). We did not adjust for glucose-lowering medication use before baseline (the time of diabetes diagnosis) because few participants reported this. We accounted for clustering of individuals by general practice using a cluster robust variance estimator. We tested the proportional hazards assumption by plotting the survival function versus time, and by modelling an interaction term between the natural log of time and each covariate. The tests indicated no departures from proportional hazards. All analyses were performed using StataCorp 2019 Stata Statistical Software (release version 15.1; StataCorp LLC, College Station, Texas).

Models for 1-year weight change included participants only from study centres that measured weight at baseline, 1 and 5 years (UK and the Netherlands). Models for 5-year weight changes included participants from all centres.

2.3.1 | Effect measure modification

We assessed effect measure modification by body mass index (BMI) category at the time of diabetes diagnosis. We modelled interaction terms between a binary variable for BMI status at baseline (≥30 vs. <30 kg/m²) and weight change. Few participants had BMI <25 kg/m² at baseline so we were not able to consider this group separately. There was no evidence of interaction with BMI for the associations of 1-year weight change and CVD or mortality, but there was interaction for the association of 5-year weight change and mortality (Wald test $P = .04$). Therefore, we present hazard ratios (HRs) for 5-year weight change stratified by BMI. We also assessed modification by age at diagnosis (≥65 vs. <65 years), by modelling an interaction term between a variable for age at baseline (≥65 vs. <65 years) and weight change. There was no evidence of interaction with age in any models (Wald test $P > .05$).

2.3.2 | Sensitivity analyses

We excluded separately those individuals with a self-reported history of myocardial infarction or stroke before diabetes diagnosis ($n = 243$). We also performed separate analyses adjusting for glycated haemoglobin (HbA1c) at baseline. As the Denmark centre was not included in the analyses of the 1-year weight change and CVD, we performed analyses of the 5-year weight change separately among the Danish participants ($n = 1363$) and then among participants from the remaining study centres ($n = 1367$).

3 | RESULTS

3.1 | Descriptive analyses

This study includes 2730 participants followed for a mean of 5.0 years (SD = 1.1 years) for incident CVD events, accumulating a total of 13 549 person-years of follow-up. The mean change in weight from baseline to 1 year was -3.3 kg (SD = 6.4 kg) (centres in the UK and Netherlands) and the mean change from baseline to 5 years was -2.1 kg (SD = 7.4 kg) (all centres) (Table 1 and Figure 2). Overall, 88.2% of participants who had their weight measured at baseline also had their weight measured at 5 years. People who had missing information on weight at 5 years were similar with respect to weight at baseline, age, sex and CVD risk factors compared with participants not missing weight at 5 years; however, they were probably current smokers at baseline (36.7% vs. 25.6%) (data not shown). There were no substantial differences in weight change or CVD risk factors across the study centres and the analyses were based on data from all centres combined.

Weight loss maintenance was determined among 1209 participants from study centres in the UK and Netherlands who had their

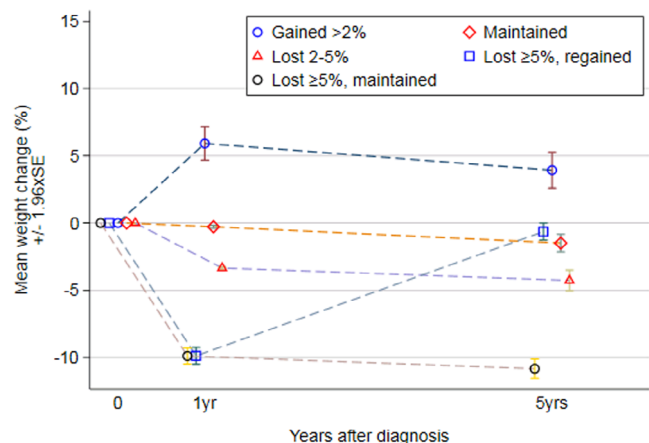


FIGURE 2 Patterns of percentage weight change over 5 years following diabetes diagnosis, by category of 1-year weight change. ADDITION-Europe 2002-2014. At 1-year follow-up, weight was measured only among participants at the study centres in the UK and Netherlands

TABLE 1 Descriptive characteristics at baseline (unless otherwise noted) by study centre: ADDITION-Europe 2002-2014

Characteristic	Total (N = 3057)		Denmark (N = 1533)		Cambridge (N = 867)		Leicester (N = 159)		Netherlands (N = 498)											
	Total	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD										
Age at diagnosis (years)	3057	60.2 ± 6.9	1533	59.9 ± 6.9	867	61.1 ± 7.1	159	57.7 ± 8.0	498	60.5 ± 5.2										
BMI (kg/m ²)	2957	31.6 ± 5.6	1450	30.8 ± 5.4	861	33.5 ± 5.7	156	30.8 ± 5.4	490	30.9 ± 5.2										
Weight (kg)	2959	90.6 ± 17.6	1450	89.2 ± 17.6	863	94.4 ± 17.8	156	85.8 ± 17.1	490	89.5 ± 16.1										
Weight at 1 year (kg)	1221	89.3 ± 17.5	—	—	733	91.2 ± 17.7	151	84.6 ± 19.0	337	87.4 ± 15.7										
Change weight 0-1 year	1209	-3.3 ± 6.4	—	—	730	-3.6 ± 5.5	148	-2.2 ± 5.9	331	-3.1 ± 8.2										
% Change in weight 0-1 year (%)	1209	-3.5 ± 6.7	—	—	730	-3.7 ± 5.7	148	-2.7 ± 6.0	331	-3.2 ± 8.7										
Weight at 5 years (kg)	2683	88.8 ± 18.0	1326	88.5 ± 18.0	773	90.5 ± 18.3	139	83.1 ± 18.3	445	88.4 ± 17.0										
Change weight 0-5 years	2611	-2.1 ± 7.4	1266	-1.1 ± 7.1	770	-4.0 ± 7.3	137	-3.0 ± 6.4	438	-1.4 ± 7.7										
% Change in weight 0-5 years (%)	2611	-2.2 ± 7.8	1266	-1.1 ± 7.7	770	-4.1 ± 7.5	137	-3.5 ± 7.1	438	-1.5 ± 8.2										
Alcohol (units/week)	2675	9 ± 12	1372	10 ± 11	853	8 ± 12	90	11 ± 9	360	9 ± 16										
Systolic BP (mmHg)	2963	149 ± 22	1451	148 ± 20	865	142 ± 20	158	146 ± 17	489	165 ± 23										
Diastolic BP (mmHg)	2964	86 ± 11	1451	88 ± 11	865	82 ± 10	158	89 ± 10	490	89 ± 11										
Total cholesterol (mmol/L)	2893	5.6 ± 1.1	1410	5.6 ± 1.1	848	5.4 ± 1.1	159	5.6 ± 1.2	476	5.6 ± 1.1										
LDL-cholesterol (mmol/L)	2749	3.4 ± 1.0	1324	3.4 ± 1.0	817	3.3 ± 1.0	142	3.5 ± 1.0	466	3.7 ± 1.0										
Observed time at risk for events (years)	2730	5.0 ± 1.1	1363	4.9 ± 1.0	777	5.1 ± 1.2	140	5.1 ± 0.7	450	4.9 ± 1.0										
	n	Median	Q1	Median	Q1	Median	Q1	Median	Q1	Median	Q1	Q3								
HbA1c (%)	2889	6.6	6.1	7.3	1477	6.4	6.0	7.0	846	6.8	6.4	7.6	407	6.8	6.3	7.6				
HbA1c (mmol/mol)	2889	48.6	43.2	56.3	1477	46.4	42.1	53.0	846	50.8	45.4	60.7	159	50.8	46.4	59.6	407	50.8	45.4	59.6
Triglycerides (mmol/L)	2874	1.7	1.2	2.4	1391	1.6	1.1	2.3	847	1.8	1.1	2.5	159	1.8	1.1	2.5	477	1.6	1.2	2.4
	Total n	%	n	%	Total n	%	n	%	Total n	%	n	%	Total n	%	n	%	Total n	%	n	%
Sex	3057	42	1286	1533	43	660	867	39	337	159	498	46	230							
Women	3057	42	1286	1533	43	660	867	39	337	159	498	46	230							
Smoking	2996	27	819	1513	34	518	865	18	158	159	16	25	459	26	118					
Current	2996	40	1200	1513	37	554	865	44	383	159	27	43	459	48	220					
Former	2996	33	977	1513	29	441	865	37	324	159	57	91	459	26	121					
Never	2996	45	1337	1466	43	634	865	58	499	159	42	67	459	30	137					
Medication use before diabetes diagnosis	2949	16	480	1466	13	185	865	24	204	159	21	34	459	12	57					
Antihypertensive	2949	42	899	1039	13	131	657	72	474	139	65	91	319	64	203					
Lipid-lowering	2154	42	899	1039	13	131	657	72	474	139	65	91	319	64	203					
Left full-time education ≤ 16 years old	2154	42	899	1039	13	131	657	72	474	139	65	91	319	64	203					

TABLE 1 (Continued)

	Total n	%	n	Total n	%	n	Total n	%	n	Total n	%	n
History of CVD before diabetes diagnosis	2857	9	243	1460	8	112	855	12	99	104	7	438
Incident CVD events ^a	2730	8	229	1363	8	114	777	10	75	140	6	450
Incident all-cause mortality ^b	2706	8	225	1353	9	119	766	9	69	140	2	447

Abbreviations: BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; SD, standard deviation; HbA1c, glycated haemoglobin; LDL, low-density lipoprotein.

^aIncident CVD events are defined as first event occurring during the follow-up period, beginning 5 years after diabetes diagnosis.

^bIncident all-cause mortality events exclude events occurring in the first year of the follow-up period; therefore, follow-up for all-cause mortality begins 6 years after diabetes diagnosis.

weight measured at baseline, 1 year and 5 years: among the 413 (34%) participants who lost $\geq 5\%$ weight during the year following the diabetes diagnosis, 165 (40%) regained $>50\%$ of the weight lost, and 248 (60%) maintained the weight loss. Baseline weight was similar among those who maintained, gained or lost weight. The participants who maintained weight loss at 5 years had a similar average weight at 1 and 5 years; however, participants who regained their weight had an average weight at 5 years similar to their baseline weight (Table 2; Figure S1).

The 5-year weight change was measured among 2611 participants at all study centres. Among them, 341 (13%) had $\geq 10\%$ weight loss, 512 (20%) had 5%-10% weight loss, 462 (18%) had 2%-5% weight loss, 594 (23%) maintained their weight, 324 (12%) gained 2%-5% weight, and 378 (14%) gained $>5\%$ weight. Baseline weight was similar across the groups. Among participants who lost $\geq 10\%$ weight at 5 years, average weight change during the year after diabetes diagnosis was -7.7% (centres in the UK and Netherlands), and average weight change at 5 years was -15.1% . Therefore, participants in this group had progressive weight loss across the study period (Table 2; Figure S2). In contrast, among those who lost $\geq 5\%$ weight during the year after diabetes diagnosis, there was no further weight loss from 1 to 5 years (Figure S1).

3.2 | Maintenance of weight loss following diabetes diagnosis and incidence of cardiovascular disease and mortality

Compared with those who maintained their weight, those who lost $\geq 5\%$ weight at 1 year, whether it was maintained or regained, had a similar lower hazard of CVD at 10 years, but the confidence intervals (CIs) around these associations were wide and overlapped the null [HR (95% CI) $\geq 5\%$ weight loss followed by regain: 0.62 (0.23, 1.62); $\geq 5\%$ weight loss without regain: 0.65 (0.29, 1.46)]. Weight loss during the year after diabetes diagnosis, as well as weight gain $>2\%$, was associated with higher hazard of all-cause mortality [HR (95% CI) for weight loss $\geq 5\%$ with regain: 2.72 (1.17, 6.30); HR (95% CI) for weight gain $>2\%$: 3.18 (1.30, 7.82)]. Weight loss $\geq 5\%$ that was maintained was suggestively associated with all-cause mortality [HR (95% CI) 2.47 (0.99, 6.21)] (Table 3). Among participants without a history of CVD, the associations between weight changes, CVD and mortality were similar (Table S1), where the association between weight loss $\geq 5\%$ and mortality was stronger among those who regained weight compared with those who maintained their weight loss.

3.3 | Weight change at 5 years and incidence of cardiovascular disease and mortality

A large weight loss ($\geq 10\%$) in the 5 years following diabetes diagnosis was associated with higher hazard of all-cause mortality [2.04 (1.17, 3.55)]. This association was modified by BMI at baseline. Stratifying by BMI at baseline, the association between large weight loss and mortality was strong among participants with BMI $<30 \text{ kg/m}^2$ [4.62 (1.87, 11.42)], while there was no association among participants with

TABLE 3 Hazard ratios (HRs) for the associations of 1- and 5-year weight change following diabetes diagnosis and incident cardiovascular disease (CVD) and mortality over 5 years of follow-up

	N cases/total	HR (95% CI) CVD ^a	N cases/total	HR (95% CI) all-cause mortality ^a
1-year weight change: study centres in the UK and Netherlands (N = 934)				
>2% weight gain	8/106	0.86 (0.42, 1.76)	10/105	3.18 (1.30, 7.82)
Maintained weight	28/272	1	10/271	1
2%-5% weight loss	21/232	0.98 (0.50, 1.90)	15/230	1.81 (0.84, 3.86)
Lost ≥5% and regained ^b	7/115	0.62 (0.23, 1.62)	11/115	2.72 (1.17, 6.30)
Lost ≥5% and maintained ^c	11/209	0.65 (0.29, 1.46)	17/208	2.47 (0.99, 6.21)
5-year weight change: all study centres (N = 1990)				
Full cohort				
Gained >5%	16/276	0.92 (0.50, 1.70)	21/274	1.27 (0.72, 2.22)
Gained 2%-5%	23/247	1.35 (0.81, 2.24)	21/246	1.31 (0.79, 2.20)
Maintained	33/471	1	30/469	1
>2% to <5% weight loss	34/361	1.44 (0.87, 2.39)	26/360	1.12 (0.66, 1.92)
≥5% to <10% weight loss	28/393	1.05 (0.62, 1.80)	22/392	0.85 (0.47, 1.54)
≥10% weight loss	20/242	1.50 (0.85, 2.66)	27/239	2.04 (1.17, 3.55)
BMI ≥30 kg/m ² at diagnosis (n = 1222)				
Gained >5%	7/140	0.87 (0.35, 2.15)	12/139	1.42 (0.68, 2.93)
Gained 2%-5%	19/139	2.34 (1.27, 4.32)	13/138	1.37 (0.70, 2.69)
Maintained	18/277	1	19/276	1
>2% to <5% weight loss	21/216	1.63 (0.85, 3.13)	18/215	1.22 (0.62, 2.40)
≥5% to <10% weight loss	19/273	1.10 (0.56, 2.15)	15/273	0.73 (0.36, 1.46)
≥10% weight loss	14/179	1.49 (0.70, 3.14)	15/176	1.27 (0.61, 2.63)
BMI <30 kg/m ² at diagnosis (n = 766)				
Gained >5%	9/127	0.87 (0.36, 2.08)	9/135	1.05 (0.39, 2.80)
Gained 2%-5%	4/108	0.46 (0.16, 1.38)	8/108	1.25 (0.46, 3.37)
Maintained	15/194	1	11/193	1
>2 to <5% weight loss	13/145	1.24 (0.57, 2.70)	8/145	0.95 (0.38, 2.34)
≥5 to <10% weight loss	9/122	1.05 (0.46, 2.42)	7/121	1.10 (0.41, 2.96)
≥10% weight loss	6/63	1.63 (0.59, 4.53)	12/63	4.62 (1.87, 11.42)

Note: Deaths occurred between 5 and 10 years in study. Sample sizes are where all covariates included in the model are non-missing.

Abbreviations: BMI, body mass index; 95% CI, 95% confidence interval.

^aModels are adjusted for age, gender, baseline weight, education, smoking, trial group, study centre, baseline antihypertensive or lipid-lowering medication use, changes in medication use between baseline and 5 years, and having a CVD event within 5 years after diabetes diagnosis.

^bRegained ≥50% of weight lost in the first year after diabetes diagnosis.

^cMaintenance of weight loss at 5 years classified as regaining <50% of initial loss.

BMI ≥30 kg/m² [1.27 (0.61, 2.63)]. A moderate weight loss (5%-10%) was not associated with CVD or all-cause mortality, nor was weight gain (Table 3).

Results were similar among participants from Denmark versus the other study centres (Table S2) and after adjusting for baseline HbA1c (Table S3). There were no differences in cause of death between categories of weight change (Table S4).

3.4 | Waist circumference change at 5 years

There were no associations between decreases in waist circumference and incidence of CVD or all-cause mortality (Table S5).

4 | DISCUSSION

In this observational study of long-term follow-up of participants in the ADDITION trial whose diabetes was diagnosed by screening, we have shown that hazard of all-cause mortality was three times higher in participants who gained >2% in weight between baseline and 1 year compared with those whose weight was stable. Hazard of mortality was similarly elevated among participants who lost more than 5% of weight initially but subsequently regained it. Large weight loss among those who did not have obesity at baseline was associated with a 4.6-fold higher mortality compared with the group who maintained weight, whereas there was no association among those who had obesity at baseline. This is the first research

to suggest that weight loss may differently affect people with type 2 diabetes dependent on BMI.

Few studies have considered the associations between weight loss and long-term incidence of CVD and mortality among people with diabetes. Observational analyses in the Look AHEAD trial showed that participants who achieved $\geq 10\%$ weight loss in 1 year had a 20% lower 10-year hazard of CVD compared with those who had stable weight or gained weight.¹ In the ADDITION-Cambridge study, more moderate 5% weight loss during the year after diabetes diagnosis was associated with similar reductions in CVD events.² No studies have considered how maintenance of this weight loss is associated with outcomes.

Our study did not find evidence of an association between maintenance of weight loss during the year after diabetes diagnosis and CVD; however, participants who lost weight had a higher hazard of all-cause mortality compared with those who maintained their weight. It is unclear whether maintenance of weight loss, or weight loss followed by regain, showed different associations with mortality as the HRs were very similar, although the CI on the estimate for maintained weight loss included the null. These findings are somewhat in contrast to results from the Look AHEAD trial that showed that people with type 2 diabetes who lost weight and then regained it had improvements in cardiovascular risk factors compared with participants who had never lost weight.¹⁶ However, a study in the Scottish Care Information Diabetes Collaboration showed that weight variability was associated with increased risk of mortality.²¹ In the DiRECT trial, large weight loss was associated with remission of diabetes after 2 years,¹⁷ but the study has not yet reported follow-up for CVD events or mortality. In contrast to other studies, our study included people with a history of CVD. After excluding individuals with a history of CVD before diabetes diagnosis, we saw marginally stronger protective associations between maintenance of weight loss and CVD, but the adverse associations with mortality remained. We were unable to perform analyses of cause-specific mortality due to small numbers of events.

Loss of $\geq 10\%$ weight over 5 years was associated with higher hazard of mortality. However, this association was not apparent when we considered changes in waist circumference as a measure of central adiposity (Table S5). Unintentional weight loss due to underlying disease may have contributed to the observed associations. Information on intention to lose weight is not available in the ADDITION study, but among Cambridge participants only ($N = 867$), we collected questionnaire data on health behaviours. We previously showed that reductions in alcohol use and total calorie intake were associated with the lower 10-year hazard of CVD,²² but participants who made these changes did not necessarily lose weight. We did not count deaths during the year after weight change was assessed to reduce the chance of confounding by unintentional weight loss. Other research has estimated the potential impacts of confounding due to unintentional weight loss, and concluded that this bias may be small. In the Nurses' Health Study, there was no association between weight loss and mortality, and results were unchanged in a sensitivity analysis applying lag times to account for weight loss due to undiagnosed chronic disease

or frailty.²³ However, other research has shown that weight loss among people with type 2 diabetes may increase risk of mortality if weight loss is unintentional,²⁴ and frailty may be higher in the diabetes population.⁶

Weight loss occurring during the year after diabetes diagnosis may be more representative of intentional weight loss, which may be motivated by the recent diabetes diagnosis and associated recommendations from practitioners. Participants in our study were diagnosed via screening and most were overweight or obese. Consequently, they may have been more motivated by clinician advice to lose weight compared with other cohorts of patients that had a longer duration of diabetes. Among participants from the Cambridge centre, where data are available on changes in diet and physical activity following diabetes diagnosis, over 90% of participants reported making changes to their lifestyle that would facilitate weight loss. However, we have no information concerning whether weight losses were intentional or not. We explored the causes of death by category of weight loss, but there was no difference in cause of death between the weight loss groups (Table S4). Other research on weight loss following bariatric surgery has shown that a large weight loss reduces the risk of CVD and mortality.^{25,26} However, metabolic changes following bariatric surgery may play a role in these associations, independent of weight loss.²⁷ It is possible that a large weight loss is beneficial for some people with diabetes but not for others. In post hoc analyses in the Look AHEAD trial, the intensive lifestyle intervention helped some patients to reduce their risk of CVD while patients with well-controlled diabetes but poor self-rated health were harmed.^{8,28} While we did not see any clear differences in baseline cardiovascular risk factors between the weight change groups, there were small differences in EQ-5D scores by category of weight change, where participants who lost $\geq 10\%$ weight over 5 years had a lower baseline median EQ-5D compared with the other groups (Table S6). Participants who lost the most weight may have had poorer underlying health and therefore weight loss may have been unintentional in this group.

In our study, we also observed heterogeneity, where large weight loss was strongly associated with mortality among adults who had BMI $< 30 \text{ kg/m}^2$ and there was no apparent harm, or benefit, among participants with BMI $\geq 30 \text{ kg/m}^2$. There were little baseline differences in cardiovascular risk factors between the groups with and without obesity, so it is unlikely that the disparities in outcomes are purely driven by underlying health differences (Table S7). Furthermore, baseline EQ-5D scores were higher among participants without obesity compared with participants with obesity, suggesting a higher health-related quality of life among participants without obesity. This information does not support that heterogeneity in the effects of weight loss across BMI groups would be due to poorer health among participants with lower baseline BMI. Furthermore, moderate 5%-10% weight loss over 5 years was not associated with CVD or mortality. Results suggest that the amount of weight loss, as well as the timing of weight loss in the course of the disease, may differentially affect risk of CVD and mortality. The observed heterogeneity by BMI shows that among individuals who are overweight rather than obese, weight loss may be associated with higher hazard of mortality. However, we

note that the estimated HRs had low precision, reflected by wide CIs, and therefore should be interpreted with caution.

There are several limitations that may affect the inferences from this study. As in any observational study of weight change, we cannot distinguish between intentional and unintentional weight loss. However, among people with diabetes, intentional weight loss may be most common during the period following the diabetes diagnosis.²⁴ Furthermore, we do not know in which component (bone, fat, muscle) the weight loss is occurring when we consider weight change. Loss of muscle mass and bone mass are components of frailty, and people with diabetes experience more frailty with ageing compared with the general population.⁶ Our finding of less marked effects in analyses focused on waist circumference compared with weight support that weight loss in the cohort may have occurred in the non-fat components. If the primary compartments of weight loss differed between the obese and non-obese participants, this may have contributed to the observed heterogeneity in associations by BMI. While we saw heterogeneity in associations by baseline BMI, differences in health across BMI groups may influence these results. BMI was part of the diabetes risk assessment used to identify individuals for screening in centres in the Netherlands, Denmark and Cambridge. Therefore, study participants with lower BMI would have had other indicative risk factors, such as family history of diabetes or older age to be selected. However, as noted above, we did not observe differences in blood pressure, lipid levels or HbA1c between the BMI groups and EQ-5D was somewhat higher in the non-obese groups. At baseline, many participants reported antihypertensive medication use, and smoking was somewhat common in the cohort (27% current and 33% former smokers). The strong effects of smoking and hypertension on CVD incidence may have reduced our ability to detect an effect of weight change on CVD; however, we adjusted for smoking status and medication use in all analyses. Weight at 1 year was not measured among participants in Denmark, which substantially reduced the number of participants included in our analyses of weight loss maintenance. For this reason, we discuss our results in light of not only the magnitude of associations but precision of the estimates, reflected in the CIs. Results may have been sensitive to our definition of weight regain as 50% regain of weight lost during the year after diabetes diagnosis. However, our results were unchanged when using an alternative 25% weight regain definition (data not shown), which has been used previously.²⁹ Although the study had a relatively small number of events resulting in wide CIs around the estimated HRs, results are hypothesis generating for future studies to address this question among larger cohorts with longer follow-up and among trials of weight loss interventions.

The ADDITION-Europe trial was a pragmatic population-based cardiovascular outcomes trial in which people with diabetes were diagnosed by screening.³⁰ There were high rates of attendance at screening and high rates of enrolment, and therefore the study sample is probably representative of the underlying target population of adults with newly diagnosed type 2 diabetes from the regions included in the study. However, the majority of the study population were white Europeans who were overweight or obese, and results

may not be generalizable to other groups. This is the first study to assess maintenance of weight loss following diabetes diagnosis and CVD events and mortality. As the study featured multiple measurements of weight following diabetes diagnosis, we were able to assess weight changes early in the course of the disease. Furthermore, as participants were diagnosed by screening, they were seen earlier in the diabetes progression trajectory than they would be if they had received a clinical diagnosis. The study also features near complete ascertainment of CVD outcomes and mortality due to linkage with national registers, and all outcomes were independently adjudicated.

In conclusion, losing weight during the year after diabetes diagnosis may be associated with a lower hazard of CVD events, but a higher hazard of all-cause mortality, regardless of whether weight loss was maintained. One-year weight gain was associated with all-cause mortality. A large weight loss over 5 years was also associated with mortality, except among participants with BMI ≥ 30 kg/m² at diagnosis. In contrast, moderate (5%-10%) 5-year weight loss was not associated with mortality. The results highlight the heterogeneity of the effects of weight loss on long-term outcomes among people with type 2 diabetes. While future studies in larger populations should address this question more definitively, this study raises questions as to whether the current one-size-fits-all approach to weight loss is appropriate for all people with type 2 diabetes, particularly among those who do not have obesity at the time of diagnosis. Although recent results from the DiRECT trial showed that a large weight loss can lead to diabetes remission,¹⁷ there is little evidence supporting long-term cardiovascular benefits of weight loss among people with diabetes. Our results highlight the need for larger studies of weight loss interventions with longer follow-up periods to investigate the varying impact of different magnitudes of weight loss occurring earlier as opposed to later in the course of the disease, and effects on CVD events and mortality. The findings from this study emphasize the relevance of heterogeneity in the health effects of weight loss among people with type 2 diabetes. Further research is warranted to improve understanding of this heterogeneity to inform more personalized strategies and recommendations.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

J.S. designed the study and the analysis plan, analysed the data, and wrote the manuscript. S.J.S. and S.J.G. also contributed to the design of the study and the analysis plan. S.J.S., K.K., R.C.V., G.E.H.M.R., D.R.W., A.S., D.R.W., N.J.W. and S.J.G. contributed to the interpretation of the results and edited the manuscript. S.J.G. is the guarantor of this work.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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