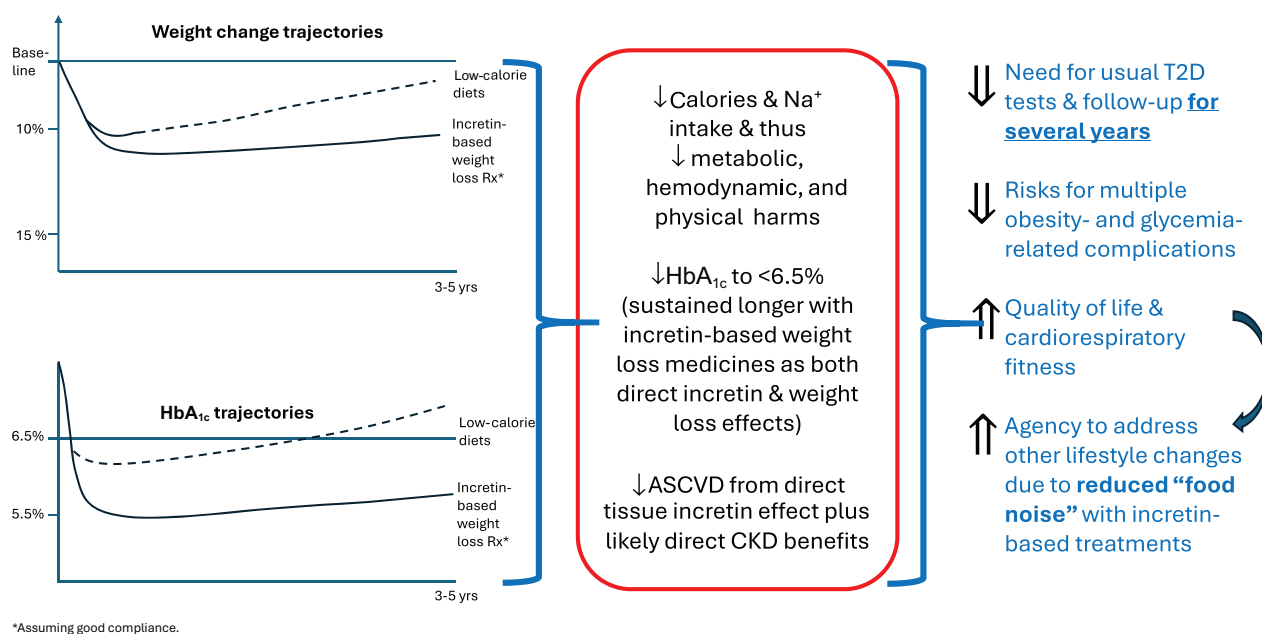


Why Early, Large-scale Weight Loss Is the Future of Type 2 Diabetes Care

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The Potential Impact of Large-Scale Weight Loss Early After Type 2 Diabetes Diagnosis by Lifestyle and Incretin-Based Weight Loss Modalities: The Future of Type 2 Diabetes Care?



ARTICLE HIGHLIGHTS

• **Why did we undertake this study?**

Despite growing recognition that weight loss is central to type 2 diabetes treatment, uncertainty remains regarding the optimal timing and modalities for achievement of durable benefits.

• **What specific question(s) did we want to answer?**

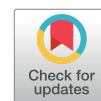
We examined the potential advantages of inducing substantial weight loss at the time of type 2 diabetes diagnosis, comparing potential outcomes across different approaches.

• **What did we find?**

Incretin-based therapies reduce food-related cognitive burden (“food noise”), facilitate more durable weight loss than dietary interventions alone, and confer direct metabolic benefits, thereby offering broad clinical advantages with the potential to substantially reduce long-term treatment needs.

• **What are the implications of our findings?**

If cost constraints were addressed, early implementation of incretin-based weight loss strategies could markedly improve patient outcomes and health system efficiency.



Why Early, Large-scale Weight Loss Is the Future of Type 2 Diabetes Care

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Type 2 diabetes has traditionally been viewed as a chronic, progressive condition. However, recent innovations, such as accessible low-calorie diets and newer weight loss medications, are challenging this paradigm. Evidence from clinical trials and mechanistic studies indicates that intentional weight loss, especially early in the disease course, can meaningfully alter its trajectory through reducing ectopic fat and glycemic levels. New medications that reduce “food noise” are particularly valuable in today’s obesogenic environments, helping patients regain some control over calorie intake and supporting sustainable lifestyle changes. These therapies can lead to weight loss of $\geq 10\%$ in type 2 diabetes and may enable newly diagnosed individuals to achieve and maintain normoglycemia for many years. Early, substantial weight loss combined with glycemic normalization has the potential to extend life expectancy, reduce or delay complications associated with obesity and hyperglycemia, improve quality of life, and lower long-term care needs. Beyond weight reduction, additional health benefits are offered by these medications, as they also slow atherosclerosis and preserve kidney function. Building on recent American Diabetes Association–European Association for the Study of Diabetes guideline recommendations, we propose that intentional weight loss at or near the time of diagnosis be considered a central strategy in type 2 diabetes management. To support this shift, proof-of-concept trials should be conducted for assessment of the long-term efficacy and durability of this approach. With success, increased competition and broader access to weight loss medications could lower costs and expand availability—even in low- and middle-income countries, where diabetes rates are rising rapidly—supporting a transformative change in the global standard of care.

Traditionally, type 2 diabetes has been viewed as a chronic, progressive disease—a belief that has endured for decades but is now being reconsidered with the availability of accessible tools that can aid in the achievement of considerable weight loss, sustainable for various periods of time. In this article, we examine emerging evidence from recent observational studies and clinical trials to argue that in future management of type 2 diabetes intentional weight loss should be prioritized at diagnosis to alter the disease’s natural course and place patients into ‘remission’ for a few years. By reducing “food noise,” newer incretin-based weight-loss medications may best sustain intentional weight loss and may offer patients more autonomy to address lifestyle factors beyond diet. Accordingly, this article suggests a potential to meaningfully extend weight-related management strategies outlined in the latest American Diabetes Association–European Association for the Study of Diabetes guidelines (1).

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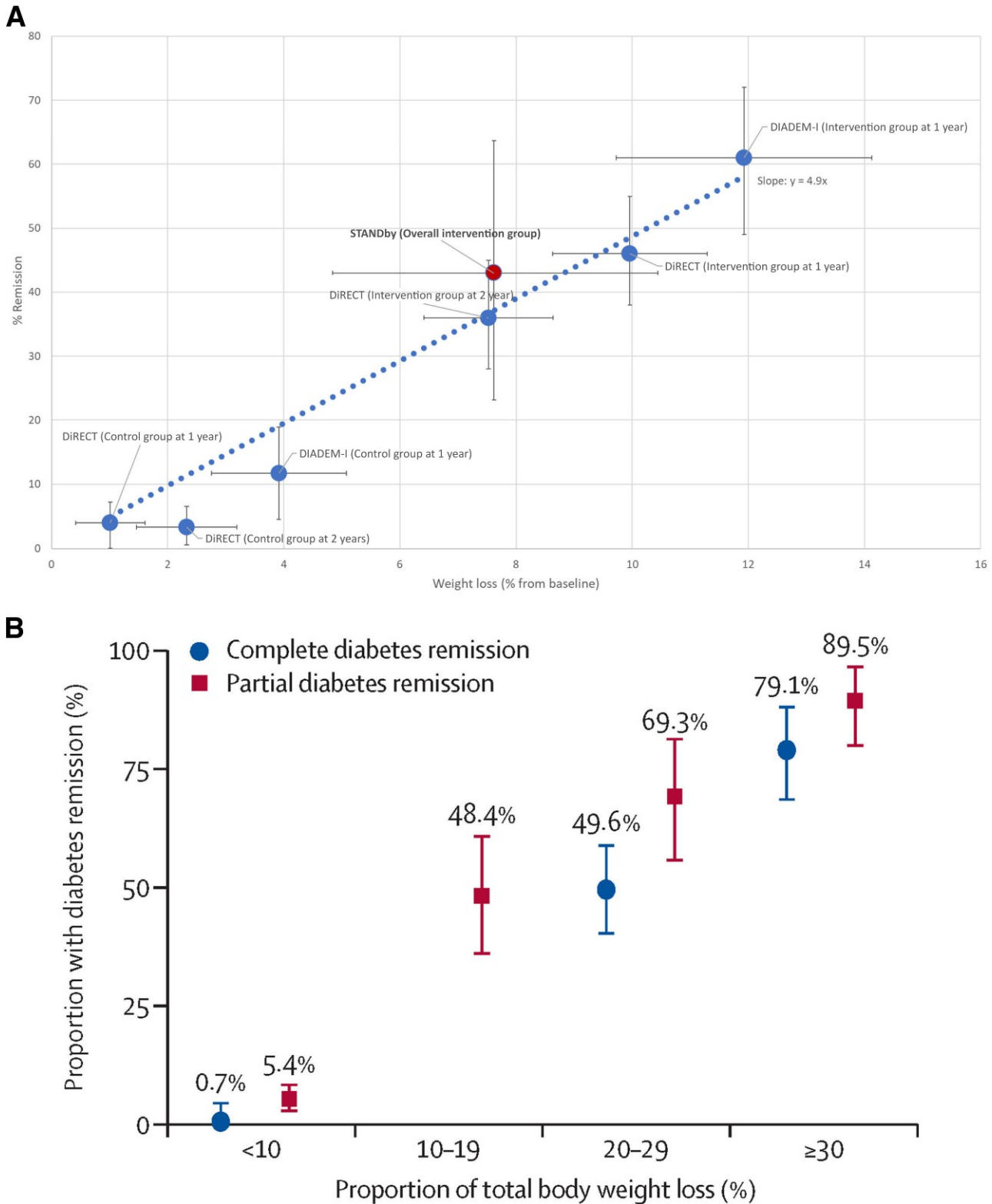


Figure 1—A: Relationship between relative weight loss and achieving remission in STANdbY, DiRECT 1- and 2-year follow-up studies, and DIADeM-I, all trials with duration of diabetes <6 years. Bars are 95% CI (4). B: Pooled mean proportion of participants with diabetes remission, with categorization by the proportion of total body weight loss across multiple trials. Error bars represent 95% CIs of the pooled estimates. For every 1 percentage point decrease in body weight, the probability of reaching complete remission increased by 2.17 percentage points (95% CI 1.94–2.40) and the probability of reaching partial remission increased by 2.74 percentage points (2.48–3.00) (8).

Table 1—Range of evidence to support weight as causal for type 2 diabetes and weight loss as a key factor in its treatment

Type of evidence	Top-line findings
Epidemiology	<ul style="list-style-type: none"> Relative risks for incident type 2 diabetes approach 20-fold in comparing individuals with BMI near 40 kg/m² vs. BMI of 23 kg/m² (9)
Observational	<ul style="list-style-type: none"> Clinically, weight and HbA_{1c} seem to track in individual patients Follow-up of lifestyle trial evidence shows near-identical weight-to-glycemia patterns (e.g., as in Look AHEAD) (10)
Surgical	<ul style="list-style-type: none"> Multiple reports of patients coming off insulin following bariatric surgery (17) suggesting that endogenous insulin secretory capacity can be regained in many.
Randomized trials	<ul style="list-style-type: none"> Multiple LCD studies show that weight loss can lead to diabetes remission, with the relationship appearing linear, regardless of whether interventions occur soon after diagnosis or later in the diabetes lifecourse (4,8) The estimated contribution of weight loss to HbA_{1c} reductions appears greater with incretin-based therapies when weight loss levels are more substantial (35)
Mechanistic	<ul style="list-style-type: none"> Liver fat appears causal for type 2 diabetes (12,13) Intentional weight loss reduces liver fat and pancreatic fat (14) Clamp evidence of β-cell function improvement on remission (14)

weight loss reduces many of the other risks that patients with type 2 diabetes commonly face. As recently reviewed (19), obesity is a causal factor in several major complications of type 2 diabetes—including cardiovascular disease (particularly heart failure with preserved ejection fraction and related arrhythmias), kidney dysfunction, and the development and progression of metabolic dysfunction-associated steatotic liver disease (MASLD), which is an umbrella term under which is included metabolic dysfunction-associated steatohepatitis (MASH). Growing evidence shows that intentional weight loss can meaningfully reduce the development or the severity of many of these outcomes (20).

Large-scale intentional weight loss rapidly lowers systolic blood pressure (21) and reduces the risk of numerous other obesity-related conditions such as obstructive sleep apnea, osteoarthritis, respiratory difficulties, and potentially some cancers, though such benefits will emerge over different timescales (20).

Of further relevance, the excess adiposity and ectopic fat that characterize type 2 diabetes must accumulate over several years before its onset, before and throughout the prediabetes phase and beyond. This explains why many obesity-related complications are already present by the time of type 2 diabetes diagnosis or their risks strongly increased. For example, sustained circulating elevations in triglycerides and ALT, reflecting

ectopic fat in circulation and in the liver, respectively, often precede diabetes onset (22). In addition, hypertension, also linked to excess salt intake, is a well-established predictor of type 2 diabetes (23).

This prolonged, over decades, exposure to excess weight and ectopic fat, along with the accompanying caloric and sodium excess, causes subclinical (and sometimes overt) damage to multiple organ systems—such as the kidneys, cardiovascular system, and joints—even before diabetes develops, and some harms may therefore not be fully reversible, even with weight loss or diabetes remission. The potential for organ damage prevention or reversal likely depends on several factors, including the patient's age, the duration and magnitude of excess weight, and the duration of diabetes (24). These factors also suggest that the ideal way to prevent type 2 diabetes is to change the obesogenic environment so that most people can maintain healthier weight throughout the life course without conscious effort. Sadly, most countries are seeing worsening rather than improving obesogenic environments, and willpower is not enough to change weights in the majority (25,26).

Nonetheless, regardless of where a patient falls on the dysglycemia spectrum, substantial intentional weight loss, primarily through caloric (and often sodium) reduction, can help diminish the “toxic metabolic fuel” and “excess volume” that drive continued organ damage

associated with obesity. These caloric reduction or weight loss effects are especially impactful in individuals with type 2 diabetes, as weight loss can also normalize the damaging dysglycemia to prevent further glucose-related harm.

Beyond reducing harm, improving fitness, relieving fatigue (27), and restoring vitality can also result from large-scale intentional weight loss, enhancing quality of life. Unlike other type 2 diabetes therapies, weight loss offers benefits beyond glycemic control. In reducing “food noise,” incretin-based therapies may better sustain weight loss and support lifestyle changes by giving patients more autonomy and mental bandwidth—a concept that warrants urgent study.

ABSOLUTE WEIGHT LOSS LEVELS NEEDED FOR REMISSION ARE ON AVERAGE HIGHER IN THE YOUNG, BUT LOWER IN NON-WHITES

Physical activity that builds muscle and reduces fat mass undoubtedly contributes to lowering diabetes risk. However, the global increase in obesity is driven primarily by a chronic overconsumption of calories, a trend largely shaped by increasingly obesogenic food environments. As such, the central focus in clinical practice must be to support patients in achieving and maintaining reductions in caloric intake. This remains the cornerstone of effective weight loss and the reversal of weight-related conditions—most notably type 2 diabetes.

Ample evidence suggests that far greater weight gain is required to trigger type 2 diabetes at younger ages (28). Younger individuals have greater muscle mass, more effective islet function, and a higher capacity for peripheral fat storage in comparison with older adults. As a result, a larger accumulation of ectopic fat is required to overwhelm this greater metabolic buffering capacity in the young and trigger type 2 diabetes. Hence, type 2 diabetes at younger ages is commonly accompanied by rapid, greater weight gain. Also, in comparison with age-matched peers without diabetes, younger people with type 2 diabetes exhibit significantly greater increases in blood pressure (perhaps via more salt intake, or associated lower activity levels), triglyceride levels, and glycemia than people who develop diabetes later in life, as demonstrated in analyses of primary care data from England (28) (Fig. 3).

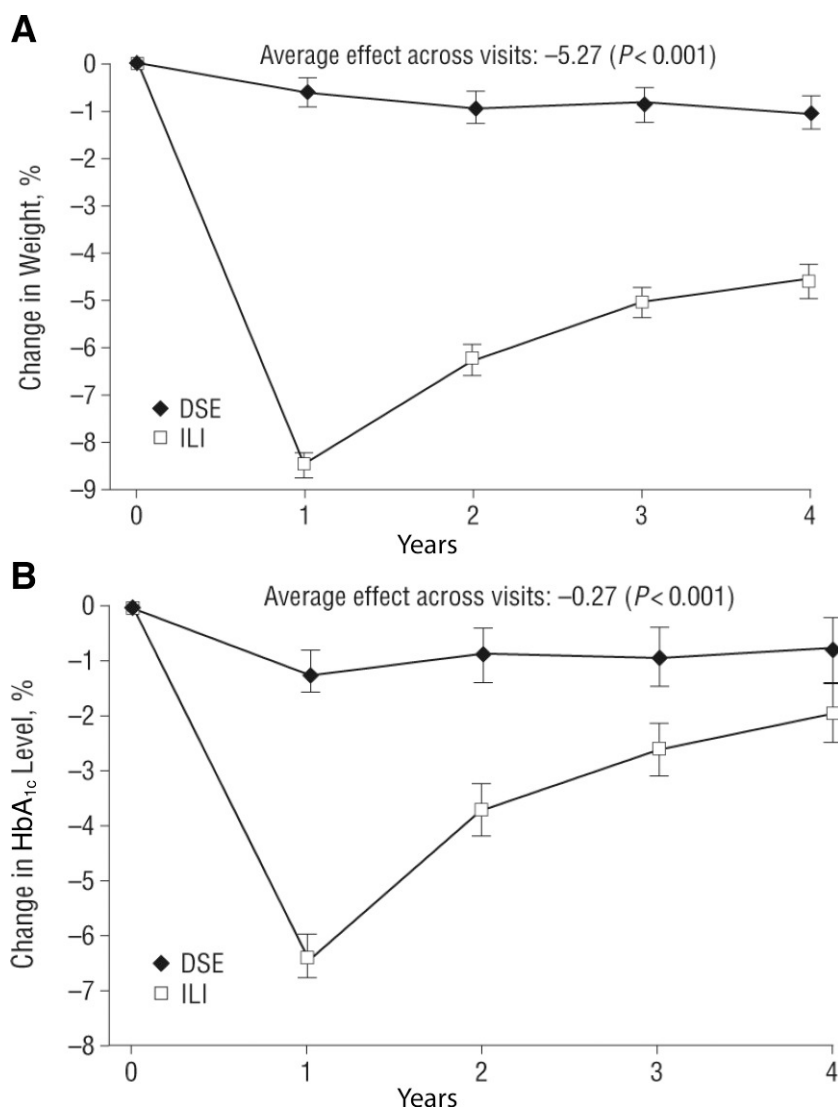


Figure 2—Trajectories of weight (A) and HbA_{1c} (B) changes following intensive lifestyle intervention in Look AHEAD (10).

In many non-White ethnicities, because of greater propensity for ectopic fat for a given BMI, less efficient β -cell functional capacity, or differences in muscle mass or function, less overall weight gain is needed across the life course to trigger type 2 diabetes than in Whites (28) (Fig. 4); i.e., the metabolic susceptibility to a given weight gain is greater in many non-Whites than in Whites. The consequence is that young-onset type 2 diabetes is more common in non-Whites, developing at lower average BMIs, with less weight gain.

In many non-White populations, a greater susceptibility to type 2 diabetes at lower BMIs means its development often occurs a decade earlier (28) so that many ethnicities face greater and earlier exposure to hyperglycemia, which also progresses more rapidly. Whether the

relative impact of excess weight versus hyperglycemia on future complications differs between ethnic groups remains an open question. Nevertheless, weight loss can reverse type 2 diabetes in many non-White ethnicities (e.g., South Asians, Afro-Caribbeans, Qataris), as shown in a few trials across the world (3,4,6). At the same time, intentional weight loss reverses clinically evident factors (e.g., blood pressure, dyslipidemia) and less visible pathological processes—including inflammatory, hemodynamic, and cellular stress pathways—linked to excess or ectopic fat in all ethnicities.

COMPARING AND CONTRASTING TOOLS FOR LARGE-SCALE WEIGHT LOSS AND EARLY REMISSION

Robust evidence from randomized controlled trials points to three primary,

evidence-based weight loss strategies to achieve normoglycemia: 1) cutting caloric intake via the use of low-calorie diets (LCD), often in the form of soups and shakes, for a few months; 2) use of incretin-based weight loss medicines (GRAPHICAL ABSTRACT); or 3) bariatric surgery. Obviously, these approaches can be combined. The pros and cons, including side effects, of each approach merit thoughtful discussion.

LCD

LCD, typically ~ 850 kcal/day for 3–5 months followed by food reintroduction and lifestyle support, produce substantial weight loss averaging $\sim 10\%$ at 1 year. Randomized trials, including DiRECT, show remission of type 2 diabetes in $\sim 40\%$ – 60% of participants at 1 year (2,3). Remission rates decline over time ($\sim 33\%$ at 2 years, $\sim 13\%$ at 5 years) (29,30), but many maintain improved glycemic control and lower weight.

In DiRECT, mean weight reduction sustained at year 5 was 6.1 kg for participants receiving continued low-intensity support during years 3–5 (30). They also spent significantly more time with $>5\%$ weight loss and HbA_{1c} < 48 mmol/mol in comparison with control participants. Over 5 years, 27% of intervention participant visits showed them to be in remission vs. 4% of the time for control participants.

These findings indicate that structured calorie restriction can achieve meaningful weight loss and remission, with years of reduced exposure to excess weight and dysglycemia—likely lowering complications. In support, serious adverse events were significantly less frequent in the DiRECT intervention group (4.8 vs. 10.2 per 100 patient-years; $P = 0.0080$) (30). More definitive evidence is needed, however, as adverse event numbers were small.

The Pros and Cons of LCD

LCD offer several advantages over other modalities, including relatively low cost and that it can be delivered virtually, as demonstrated in a recent weight loss trial (27). Also, conclusions from first-year data from the National Health Service Type 2 Diabetes Path to Remission (T2DR) program in England are that remission of type 2 diabetes is possible outside of research settings, through at-scale service delivery, though with somewhat lower remission rates than seen in trials (31). Longer-term follow-up of this

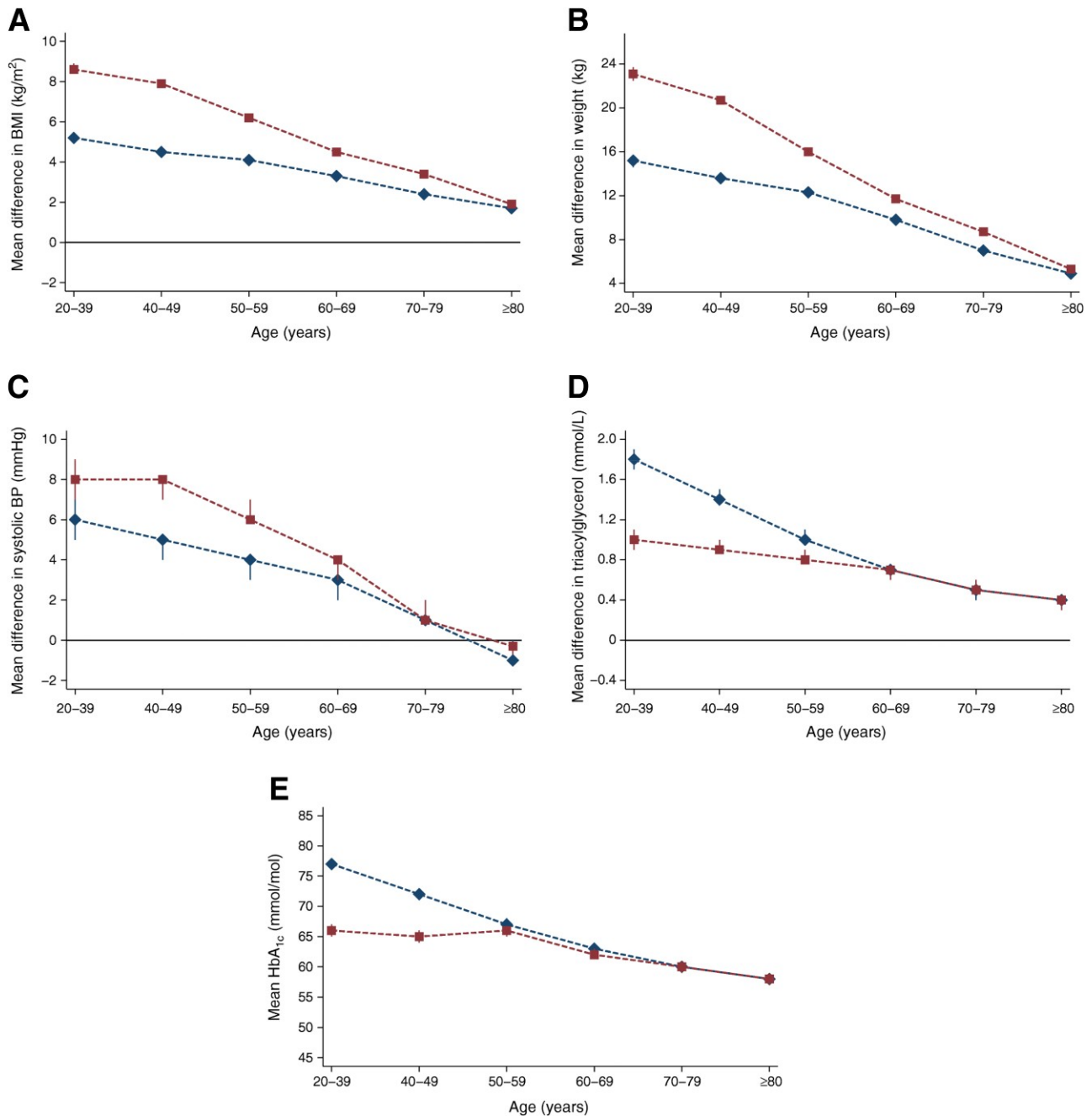


Figure 3—Adjusted age-specific mean differences (95% CI) in BMI (A), weight (B), systolic blood pressure (BP) (C), and triglyceride level (D) in men and women recently diagnosed with type 2 diabetes in comparison with men and women without diabetes. E: Age-specific mean HbA_{1c} levels in men and women recently diagnosed with type 2 diabetes (28). Diamonds, blue, men; squares, red, women.

latter program has not been reported. Common short-term side effects of LCD include fatigue, headaches, nausea, constipation, diarrhea, and dizziness, though most largely fade over time.

In low- and middle-income countries, meeting similar calorie targets can often be achieved using inexpensive, locally available foods in place of commercial meal replacements, making the approach globally relevant. However, improving the long-term sustainability of LCD remains a

critical challenge. While effective in the short term, maintaining weight loss in the context of highly obesogenic environments is difficult, as seen in the 5-year DIRECT data (30). Persistent exposure to external food cues—“food noise”—drives relapse, suggesting that interventions directly targeting appetite regulation may be more effective over the long term.

Additionally, not all patients are willing to undertake such interventions. In DIRECT, only approximately one-quarter

of eligible individuals within the first 6 years of diagnosis chose to participate in the LCD program (2), which was delivered in person and required considerable motivation and effort. Uptake may improve with now proven virtual delivery methods, but likely fewer than one-half of patients would engage with such an intensive strategy, given the high demands on willpower and self-regulation—factors often influenced by broader socioeconomic and psychological constraints.

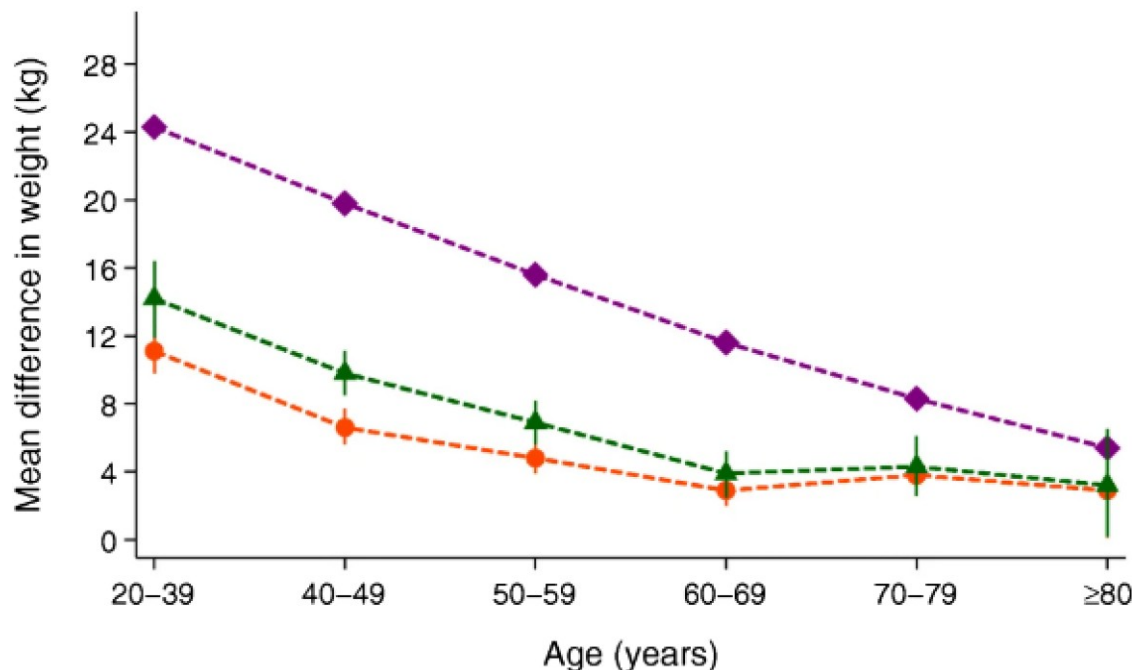


Figure 4—Adjusted age-specific mean differences (95% CI) in weight in White (diamonds, purple), South Asian (circles, orange), and Black (triangles, green) individuals recently diagnosed with type 2 diabetes in comparison with individuals without diabetes (28).

INCRETIN-BASED WEIGHT LOSS MEDICINES, WEIGHT LOSS, POTENTIAL FOR REMISSION, AND MULTIPLE OTHER WEIGHT-RELATED BENEFITS IN TYPE 2 DIABETES

Robust evidence now demonstrates that certain incretin-based medications can induce meaningful weight loss in people with and without type 2 diabetes. In individuals with type 2 diabetes averaging ~8 years' duration and HbA_{1c} ~8%, mean weight losses of 9.6% (6.2% placebo corrected) and 14.7% (11.5% placebo corrected) were reported with semaglutide 2.4 mg (32) and tirzepatide 15 mg (33), respectively. These are the only two agents currently licensed for both obesity and type 2 diabetes that consistently produce weight loss of approximately ≥10% in this population. Importantly, in A Study of Tirzepatide (LY3298176) in Participants With Type 2 Diabetes Who Have Obesity or Are Overweight (SURMOUNT-2), tirzepatide 15 mg for 72 weeks produced significantly greater placebo-corrected weight loss (−17.7%) in patients with type 2 diabetes when HbA_{1c} was <7% at baseline than in those with HbA_{1c} >9%, in whom average placebo-corrected weight loss was near half that at 9% (34). This important observation supports the potential for meaningfully more weight loss, which

patients desire, with initiation of incretin-based weight loss therapies soon after diagnosis.

Sustained weight loss with these agents has also now been demonstrated in individuals without diabetes at least over 3–4 years in trials such as A Study of Tirzepatide (LY3298176) in Participants With Obesity or Overweight (SURMOUNT-1) (35) and Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity (SELECT) (36). If similar durability of weight loss is seen in type 2 diabetes, this would be a major advantage over the steady weight regain seen after LCD, as reported in the 5-year DiRECT data (30). This latter observation does not diminish the value of lifestyle interventions but, rather, underscores the known difficulty of maintaining weight loss through nonpharmacological means—particularly in the context of obesogenic environments.

Incretin-based therapies suppress appetite and modulate food-related cues, aiding in the reversal of hyperglycemia and reduction of obesity-related complications affecting the liver, heart, kidneys, joints, and lungs. Semaglutide and tirzepatide further improve glycemic control through direct actions on pancreatic α - and β -cells. The contribution of weight loss to glycemic improvement increases with the degree of weight reduction,

from approximately 25% in SELECT (37) to 55% in SURMOUNT-1 (35). Additionally, these agents lower atherosclerotic cardiovascular disease risk by ~14% independently of weight loss (38) and enhance quality of life and self-esteem (2,39).

Given that cardiovascular risk rises many years before type 2 diabetes diagnosis, as demonstrated by Danish colleagues (40), early intervention with these agents is further suggested. It follows that in targeting appetite, weight, glycemia, and the broad risk of complications and comorbidities, initiating incretin-based weight loss therapies at or soon after diagnosis has the best potential to normalize glycemia, reverse weight-related harms, and halt metabolic decline for years, while at the same improving overall health and daily functioning. (See graphical abstract available in the online version of the article.)

Improved appetite control with these agents may also enable patients to be more receptive to other lifestyle changes, such as increased physical activity, that are often difficult amidst constant food-related cues. Widespread early use of these medications could thereby reduce clinical visits, screenings, and complications, substantially lowering health care costs. Indeed, sustained diabetes remission over several years—though debate remains as to the definition of remission

2. Intermittent versus continuous therapy: Can weight loss medications be given intermittently—e.g., during more challenging periods like winter months—or is continuous use preferable to maximize atherosclerotic benefit, which may largely derive from the drugs' direct tissue effects? For those with lower calculated cardiovascular risk, and already protected by other cardioprotective agents, it may be acceptable to consider intermittent treatment if weight losses are sustained to keep HbA_{1c} levels normal.
3. Combination therapy with SGLT2 inhibitors: Given that SGLT2 inhibitors also reduce risks of chronic kidney disease and heart failure through different mechanisms and may provide additive weight loss benefits in combination with incretin-based therapies (48), should these drugs be co-prescribed at the onset of type 2 diabetes? Or is it enough to give incretin therapies first for most and only add SGLT2i when specific risks—i.e., chronic kidney disease, heart failure—are identified or for further glycemic improvements?
4. Targeted patient selection: Rather than aiming for large-scale weight loss in all newly diagnosed patients regardless of age or BMI, it may be more cost-effective to initially focus intensive weight loss efforts on individuals below a certain age and above a BMI threshold, e.g., those age <55 years, with BMI >30 kg/m² for White populations, with lower BMI cutoffs for non-White populations (e.g., >27.5 kg/m²). This approach prioritizes those who stand to benefit most. Indeed, younger individuals with type 2 diabetes and obesity tend to lose more life years (49) and experience more obesity-related complications than those diagnosed later in life. In contrast, many leaner people presenting with type 2 diabetes, often when older, tend to do well on lower-cost medications, and their lower adiposity means less obesity-related complications. Similarly, different approaches may be needed in lean diabetes in younger people. Thus, a personalized approach remains important.
5. Targeted weight loss needs: It is impossible to give one target weight loss figure to achieve remission for all patients presenting with new diabetes because of the differences in weights with development of type 2 diabetes, varying by age, sex, and ethnicity, as in Fig. 3. However, on average, people with type 2 diabetes at diagnosis are ~3–4 BMI units heavier than their nondiabetes counterparts—so ~9–15 kg heavier, hence the ~10% on average. But some may do well with weight loss of, say, 5%, and others will need to lose more.
6. Adjusting clinical monitoring: For patients who achieve rapid remission, is it safe to reduce the frequency of routine annual tests and care processes, particularly if initial evaluations show no retinopathy and normal kidney function? In other words, if glycemia levels are normalized post-LCD or with relevant incretin therapy, the potential of any diabetes-related microvascular harm is markedly reduced, perhaps becoming negligible, so that all the usual routine diabetes care processes could be avoided. Patients achieving remission could also be classified accordingly, which may positively affect their insurance status—with only an annual HbA_{1c} test required for ongoing monitoring.
7. Optimizing lifestyle strategies with incretin-based weight loss therapies: Uncertainty remains as to the optimal lifestyle interventions to pair with incretin-based weight loss therapy, and the best timing for them. Some evidence suggests that initiating intensive lifestyle programs concurrently may not provide significant additional weight loss, and further research is needed to clarify the role of targeted physical activity in enhancing functional outcomes in this context.
8. The sustainability and long-term consequences of incretin-based weight loss therapies: Uncertainty remains as to whether patients can maintain long-term use of these medicines with good adherence. Trials suggest this may be feasible for up to 4 years for most patients prescribed such medicines (36), but more real-world evidence is needed, particularly once current supply, insurance, and cost barriers become less limiting. The long-term consequences of incretin-based weight loss therapy also remain unclear, and ongoing pharmacovigilance is warranted.
9. Measures of adiposity: BMI may not be the ideal marker for adiposity, the effect of excess fat mass to drive pathological consequences, in all individuals below a certain BMI level. Current product labeling for GLP-1-based therapy in the U.S. does not stipulate BMI as a marker for use of the products for weight loss or diabetes indications. Developing validated, low-cost, low-burden, reproducible, scalable measures of adiposity may be impactful in clinical decision-making for a subset of individuals with diabetes and, more generally, a topic of intense interest.

Of course, many of these issues remain unresolved, highlighting the urgent need for further research to optimize weight loss strategies and improve outcomes in type 2 diabetes. However, the direction of travel seems clear and the sooner such research is done the better for future diabetes care.

CONCLUSIONS

Accumulating evidence suggests that scalable tools now exist to restore and maintain normoglycemia over the long term through substantial weight loss, effectively removing type 2 diabetes and many of its associated care costs for years, a major potential benefit for many people and health care systems.

Appetite-suppressing, satiety-enhancing medications that reduce “food noise” can produce weight loss of ≥10%, helping many newly diagnosed patients sustain glycemic control and delay obesity-related complications. Beyond reducing ectopic fat, these therapies slow atherosclerosis, protect kidney function, and support better appetite control—potentially supporting more long-lasting lifestyle changes.

For establishing this treatment model, proof-of-concept trials are needed to confirm the long-term efficacy and feasibility of early, weight-focused interventions, perhaps in particular incretin-based therapies. With success, increased availability and competition among incretin-based therapies could reduce costs and support a transformative change in the global standard of care.

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