

<b>Institution:</b> Newcastle University		
<b>Unit of Assessment:</b> UoA1		
<b>Title of case study:</b> Remission of type 2 diabetes using a low calorie diet		
<b>Period when the underpinning research was undertaken:</b> 2008-2019		
<b>Details of staff conducting the underpinning research from the submitting unit:</b>		
<b>Name(s):</b>	<b>Role(s) (e.g. job title):</b>	<b>Period(s) employed by submitting HEI:</b>
Prof Roy Taylor	Professor of Medicine and Metabolism	1/8/81 to present
Dr Kieren Hollingsworth	Reader in Magnetic Resonance Physics	20/2/06 to present
Prof John Mathers	Professor of Human Nutrition	1/10/83 to present
Prof Ashley Adamson	Professor of Public Health Nutrition	19/9/94 to present
Prof Falko Sniehotta	Professor of Behavioural Medicine & Health Psychology	1/6/10 to present
Prof James Shaw	Clinical Professor/Consultant	18/5/01 to present
Dr Ee Lim	Clinical Research Associate	1/1/07 to 23/7/12
Dr Benjamin S Aribisala	Research Associate	8/6/06 to 7/6/11
Miss Mei Jun Chen	Postgraduate Student	1/11/08 to 31/10/11
Dr Sarah Steven	Clinical Research Associate	4/8/10 to 31/12/13
Dr Ahmad Al-Mrabeh	Senior Research Associate	13/1/12 to present
Prof Ann Daly	Professor of Pharmacogenetics	8/7/85 to present
Dr Leah Avery	Senior Research Associate	1/7/10 to 7/10/18
Dr Carl Peters	Clinical Research Associate	16/12/13 to 29/11/15
Ms Alison Barnes	Lecturer in Human Nutrition and Dietetics	21/4/14 to present
Dr Angela Rodrigues	Research Associate	14/1/14 to 31/7/20
Dr Lucia Rehackova	Research Associate	29/4/19 to present
Dr Sviatlana Zhyzhneuskaya	Clinical Research Associate	7/9/15 to present
Dr Michael White	Research Associate	1/10/13 to 30/4/20
Dr Renae Stefanetti	Research Associate	1/12/15 to present
Prof Mike Trenell	Professor of Movement & Metabolism	21/8/06 to present
Dr Catherine McParlin	Research Associate	1/3/08 to 28/2/20
Prof Steven Robson	Professor of Foetal Medicine	1/8/09 to present
Prof Vera Araujo-Soares	Senior Lecturer in Health Psychology	1/12/10 to 28/2/15
		1/6/10 to 31/7/20
<b>Period when the claimed impact occurred:</b> 2013–present		
<b>Is this case study continued from a case study submitted in 2014?</b> No		
<b>1. Summary of the impact</b>		
<p>In the UK, type 2 diabetes (T2D) affects over 4.2 million people and the overall costs exceed £23 billion. Although it was previously thought to be inevitably progressive, Newcastle research showed that remission of T2D was possible when it is diagnosed within 10 years. A specific low calorie diet returns insulin secretion to normal in approximately half of participants. This paradigm-shifting research informed the 2016 WHO Global Report on Diabetes and the 2019 NHS Long Term Plan. In 2020, over 500 patients in England were enrolled in an NHS pilot scaling up Newcastle clinical trial techniques. Over the next 2 years, 5,000 patients will be enrolled into this pilot. A similar low calorie diet intervention has been implemented across Scotland. These pilots offer hope to millions of patients that their T2D can be reversed.</p>		
<b>2. Underpinning research</b>		
<u>Diabetes burden</u>		
By 2040, approximately 642 million people (10% of the world's population), are expected to be affected by diabetes. In the UK, about 4.7 million people live with diabetes, of which over 90%		

have type 2 (T2D). The annual amount directly spent on diabetes treatment (including type 1), complications and associated diseases (including cardiovascular disease, kidney disease, retinopathy, amputation, neuropathy and depression) is over £23 billion.

#### Identification of the cause of T2D

Before Newcastle University research, the causative mechanism of T2D was unclear, although caloric restriction (for example through gastric surgery) was known to improve glucose control in some patients. The Twin Cycle hypothesis, proposed following research from Newcastle (R1, R2) and elsewhere, postulated that modest but prolonged excess calorie intake promotes a fatty liver and hepatic insulin resistance. The compensatory increase in insulin further stimulates conversion of sugar to fat in the liver, setting up a vicious cycle. This also increases liver output of plasma triglyceride. As a consequence, fatty acids delivered to and taken up by islets in the pancreas cause metabolic stress on the beta cells, decreasing their ability to produce insulin after meals. The hypothesis implies that a sudden decrease in calorie intake should decrease liver insulin resistance, with normalisation of overnight plasma glucose, and allow return of normal insulin secretion.

#### Successful remission of T2D

To test the Twin Cycle hypothesis, a practical and reproducible method of achieving 15kg weight loss in research participants within 8 weeks during everyday life was developed from clinical insight and previous study knowledge. Substantial weight loss was achieved and recorded *in vivo*. Detailed metabolic testing, coupled with new MRI techniques, determined the change in the fat content of the liver and pancreas (R3). The Counterpoint (R3) and Counterbalance (R4) studies used this 8 week, 600-800 calorie per day liquid diet to achieve successful T2D remission in patients and establish that:

- Liver fat, fasting liver glucose production and fasting blood glucose levels normalise within a month.
- Intra-pancreatic fat and first-phase insulin secretion (previously thought to be irreversibly lost in T2D) gradually returned to normal over 8 weeks, permitting post-meal control of blood glucose to be normalised and maintained over 8 months.

Importantly, these studies established that T2D remission is achievable in 50% of patients diagnosed within 10 years, and that starting the diet closer to initial diagnosis improved remission success (90% response within 4 years of diagnosis, R4).

#### DiRECT trial of T2D remission

Following this success, Newcastle and colleagues from the University of Glasgow conducted the Diabetes Remission Clinical Trial (DiRECT), a cluster-randomised controlled trial designed to test diet applicability in a routine primary care setting (R5). A total of 306 patients with a time-after-onset of less than six years were recruited from 49 GP surgeries in Scotland and North East England. Patients were given Counterweight-Plus, a specific low calorie diet (LCD) involving a 12 week period of 800 calories a day, followed by food reintroduction and continued weight maintenance for a total of 12 months. After 12 months, 46% of LCD participants achieved remission (defined as glycated haemoglobin of less than 6.5% after 2 months off antidiabetic medication) contrasted with only 4% of the control group. In the intervention cohort, remission correlated with weight loss (R5), and a 2-year follow up of DiRECT patients showed that remission persisted in patients who maintained weight loss (R6). Studies on the Newcastle cohort of DiRECT confirmed the long term improvement in liver and pancreas function during remission of diabetes, and that weight regain (in a minority) caused accumulation of fat in liver and pancreas with redevelopment of diabetes, confirming the final aspect of the Twin Cycle Hypothesis.

Newcastle research also disproved the widely-held belief that T2D is caused by death of beta cells, finding instead that these simply become “dormant”. R7 reported that the functional beta cell mass, decreased by 50% in diabetes, gradually returned to normal by 12 months then remained steady to 24 months. Secondly, R8 showed the shrunken pancreas typical of T2D gradually returned to normal. These findings explain why T2D can be reversed, and also why this is more likely in patients with shorter-term T2D. The impact of this paradigm-shifting research is described below.

### 3. References to the research

SciVal field-weighted citation impact (FWCI) as of December 2020. Newcastle researchers in **bold**.

- R1. **Taylor R.** (2008) Pathogenesis of type 2 diabetes: Tracing the reverse route from cure to cause. *Diabetologia*. 51(10):1781-1789. DOI: 10.1007/s00125-008-1116-7. FWCI: 2.97.
- R2. **Taylor R.** (2013) Type 2 Diabetes Etiology and reversibility. *Diabetes Care*. 36(4):1047-1055. DOI: 10.2337/dc12-1805. FWCI: 2.88.
- R3. **Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R.** (2011) Reversal of type 2 diabetes: Normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia*. 54(10):2506-2514. DOI: 10.1007/s00125-011-2204-7. FWCI: 16.25.
- R4. **Steven S, Hollingsworth KG, Al-Mrabeh A, Avery L, ... Taylor R.** (2016) Very low-calorie diet and 6 months of weight stability in type 2 diabetes: Pathophysiologic changes in responders and nonresponders. *Diabetes Care*. 39(5):808-815. DOI: 10.2337/dc15-1942. FWCI: 11.72.
- R5. **Lean MEJ, ... Barnes AC, ... Peters C, Zhyzhneuskaya S, Al-Mrabeh A, Hollingsworth KG, Rodrigues AM, Rehackova L, Adamson AJ, Sniehotta FF, Mathers JM, ... Stefanetti R, Trenell M, ... Taylor R.** (2017) Primary care weight-management for type 2 diabetes: the cluster-randomised Diabetes Remission Clinical Trial (DiRECT). *Lancet*. 391(10120):541-551. DOI: 10.1016/S0140-6736(17)33102-1. FWCI: 96.71.
- R6. **Lean MEJ, ... Barnes AC, ... Peters C, Zhyzhneuskaya S, Al-Mrabeh A, Hollingsworth KG, Rodrigues AM, Rehackova L, Adamson AJ, Sniehotta FF, Mathers JC, ... Taylor R.** (2019) Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *The Lancet Diabetes and Endocrinology* 7(5):344-355. DOI: 10.1016/S2213-8587(19)30068-3. FWCI: 31.24.
- R7. **Taylor R, Al-Mrabeh A, Zhyzhneuskaya S, Peters C, Barnes A, Aribisala B, Hollingsworth KG, Mathers JC, Sattar N, Lean MEJ.** (2018) Remission of human type 2 diabetes requires decrease in liver and pancreas fat content but is dependent upon capacity for beta cell recovery. *Cell Metabolism*. 28(4):547-556.e3. DOI: 10.1016/j.cmet.2018.07.003. FWCI: 8.85.
- R8. **Al-Mrabeh A, Hollingsworth KG, Shaw JAM, McConnachie A, Sattar N, Lean MEJ, Taylor R.** (2020) 2-year remission of type 2 diabetes and pancreas morphology: a post-hoc analysis of the DiRECT open-label cluster-randomised trial. *The Lancet Diabetes and Endocrinology* 8(12):939-948. DOI: [https://doi.org/10.1016/S2213-8587\(20\)30303-X](https://doi.org/10.1016/S2213-8587(20)30303-X). FWCI: 0.66.

### 4. Details of the impact

#### Impacts on policy and health services

Newcastle research informed several high-level policies, which underpinned subsequent impacts on health services.

First, R2 informed the 2016 WHO Global Report on Diabetes (EV1), the first of its kind to discuss the global challenges facing diabetes treatment and current recommendations. Newcastle research supports the section on T2D remission through weight loss, stating “*It has been suspected for some time that energy restriction through a very low-calorie diet can lead to the reduction of symptoms or to the reversal of hyperglycaemia typical of type 2 diabetes – the reversal may be maintained so long as weight is not regained [R2].*”

The Scottish Government’s 2018 framework (EV2) provides guidance to partners delivering a £42 million 5-year strategy to combat T2D. Newcastle research on the potential for T2D remission (R3, R4) informs the background to “Level 3 – Targeted intervention”, and suggests DiRECT total diet replacement techniques (R5) as a successful strategy for T2D remission. The Scottish Government began implementation of the framework in 2018 in 3 early-adopter NHS Scotland Boards including the East region, Tayside and Ayrshire and Arran (EV3). By April 2019, all 14 Boards were implementing the framework (EV4). Counterweight-Plus, the same diet replacement

formula provided during the DiRECT study, is the only programme currently recommended by NHS Scotland for eligible patients and, as of the end of 2020, is used by 13 Boards (EV3, EV4).

The 2019 NHS Long-Term Plan cites R5 in section 2.17: *“some people with type 2 diabetes can achieve remission through adoption of a very low calorie diet. This allowed nearly half of patients to stop taking anti-diabetic drugs and still achieve non-diabetic range glucose levels [R5]”*. Furthermore, the document commits to an NHS programme which uses diet as an intervention for T2D. *“We will therefore test an NHS programme supporting very low calorie diets for obese people with type 2 diabetes”* (EV5).

NHS England began this low calorie diet (LCD) pilot programme in September 2020, delayed from March 2020 due to the COVID-19 pandemic. The pilot is a joint initiative between NHS England, Public Health England and Diabetes UK to test LCDs and total diet replacement (TDR) approaches informed by DiRECT on a nationwide scale, to achieve T2D remission (EV6a, EV7).

#### Impacts on patients and healthcare providers

Ultimately, the goal of the NHS pilot and Scottish implementation is to treat patients. The NHS LCD programme is committed to recruiting 5,000 patients to the implementation pilot over 2 years: as of December 31<sup>st</sup> 2020, around 500 patients have been enrolled and begun remission intervention (EV7). The 10 NHS England LCD pilot sites are supported by service providers and as an example of the impacts to them, Momenta Newcastle Ltd (the Birmingham and Solihull CCG provider) confirms that the 3-phase DiRECT model is the core of the intervention, delivered as *“20 group sessions plus an individual phone call in three phases over 12 months to groups of up to 15 participants”* (EV8).

Although national data for Scotland is not yet available, 500 patients were anticipated in 2019-2020 (EV4). In 2020, 77 patients were enrolled in the East region NHS board (47% of the region's T2D patients), with 15 completing TDR and achieving a median weight reduction of 19kg 6 months after returning to a normal diet (EV9). Enrolment in both countries was delayed due to the COVID-19 pandemic, reducing patient numbers, but enrolment has now resumed (EV3, EV7).

A survey of GPs from 19 practices in Scotland and Tyneside who participated in DiRECT found that 90% have consequently changed their routine treatment of T2D patients (EV10). Comments included an increased focus on recommending weight loss and lifestyle changes as a method of diabetes treatment, especially in newly-diagnosed patients.

DiRECT findings have also expanded beyond the NHS to inform diabetes remission programmes delivered by other healthcare providers. One example is Diabetes 800 from Oviva (EV11), and since it is delivered digitally patients can be given personalised feedback. Since January 2020, 52 people from the Wolverhampton and East Riding CCGs have used this programme (EV11).

#### Economic impacts

Counterweight Ltd., a spin-out of Robert Gordon University, provided the specially formulated Counterweight-Plus LCD for DiRECT in 2014. Following involvement with other research projects, Counterweight Ltd. was incorporated as a new company in March 2018. The CEO confirms that *“Without DiRECT and the wide coverage of the results, Counterweight Limited would not now exist, nor would the company have been in a position to raise any funds”* (EV4). A small company, as of 2020 they directly employ 7 people but also outsource services to a network of 150 Counterweight-trained freelance dietitians. Counterweight Ltd. provide Counterweight-Plus to 13 NHS Scotland Boards and hold contracts to support several NHS weight-management teams in England and Wales (EV4).

#### Impacts on education about T2D remission

Remission of T2D has been met with considerable enthusiasm from charities and patient groups. In 2017, independent research by the James Lind Foundation for Diabetes UK, the leading UK diabetes charity, found that diabetes remission was the most important research question for people with type 2 diabetes (EV6b). Diabetes UK has since made remission one of their four

priorities and included it as a key part of their research strategy (EV6a). Diabetes UK have also made significant updates to information provided to the general public and practitioners, such as a freely available “Information Prescription” document used by primary care staff when discussing T2D remission with patients. They have fully updated their website, adding pages explaining the results of DiRECT and including resources on T2D remission. These pages were accessed 380,000 times between January 2019 and 30<sup>th</sup> June 2020 (EV6a).

#### In summary

Newcastle research determined the cause of T2D and showed that remission is possible through an LCD, and that the DiRECT intervention framework provides suitable strategies at the clinical level. Following high-level policy changes, DiRECT principles have been implemented across Scotland and are being trialled at 10 NHS England sites, supporting thousands of patients with T2D.

### **5. Sources to corroborate the impact**

- EV1. 2016 WHO Global Report on Diabetes, page 51. PDF
- EV2. A Healthier Future – Framework for the prevention, early detection and early intervention of type 2 diabetes. 2018. Page 30. PDF.  
<https://www.gov.scot/publications/healthier-future-framework-prevention-early-detection-early-intervention-type-2/pages/7/>
- EV3. Letter of support from the Scottish Government Professional Advisor for the ‘Type 2 Diabetes Prevention, Early Detection and Early Intervention Framework Implementation’. PDF
- EV4. Letter of support from the CEO of Counterweight Ltd. PDF
- EV5. NHS Long-Term Plan, page 37, section 2.17. PDF
- EV6. Evidence from Diabetes UK
  - EV6a. Letter of support from the Diabetes UK Director of Research. PDF available on request
  - EV6b. Diabetes UK. Your priorities for Type 2 diabetes research: The top 10. 2017. PDF
- EV7. Letter of support from the National Clinical Director for Diabetes and Obesity, NHS England & NHS Improvement. PDF available on request
- EV8. Letter of support from the Director of Discover Momenta and Momenta Newcastle Ltd. PDF
- EV9. NHS Scotland, East Region, Excel data of patients enrolled in LCD intervention as of 2020. Available on request.
- EV10. Survey results of GPs, healthcare practitioners and patients taking part in DiRECT. Data available on request. Refer to corroborator 1 details.
- EV11. Letter of support from the Clinical Research Lead of Oviva. PDF