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# Intensive Lifestyle Intervention for Remission of Early Type 2 Diabetes in Primary Care in Australia: DiRECT-Aus

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## Intensive weight management using a low-energy total diet replacement achieves remission of type 2 diabetes in an Australian primary care setting

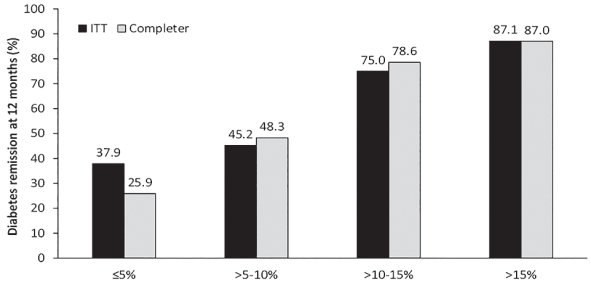
### Intervention

- Participants with recently diagnosed type 2 diabetes and BMI >27 kg/m2 recruited from 25 primary care practices across New South Wales.
- 13-week low-energy total diet replacement (Optifast; Nestlé Health Science), 8-week structured food reintroduction, and 31-week supported weight maintenance.
- Glucose-lowering medication was withdrawn.

### Results

- Diabetes remission occurred in 86 (56%) participants with mean adjusted weight loss of 8.1% at 12 months.
- Likelihood of diabetes remission was proportional to weight loss.

**Diabetes remission by percent weight loss achieved at 12 months***




| | ≤5% | >5-10% | >10-15% | >15% |
|---|---|---|---|---|
| ITT (n) | 58 | 42 | 24 | 31 |
| Completer (n) | 27 | 29 | 14 | 23 |

*ITT (intention-to-treat) population (n=155) commenced total diet replacement. Completer (n=93) population completed total diet replacement and attended >50% of remaining study visits.

### Conclusion

- This study confirms that remission of type 2 diabetes is achievable using a structured low-energy total diet replacement in an Australian primary care setting.

## ARTICLE HIGHLIGHTS

- In individuals with recently diagnosed type 2 diabetes, a low-energy total diet replacement resulted in diabetes remission in 56% of participants at 12 months, with a mean adjusted weight loss of 8.1%.
- The likelihood of diabetes remission was proportional to weight loss, with remission achieved by 87% of participants who reduced their weight by >15%.
- The total diet replacement was well tolerated, with a few serious adverse events that were largely related to hypotension. Blood pressure should be monitored during the total diet replacement intervention.

# Intensive Lifestyle Intervention for Remission of Early Type 2 Diabetes in Primary Care in Australia: DiRECT-Aus

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BRIEF REPORT


## OBJECTIVE

**We aimed to assess whether remission of type 2 diabetes (T2D) could be achieved with a low-energy total diet replacement (TDR) in an Australian primary care setting.**

## RESEARCH DESIGN AND METHODS

**Individuals aged 20–65 years with T2D duration up to 6 years, BMI >27.0 kg/m$^2$, and not treated with insulin were prescribed a 13-week low-energy TDR (Optifast; Nestlé Health Science) followed by 8-week structured food reintroduction and 31-week supported weight maintenance. The primary outcome was T2D remission at 12 months.**

## RESULTS

**A total of 155 participants comprised the intention-to-treat population. At 12 months, T2D remission was achieved in 86 (56%) participants, with a mean adjusted weight loss of 8.1% (95% CI 7.2–9.1). Two serious adverse events requiring hospitalization related to the study intervention were reported.**

## CONCLUSIONS

**At 12 months T2D remission was achieved for one in two Australian adults in a primary care setting.**


Type 2 diabetes (T2D) is estimated to affect 1 in 20 Australians, incurring annual health care costs of AUD1.9 billion (1). Two in three Australian adults have overweight or obesity, drivers of insulin resistance and β-cell decompensation, key pathophysiological processes underpinning T2D (2,3). Increasing evidence has emerged that T2D remission is possible with weight loss (4–7). Our aim was to determine if a 12-month intervention incorporating low-energy total diet replacement (TDR) could induce T2D remission in adults with recently diagnosed T2D in an Australian primary care setting.

## RESEARCH DESIGN AND METHODS

### Study Design and Participants

An open-label single-arm intervention trial was conducted across 25 primary care practices in New South Wales, Australia. The study was approved by the Sydney Local Health District Human Research Ethics Committee (2020-ETH00474) and registered with the Australian New Zealand Clinical Trials Registry.

Eligible participants were aged 20–65 years with T2D [per Australian criteria (8)] up to 6 years in duration, $HbA_{1c}$ at study entry ≥6.5% (48 mmol/mol), BMI >27.0 kg/m$^2$, and not treated with insulin. Individuals with T2D and $HbA_{1c}$ at study entry between 6.0% (42 mmol/mol) and 6.5% (48 mmol/mol) were eligible for inclusion if taking

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**See accompanying article, p. 47.**

glucose-lowering medication. Exclusion criteria were T1D, $HbA_{1c}$ ≥10% (86 mmol/mol), weight loss ≥5 kg within 6 months, stage 3b or greater chronic kidney disease, ischemic cardiovascular event within 6 months, severe cardiac failure, pregnancy or planning pregnancy, weight loss medication within 3 months, unstable psychiatric disorder, substance abuse, allergy to Optifast (Nestlé Health Science), or participation in another research trial.

### Procedures

Participants underwent a 13-week TDR (Optifast) with fortnightly dietitian visits. If BMI ≤40 kg/m$^2$, participants were prescribed three meal replacement products (MRPs) per day (<3,400 kJ [800 kcal] per day) or, if BMI >40 kg/m$^2$, four MRPs per day (<4,000 kJ [950 kcal] per day). Participants were encouraged to consume ≥2 L low-energy fluids and 2 cups low-starch vegetables with 1 teaspoon of oil daily. Psyllium husk fiber could be added if constipation developed. This was followed by 8 weeks of structured food reintroduction, with dietitian visits every 2–4 weeks, during which MRPs were tapered and healthy low-fat meals (<30% energy from fat) reintroduced. Thereafter, participants followed an individual prescription to prevent weight regain, with monthly dietitian visits. All glucose-lowering medications were discontinued on commencing the TDR and reintroduced if indicated by glycemia. If weight regain occurred or diabetes returned ($HbA_{1c}$ ≥6.5% [48 mmol/mol]), rescue plans were offered. For a 2- to 4-kg weight regain, one MRP was reintroduced daily for 4 weeks. For a weight regain >4 kg or reemergence of diabetes, TDR was reintroduced for 4 weeks, followed by 2–4 weeks of structured food reintroduction. MRPs were provided at no cost. All participants were advised to increase daily physical activity with a target of 15,000 steps per day.

### Outcomes

The primary outcome was T2D remission at 12 months. T2D remission was defined as $HbA_{1c}$ <6.5% (<48 mmol/mol) and cessation of glucose-lowering medications for at least 2 months ± 7 days. Secondary outcomes included weight change at 12 months and T2D remission and weight change at months 3, 6, and 9. If study visits were not attended, $HbA_{1c}$ and glucose-lowering medication use were obtained from general practitioner records (within a window of ±1 month of the scheduled follow-up date). After study commencement, a consensus definition for diabetes remission of $HbA_{1c}$ <6.5% (<48 mmol/mol) measured at least 3 months after cessation of glucose-lowering pharmacotherapy was published (4). A sensitivity analysis was performed using this definition.

### Statistical Analysis

We reported percentages of participants with T2D remission at months 3, 6, 9, and 12 and T2D remission at month 12 by weight loss status at month 12 (≤5, >5 to 10, >10–15, or >15%). We calculated the percent weight change at each time point. Linear mixed models were used to determine if significant percent weight loss occurred over 12 months, adjusted for the total number of visits attended throughout the study. Analyses were conducted on the intention-to-treat (ITT) population and repeated on the completer population using last observation carried forward. The ITT population was defined as participants who started the TDR with baseline $HbA_{1c}$ measurement and at least one $HbA_{1c}$ measurement and medication status known postintervention. Participants were included in the completer population if they completed the TDR, attended >50% of study visits beyond 13 weeks, and had $HbA_{1c}$ with medication status known at 12 months.

All statistical analyses were performed using Stats/SE 14.0 (StataCorp, College Station, TX) and SAS 9.4 (SAS Institute, Cary, NC).

### Data and Resource Availability

The data sets generated during and/or analyzed in the current study are available from the corresponding author upon reasonable request.

## RESULTS

Between 6 October 2020 and 19 July 2021, 183 (73%) of 252 screened patients were eligible to participate, with 10 withdrawing before commencing the TDR. Altogether, 155 participants comprised the ITT population (18 excluded because they did not have at least one $HbA_{1c}$ measurement postintervention), with 93 participants in the completer population (Fig. 1).

In the ITT population at baseline (Table 1), there were equal numbers of male and female participants, with a mean age of 52.5 years, weight of 106.9 kg, BMI of 37.7 kg/m$^2$, $HbA_{1c}$ of 7.1% (54 mmol/mol), and mean T2D duration of 2.8 years. Glucose-lowering medications were used by 88% of participants, antihypertensive agents by 54%, and lipid-lowering medications by 50%. Mean systolic and diastolic blood pressure values were 131.1 and 82.9 mmHg, respectively, and mean total cholesterol was 4.7 mmol/L. Baseline characteristics for the completer population were similar.

At 12 months, T2D remission occurred in 86 (56%) of 155 participants in the ITT population. The number of participants achieving T2D remission was highest after completion of the TDR phase, with remission in 102 (66%) of 155 participants. At 6 and 9 months, 99 (64%) and 92 (60%) of 155 participants achieved T2D remission, respectively. The percentage of participants achieving T2D remission was similar at all time points for the completer population (Fig. 2*A*). Using the consensus definition, 98 (63%), 97 (63%), 91 (59%), and 85 (55%) of 155 participants in the ITT population achieved T2D remission at 3, 6, 9, and 12 months, respectively.

Mean (95% CI) adjusted weight loss at the end of the TDR phase was 11.2% (10.3–12.1) for the ITT population and 12.3% (11.1–13.6) for the completer population. At 12 months, mean (95% CI) adjusted weight loss was 8.1% (7.2–9.1) for the ITT population and 9.3% (8.1–10.6) for the completer population (Fig. 2*B*). Rescue plans were offered to 44% of participants and adopted by 39%. The rescue plan was adopted a median of four times to those offered a rescue plan at least once.

The likelihood of T2D remission was proportional to weight loss. In the ITT population, it was achieved by 27 (87%) of 31 participants with >15%, 18 (75%) of 24 participants with 10–15%, 19 (45%) of 42 participants with 5–10%, and 22 (38%) of 58 participants with ≤5% weight loss at 12 months (Fig. 2*C*). The completer population had similar rates of T2D remission (Fig. 2*C*). Results were similar using the consensus definition for T2D remission.

Glucose-lowering medications were discontinued at baseline in all participants, apart from nine who continued glucose-lowering medication in violation of the protocol. Of these, two participants ceased glucose-lowering medications by week 5. Of the 110 participants with an $HbA_{1c}$ measurement at 12 months, 95 (86%) were not

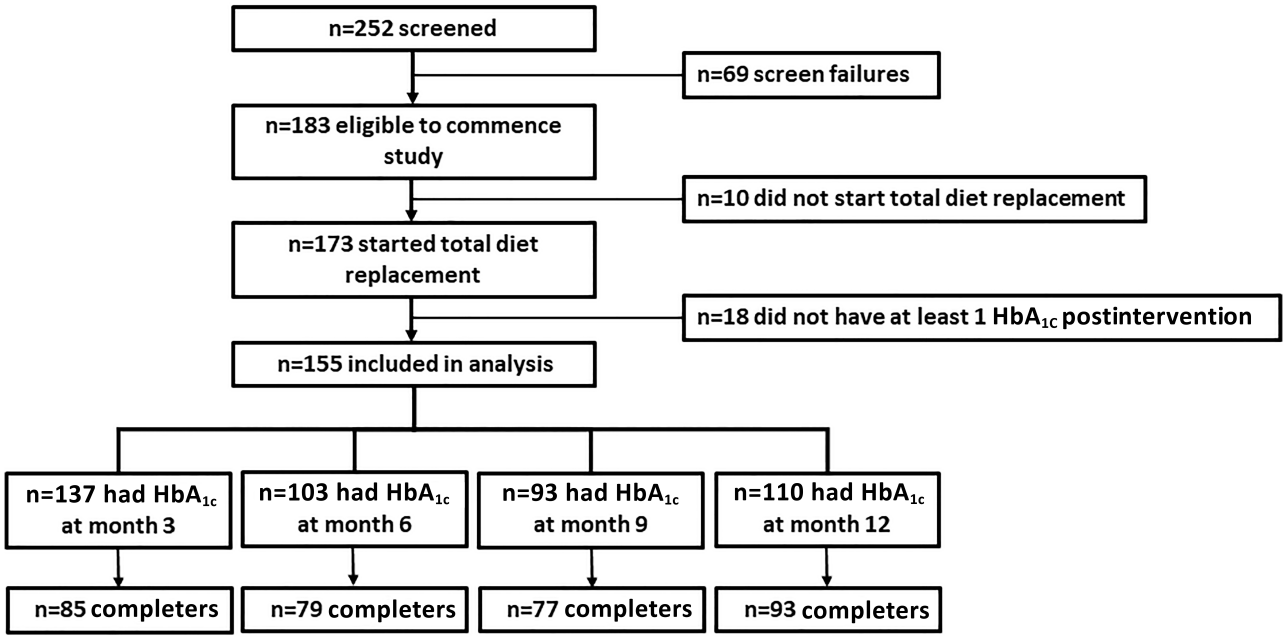


**Figure 1**—Participant flow diagram.

taking glucose-lowering medications within 60 days before completion of the study.

During the 12-month follow-up period, there were two serious adverse events related to the study intervention requiring hospitalization. Both were for hypotension, one case of which involved a participant with concomitant hypoglycemia, and required a reduction in antihypertensive medication and discontinuation of the TDR. No serious adverse events necessitated study discontinuation.

## CONCLUSIONS

This study confirms that an intensive lifestyle intervention delivered in an Australian primary care setting to individuals with recently diagnosed T2D resulted in remission of T2D for one in two participants. These findings confirm those of two previous studies in which an intensive weight management intervention in primary care resulted in remission of T2D of up to 6 years' duration (6,7). T2D remission was remarkably similar in this trial to that in both the DiRECT and DIADEM-I

**Table 1—Baseline characteristics**

| | ITT population (*n* = 155) | Completer population (*n* = 93) |
|---|---|---|
| Female sex, % | 50.3 | 50.5 |
| Age, years | 52.5 (8.5) | 53.7 (8.3) |
| Weight, kg | 106.9 (25.5) | 108.2 (27.5) |
| Waist circumference, cm | 118.9 (15.9) | 120.3 (17.4) |
| BMI, kg/m$^2$ | 37.7 (7.8) | 38.3 (8.1) |
| BMI ≥40 kg/m$^2$, % | 29.7 | 31.2 |
| $HbA_{1c}$, % | 7.1 (0.9) | 7.1 (1.0) |
| Duration of diabetes, years | 2.8 (2.1) | 2.8 (2.2) |
| Systolic blood pressure, mmHg | 131.1 (13.7) | 132.1 (13.2) |
| Diastolic blood pressure, mmHg | 82.9 (10.0) | 82.3 (9.6) |
| Total cholesterol, mmol/L | 4.7 (1.1) | 4.6 (1.0) |
| LDL cholesterol, mmol/L | 2.8 (1.4) | 2.9 (1.6) |
| HDL cholesterol, mmol/L | 1.2 (0.3) | 1.2 (0.3) |
| Triglycerides, mmol/L | 2.0 (1.5) | 2.1 (1.7) |
| Use of glucose-lowering medications, % | 87.7 | 87.1 |
| Use of antihypertensive agents, % | 54.2 | 52.7 |
| Use of lipid-lowering medications, % | 49.7 | 53.8 |

Data are given as mean (SD) unless otherwise specified.

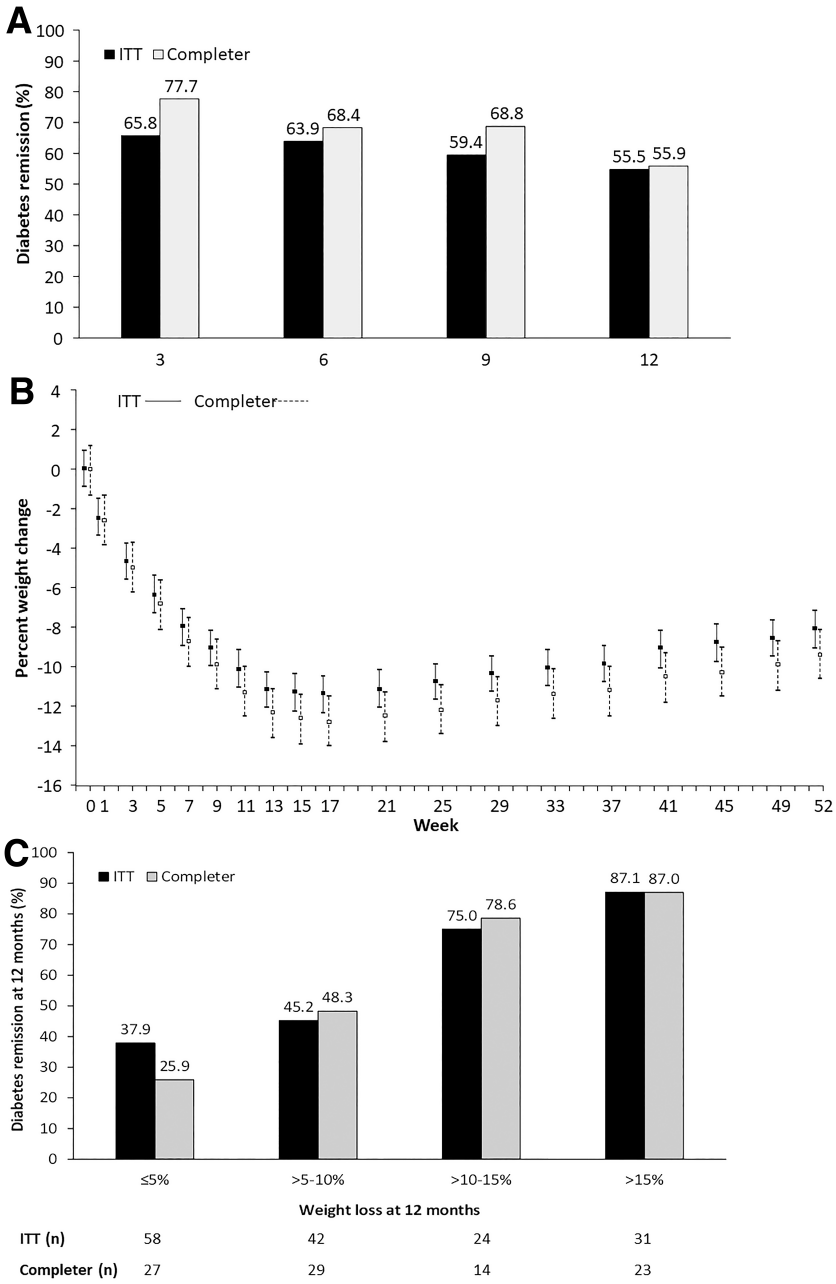


**Figure 2**—Primary outcomes and remission of diabetes in relation to weight loss at 12 months. *A*: Remission of diabetes ($HbA_{1c}$ <6.5% [48 mmol/mol]; no antidiabetic medication for 2 months) at 3, 6, 9, and 12 months for the ITT and completer populations. *B*: Mean percent weight change over 52 weeks using last observation carried forward and adjusted for number of visits attended. *C*: Diabetes remission by percent weight loss achieved at 12 months. In *A* and *C*, last observation carried forward for weight and diabetes status for ITT population and last observation carried forward for weight for completer population.

trials (56, 46, and 61% of participants, respectively), despite being conducted in different countries with participants from diverse racial backgrounds. Weight loss was also similar, with >15% weight loss achieved by 21, 24, and 21% of participants in DiRECT-Aus, DiRECT, and DIADEM-1, respectively (6,7). As in DiRECT, T2D remission was related to the amount of weight loss achieved at 12 months (6). Because T2D remission was very low in the control arms of the DiRECT and DIADEM-1 trials (4 and 12%, respectively), a control group was not deemed necessary. The number of participants withdrawing during the TDR was low and similar across trials, with 8 (5%), 15 (10%), and 8 (11%) participants withdrawing from DiRECT-Aus, DiRECT, and DIADEM-1, respectively, and serious adverse events were rare, suggesting the TDR was well tolerated and acceptable (6,7). These findings suggest that a low-energy TDR is a robust intervention for T2D remission across different ethnicities and cultures. These results indicate that T2D should be treated with an intensive lifestyle intervention, particularly within 6 years of diagnosis, to optimize the chance of attaining T2D remission with potential long-term health benefits.

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**Duality of Interest.** S.L.H. has received research grants from the Diabetes Australia Research Trust/Program and the National Health and Medical Research Council of Australia; has received honoraria for lectures from Eli Lilly, Novo Nordisk, Sanofi, AstraZeneca, Servier, and Amgen; has been or is on advisory boards for Novo Nordisk, Eli Lilly, Inova, and Pfizer; and has been an investigator for industry-sponsored clinical trials run by Novo Nordisk, Eli Lilly, Rhythm Pharmaceuticals, Millendo Therapeutics, Spruce Biosciences, and Amgen. T.P.M. has received research grants from the National Health and Medical Research Council of Australia; has been on advisory boards for Nestlé Health Sciences and Eli Lilly; and has been a principal investigator for industry-sponsored clinical trials for Novo Nordisk, Rhythm Pharmaceuticals, Millendo Therapeutics, Spruce Biosciences, Amgen, and Eli Lilly. K.E.G. is an employee of Diabetes Australia and has been a media spokesperson for Dietitians Australia. No other potential conflicts of interest relevant to this article were reported.

**Author Contributions.** S.L.H. wrote the first draft of the manuscript, and all authors edited, reviewed, and approved the final version of the manuscript. All authors were involved in the conception, design, and conduct of the study and the analysis and interpretation of the results. S.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Prior Presentation.** This work was presented in abstract form at the European Congress on Obesity, Dublin, Ireland, 17–20 May 2023.

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