Less is more: effectiveness and feasibility of a fasting-mimicking diet programme in persons with type 2 diabetes in primary care

Schoonakker, M.P.; Burg, E.L. van den


FINAL
CHAPTERS

Chapter 12

General discussion

shared authorship

The studies in this thesis aim to provide insight into the role of intermittent and periodic fasting for individuals with type 2 diabetes (T2D), specifically in the form of a fasting-mimicking diet (FMD) programme integrated into routine primary care in the Netherlands. In this final chapter, the main research findings are presented (**Figure 1**), followed by a discussion of methodological and clinical considerations. Subsequently, the implications for clinical practice are examined, along with recommendations for implementation and future research.

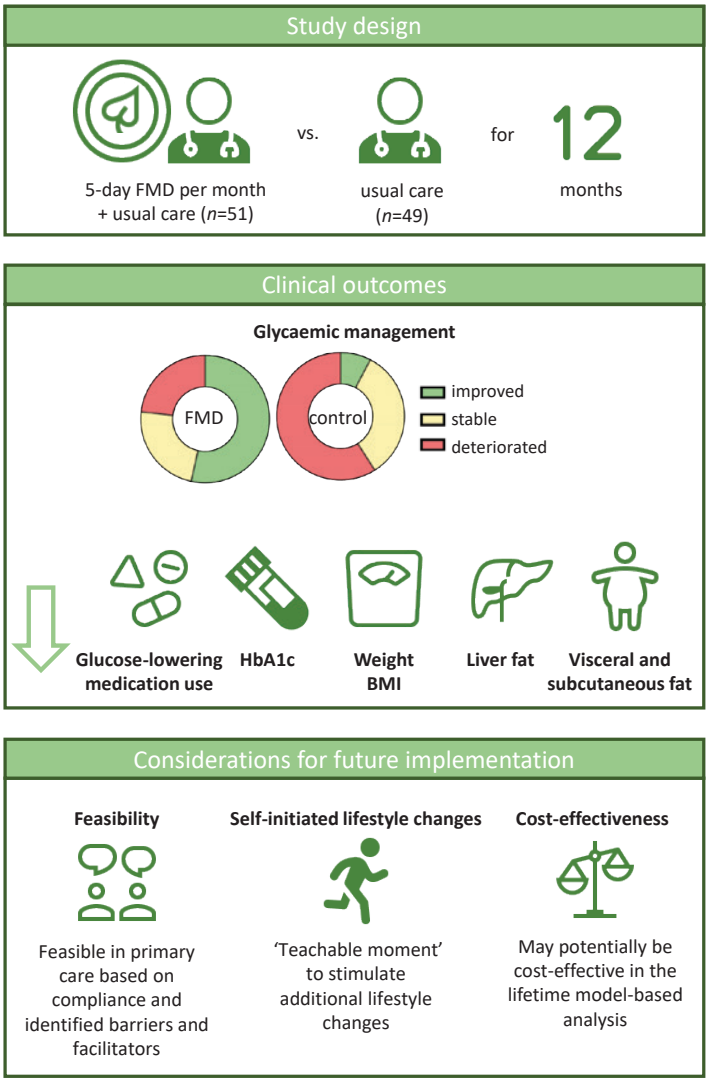

Figure 1. Summary of the main results of the FIT trial.

Main research findings

In **Part I**, three reviews summarise the available literature at the time of writing on the impact of various dietary types and patterns on different aspects of health. These reviews provide an overview of the effects of intermittent and periodic fasting on several metabolic parameters in individuals with T2D (**chapter 2, van den Burg**), effects of intermittent fasting on weight, fat mass and visceral fat (**chapter 3, Schoonakker**), and the impact of diets with different types of macronutrient restrictions on the human gut microbiome (**chapter 4, Schoonakker**). The available literature on intermittent and periodic fasting from animal studies, healthy individuals, and individuals with T2D was taken into account when designing the Fasting In diabetes Treatment (FIT) trial.

Part II of this thesis describes the rationale, methods and clinical outcomes of the FIT trial. **Chapter 5** (**van den Burg**) details the trial's rationale and methodology, outlining its randomised, controlled, assessor-blinded design. It outlines the inclusion criteria for participants, specifically individuals with T2D who are managed either with lifestyle advice alone or in combination with metformin. The protocol describes the trial's intervention, consisting of periodic 5-day FMD cycles repeated monthly over a year and the trial's primary and secondary outcomes on the feasibility and effectiveness of integrating an FMD programme in primary care for individuals with T2D.

The primary outcomes of the FIT trial—changes in HbA1c levels and glucose-lowering medication use after twelve months—differed significantly between the FMD and control groups (**chapter 6, shared first authorship van den Burg and Schoonakker**). The outcome 'glycaemic management', a combination of both HbA1c and glucose-lowering medication use, was categorized as 'improved,' 'stable,' or 'deteriorated,' and improved in 53% of the FMD group versus 8% in the control group, while it deteriorated in 23% of the FMD group compared to 59% in the control group. The FIT trial's secondary outcomes included anthropometric and laboratory measurements, showing a significant treatment effect on weight, BMI, waist circumference, body fat percentage, Matsuda index (reflecting insulin sensitivity) and HDL cholesterol after 12 months. There was no effect on fasting glucose, insulin, total cholesterol, LDL cholesterol, triglycerides, disposition index (reflecting insulin secretion), or high sensitivity CRP.

Chapter 7 and 8 describe secondary outcomes of the FIT trial derived from Magnetic Resonance Imaging (MRI). There was a reduction in liver fat (PDFF) and liver inflammation/fibrosis (cT1), both MRI-derived biomarkers, after following the FMD programme in individuals with T2D (**chapter 7, van den Burg**). Furthermore, the FMD programme significantly reduced abdominal visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), while abdominal muscle area remained unaffected (**chapter 8, Schoonakker**).

Part III of this thesis examines the feasibility of implementing the FMD programme in primary care. The FIT trial found 61% adherence, with ketone levels confirming compliance and no differences in treatment satisfaction (**chapter 9, Schoonakker**). Convenience, short cycles, and perceived health benefits facilitated adherence, whereas taste, portion size, and limited social support posed barriers, highlighting key areas to address for improving feasibility. **Chapter 10** (**van den Burg**) explored self-initiated lifestyle changes, finding no dietary differences between FMD cycles but increased physical activity in FMD participants. Focus groups highlighted following an FMD programme as a 'teachable moment' for minor lifestyle changes, with key facilitators including health awareness and fitness improvements, while barriers included health issues, work, and social events. Overall, **Chapter 11** (**van den Burg**) assessed the cost-effectiveness of a one-year FMD programme for individuals with T2D using a trial-based and lifetime model-based analysis. The FMD programme does not appear to be cost-effective over the first year of its application in this specific patient group in the context of the Dutch healthcare system, mainly due to the costs of the FMD programme that was investigated and the relatively low costs of early stage T2D treatment in current healthcare. Due to the small sample size, this conclusion should be interpreted with caution. In contrast, in the lifetime model-based cost-effectiveness analysis, a gain in QALYs in the FMD group was seen and the FMD programme' costs were largely offset by savings in the costs of diabetic complications. This suggests that adding an FMD programme to usual care may potentially be cost-effective in the long-term. When considering implementation of an FMD programme in Dutch primary care, these findings should be taken into account.

Comparison with literature

When comparing the outcomes from the FIT trial with those of other trials on intermittent and periodic fasting in individuals with T2D, as reviewed in **chapter 2**, most studies generally indicate that these approaches can improve various anthropometric and metabolic parameters, consistent with the findings of the FIT trial(1-8). Another recent review by Rivera Regalado et al.(9) also concluded that intermittent and periodic fasting, including FMDs, can improve metabolic parameters in individuals with T2D. While many studies in **chapter 2** reported improvements in fasting glucose, HbA1c and/or weight, results on blood pressure or lipid levels were less conclusive. Contrasting with the FIT trial (**chapter 6**), Tang et al.(8) observed reductions in blood pressure and improved lipid profiles after four months of FMD.

MRI data from the FIT trial revealed high rates of hepatic steatosis at baseline in both groups, which aligns with findings from earlier studies(10, 11). The FMD induces reductions in liver fat (PDFF) and inflammation/fibrosis (cT1) after twelve months in the

FMD group, suggesting potential liver-related benefits for individuals with T2D (**chapter 7**). These effects may be more pronounced in those with coexisting MASLD, though evidence remains limited, with only one supporting animal study(12) and inconsistent findings from a systematic review on intermittent fasting likely due to the heterogeneity of the included diets(13).

While previous reviews found greater reductions in subcutaneous fat (SAT) than visceral fat (VAT) across various interventions (14, 15), the FIT trial showed a more pronounced loss of abdominal VAT (**chapter 8**), which is more strongly linked to metabolic benefits (16). Unlike other weight loss approaches that often reduce muscle mass (17, 18) , FMD preserved muscle while reducing VAT and SAT. Notably, men lost more VAT relative to SAT, whereas women showed a more balanced fat loss. These findings highlight the potential of FMD and underscore the need for further research on sex-specific effects and body composition changes in T2D.

Chapter 9 focusses on the feasibility of an FMD programme for individuals with T2D. Many facilitators and barriers found in the FIT trial are described in other dietary intervention studies. Key facilitators of FMD which were not often shared by other dietary interventions are the convenience and simplicity, as well as not feeling hungry during the intervention(19-21). **Chapter 10** examined self-initiated lifestyle changes within the FIT trial, showing increased physical activity in FMD participants. Compared to existing literature, the barriers and facilitators identified in the FIT trial closely align with those reported in other qualitative studies on lifestyle changes(22-24). Common themes include family support, difficulty in changing habits, physical health and fitness, and work-related challenges, all of which frequently influence lifestyle modifications. These factors are therefore valuable to explore not only in the context of an FMD programme, but also when considering other lifestyle interventions in the general practitioner's consultation room.

The aim of **chapter 11** was to determine cost-effectiveness of a one year 5-day FMD programme for individuals with T2D, and found that the FMD programme we investigated, may potentially be cost-effective in the lifetime model-based cost-effectiveness analysis. Limited literature exists on the cost-effectiveness of FMD programmes. However, one economic evaluation found that an FMD was cost-effective compared to usual care for individuals with T2D on dual or triple medications regimens in the USA(25).

From a broader perspective, recent research on the treatment of T2D has led to the introduction of several effective drug options including glucagon-like peptide 1 receptor agonists (GLP1-RA) and sodium glucose cotransporter 2 inhibitors (SGLT2i),

which have shown positive outcomes in reducing HbA1c levels as well as other improvements such as weight loss and reduction in cardiovascular disease, kidney disease and heart failure(26-28). Whereas the treatment of T2D was previously more glucose centric, causing an increased risk of side effects such as hypoglycaemia and ketoacidosis(26), the focus has now shifted also towards the prevention of long term complications(28). For the future, the management of T2D should shift towards a pathogenesis centred approach. Obesity plays a major role in the pathogenesis of T2D, and relatively small amounts (5%) of weight loss reduce the risk of developing T2D and improve glycaemic control(29, 30), while greater amounts of weight loss may even lead to the remission of T2D(31). Lifestyle interventions target the underlying disease mechanism including reduced insulin sensitivity, abnormal adipose tissue distribution, and fat accumulation in the liver(32), and can therefore constitute a valuable component of this approach. The FIT trial demonstrates that this approach is also achievable with an FMD programme.

Methodological considerations

Limitations

Dietary intervention studies

Dietary intervention studies are important for the understanding of the impact of diet on health outcomes, however there are several limitations that affect all dietary studies and are difficult to overcome. Several limitations were encountered during the literature research (**Part I**), the execution of the FIT trial (**Part II**) and the evaluation of the feasibility of the FIT trial (**Part III**).

1. *Heterogeneity*. A key limitation encountered in the literature research (**Part I)**, was the heterogeneity among dietary intervention studies. Substantial differences were observed in dietary interventions, macronutrient composition, study designs, primary outcomes, and study duration, making it impossible to conduct meta-analyses of the included studies. Additionally, when contextualizing the results of the FIT trial within the broader landscape of dietary interventions, it is important to recognize that an FMD programme differs significantly from other forms of intermittent or periodic fasting, such as the 5:2 diet or time-restricted eating(33).
2. *The inability of blinding participants*. Not blinding participants could have led to performance bias towards the intervention(34). In the FIT trial (**Part II**), the risk of performance bias was reduced as much as possible, by blinding the outcome assessors and by choosing objective outcomes that are not affected by blinding such as HbA1c and measurements from MRI data.

3. *Assessment of compliance*. There are challenges assessing compliance, since self-reported compliance often overestimates adherence as participants tend to give social desirable answers(35). The combination of self-reported compliance and ketone measurements on the day following some FMD cycles was attempted in the FIT trial to enhance the reliability of adherence assessment (**Part III**). However, ketone levels were not found suitable for determining individual compliance due to significant interindividual variability in ketone response.

Inclusion criteria

Given the limited knowledge about periodic fasting in individuals with T2D at the time the study was designed, only participants who were either taking metformin or not using any glucose-lowering medications were included in the FIT trial. This approach aimed to effectively eliminate the risk of hypoglycaemia. Grajower et al.(36) propose a medication adjustment protocol informed by the pharmacological mechanisms of glucose-lowering medication. One trial has suggested that the FMD may be safe for individuals using sulfonylurea derivatives or insulin when strict glucose monitoring is applied in combination with a strict medication adjustment protocol during FMD cycles(7); however, this study was limited by a small sample size and an intervention period of only six months. Therefore, further research is necessary to determine how an FMD programme can be safely applied in general practice by individuals with T2D treated with a diverse range of glucose-lowering medications.

Loss to follow-up

Another specific limitation of the FIT trial was the loss to follow-up, affecting **chapters 6 to 11**. Of the 100 participants randomised, 8 did not attend the baseline visits (2 from the FMD group and 6 from the control group). During the trial, an additional 10 participants (6 FMD, 4 control) were lost to follow-up. While there were no differences in the baseline characteristics between those who were lost to follow-up compared to those who remained in the trial, the high percentage lost to follow-up must be considered.

Multiple factors contributed to the loss to follow-up. Firstly, dissatisfaction with randomisation among control group participants was noticed, although not all participants explicitly cited this as the primary reason for withdrawal. This led to a protocol amendment allowing control group participants access to two FMD cycles post-trial, which appeared to reduce dissatisfaction-related dropouts. Secondly, COVID-19 played a significant role, since concerns about infection risk during hospital visits prompted some participants to withdraw. Additionally, numerous hospital visits were cancelled resulting in missing data. Thirdly, scheduling issues further complicated participation. The trial required 13 hospital visits ranging from 15 minutes to 1.5 hours

over a year. This proved specifically challenging for employed participants. In retrospect, fewer follow-up visits may have reduced this burden.

However, while the loss to follow-up reduces statistical power, the trial still revealed notable treatment differences between groups. This may be attributed in part to the strategy of encouraging participants to continue follow-up visits, even after discontinuation of the FMD.

Focus group discussions

Regarding the focus group discussions, participants were purposively sampled to ensure diversity in gender, age, BMI and adherence to the FMD. However, there was a difference in the mean number of completed FMD cycles between focus group participants and the rest of the FMD group. This discrepancy may have influenced the findings in **chapters 9 and 10**, potentially leading to an incomplete identification of barriers to adherence to the FMD programme or factors hindering self-initiated lifestyle changes. However, in **chapter 9**, participants who completed all twelve FMD cycles identified barriers similar to those reported by participants who did not complete all cycles. This suggests that the challenges faced were consistent across both groups. Similarly, in **chapter 10**, the barriers and facilitators identified by focus group participants remain relevant and applicable to those who discontinued the FMD programme. Ultimately, after six focus groups with a total of 20 FMD participants, data saturation was achieved, suggesting that no additional barriers or facilitators would have been identified even if more individuals who discontinued the FMD earlier in the programme had participated.

Strengths

Routine monitoring and treatment in general practice

A key strength of the FIT trial is its generalizability to clinical practice. The management of T2D was overseen by general practitioners, which involved routine monitoring and treatment, including adaptation of glucose-lowering medication according to the Dutch guidelines for T2D(32). This approach was likely to yield more realistic and clinically relevant results compared to studies where treatment is tightly controlled according to the study protocol. Also, this enhances the potential for translating the intervention from research to clinical settings.

Clinically relevant outcomes

Both the primary outcomes, HbA1c levels and glucose-lowering medication use, are highly relevant in a primary care setting. However, these outcomes mutually influence each other and should thus be assessed together. As no existing outcome measure

combining HbA1c levels and glucose-lowering medication use was identified in the literature, a categorical outcome measure integrating both these primary outcomes was developed and termed ‘glycaemic management’.

Considerations and recommendations for clinical practice

In the general introduction of this thesis, the case of Mrs. Riet Suiker was presented to illustrate the associated challenges and potential benefits of the FMD programme. Her follow-up is presented here as a potential illustration of what may occur in individuals following the FMD programme.

Mrs. Riet Suiker

Mrs. Riet Suiker is informed by her general practitioner about the potential effects of following an FMD programme, as well as the possible side effects that may occur during the five-day FMD cycles. Motivated to reduce her metformin use, she decides to proceed with this dietary intervention.

Before starting her first cycle, Mrs. Suiker has an in-depth discussion with the practice nurse to identify potential barriers and facilitators relevant to her situation. She determines that the prepackaged meals with simple instructions will be a facilitator, as they will eliminate the need for decision-making about food choices and grocery shopping on FMD days, thereby reducing exposure to temptations. She also finds the structured nature of five consecutive days per month appealing, as it provides a clear framework that she believes will be manageable. Additionally, her strong motivation to reduce medication use, her primary goal, will serve as an important driver of adherence. However, she anticipates that social interactions will be her greatest challenge, as gatherings with friends often revolve around food. To mitigate this, she decides to avoid or reschedule social events that coincide with her FMD cycles. Furthermore, she discusses her plans with her husband, who, despite not having type 2 diabetes, is overweight. He chooses to join her in the FMD programme and follow the cycles alongside her, which they both believe will enhance their adherence. The practice nurse and Mrs. Suiker decide to communicate by telephone every two months to discuss difficulties, to improve adherence and to discuss other lifestyle changes. With these strategies in place, Mrs. Suiker feels well-prepared to begin the FMD programme.

After one year, Mrs. Suiker has successfully completed twelve FMD cycles. The regular phone calls from the practice nurse proved to be a valuable source of support. Over the year, she has lost 5 kg (BMI 28.7 kg/m^2), and her HbA1c has decreased to 48.4 mmol/mol,

allowing her to discontinue metformin entirely. Although she has not been able to reduce her antihypertensive or cholesterol-lowering medication, she is pleased with her progress and reports feeling significantly better overall. Feeling more energetic and healthier, she has also been able to incorporate regular physical activity: walking for at least 45 minutes each day. Encouraged by her progress, she now seeks guidance from her general practitioner on how to maintain these improvements.

The case of Mrs. Suiker illustrates how an FMD programme may serve as a valuable treatment option for individuals with T2D, at least for those who manage glycaemic control through lifestyle advices only or lifestyle advices combined with metformin as their sole glucose-lowering medication. For general practitioners and practice nurses, it is important to know not only that following an FMD programme is effective in lowering HbA1c levels and reducing glucose-lowering medication use but also that it provides additional benefits, such as weight loss, reduction of liver fat, and decreases in both visceral and subcutaneous adipose tissue, all while preserving muscle mass. The FIT trial was designed with a pragmatic approach and focussing on outcomes relevant for primary care. Although it was not an implementation study, this thesis explored several aspects of the FIT trial that should be considered when implementing an FMD programme in primary care.

Selecting a lifestyle intervention

When selecting a lifestyle intervention together with a patient, several aspects should be taken into account. In primary care, the discussion with the patient may lie with the general practitioner, practice nurse, or another primary care professional such as a dietician or a lifestyle coach. Rather than offering a one-size-fits-all approach, healthcare providers should be able to engage in collaborative discussion with individuals to determine the most suitable lifestyle interventions tailored to their needs and likely to produce favourable outcomes. Personalised strategies may help prevent disappointment and demotivation, thereby supporting long-term adherence. Evidence on the feasibility of specific lifestyle-programmes can inform these consultations, guiding the selection of interventions that match patient expectations. In these consultations, it is important to also address potential barriers and facilitators, which can further enhance adherence and success by tailoring the intervention to the patient's specific needs.

After choosing an FMD programme

When an individual with T2D opts to follow an FMD programme, several key considerations should be discussed prior to initiation:

- *Mild side-effects*. The programme is safe, though some participants experienced mild energy deficit symptoms (fatigue, headache, dizziness, nausea) during the five-day cycles, which resolved between cycles and generally did not lead to discontinuation.
- *Follow-up appointments*. During the FIT trial, participants received phone calls from the researchers during FMD cycles, which may have contributed to adherence. Participants exhibited varying preferences regarding regular contact, with some favouring consistent communication while others preferred less frequent engagement. This diversity in preferences highlights the importance of tailoring communication strategies to individual participant needs.
- *Use of supportive techniques*. Supportive techniques like motivational interviewing, collaborative goal-setting, and regular check-ins can improve adherence, which could be provided by general practitioners, practice nurses or other healthcare professionals in primary care.
- *Initiation of other life-style changes*. Participants often reported an increase in awareness of the impact of lifestyle on health when following the FMD programme. This could serve as a 'teachable moment' for participants in an FMD programme, encouraging them to consider additional lifestyle modifications, such as adopting healthier eating habits between FMD cycles or increasing physical activity. Healthcare providers should be aware of this opportunity and assess a patient's motivation for making broader lifestyle changes while following an FMD programme. It is essential to integrate lifestyle change support into the guidance process, as adopting healthier behaviour can provide additional long-term benefits.

Reimbursed care

At the moment, prescribing an FMD meal-replacement box is not part of reimbursed care by health insurance, meaning that only individuals who can afford to pay for it themselves have access to the specific FMD meal-replacement box used in the FIT trial. This exacerbates the existing 'health gap', which is a global issue, including in the Netherlands. The incidence of T2D is higher among individuals with low socioeconomic status (SES) compared to those with high SES, which could be related to the poorer diet quality(37, 38). Additionally, low education and low SES are associated with a higher risk of cardiovascular disease (39), as well as higher rates of cardiovascular mortality(40). Taking this health gap into account, it is even more crucial to ensure equitable access to treatment for all individuals.

Regarding the FMD programme, several possibilities could be considered in addressing this issue in the future:

- *Reimbursed care*. It would be beneficial if an FMD programme could be part of reimbursed care by health insurance. This may be considered by policy makers, since the FMD programme may potentially be cost-effective in the long term (**chapter 11**).
- *Increased production volumes*. The industry may reduce the cost of FMD meal-replacement boxes if a larger number of individuals begin using the product, leading to increased production volumes.
- *Tailored diet without meal-replacement products*. Individuals could create a tailored FMD themselves without relying on meal-replacement products. In their trajectory towards 'healthy cooking' and more, they should be supported with structured programmes. While this option offers advantages, such as allowing individuals to select preferred foods, which may improve adherence, it also has disadvantages, as one key facilitators identified in the FIT trial was the ease of the FMD meal-replacement products and the reduced need for food-related decision-making(**chapter 9**). Further research is needed to explore the (cost-) effectiveness of this option.

Recommendations for future research

While the one-year FMD programme demonstrated positive effects on various health parameters in individuals with T2D, further research is warranted to fully understand its long-term benefits and potential applications. Throughout the trial, several considerations emerged.

- *Larger study population*. A larger study population would allow for a more in-depth analysis of patient characteristics and may help identify which factors are associated with successful or unsuccessful outcomes after following an FMD programme.
- *Flexibility within the FMD programme*. An interesting area for investigation would be the flexibility of the FMD programme. For example, it would be valuable to examine whether participants unable to adhere to monthly cycles can still achieve positive health outcomes when following bi-monthly cycles instead. While randomised controlled trials typically require strict protocols that limit such adaptations, research in a real-world implementation setting may provide insight into a flexible approach.
- *Long-duration follow-up period*. Even though studies lasting twelve months or longer are relatively scarce (**chapter 2**), a longer study duration would provide the opportunity to assess the 'maintenance phase', examining how participants sustain their progress once initial health goals have been achieved. In addition,

it would be interesting to determine the minimum number of FMD cycles required to sustain improvements in HbA1c levels and glucose-lowering medication use in this 'maintenance phase'.

- *Patient groups other than T2D*. Other patient groups may benefit from following an FMD programme. Based on the findings of the FIT trial, two specific populations warrant further investigation: (1) individuals with metabolic dysfunction-associated steatotic liver disease, to assess the effects of an FMD programme on liver fat and liver inflammation/fibrosis, and (2) individuals who are overweight or obese, to determine whether an FMD programme could help prevent comorbidities such as T2D. Expanding research to these populations could provide valuable insights into the broader applicability of FMD as a therapeutic intervention.
- *Effect on the microbiome*. Based on the literature review in **chapter 4**, it was hypothesized that following an FMD programme would have an impact on the gut microbiome. As a result, the collection of faecal samples was incorporated into the study protocol of the FIT trial. However, analysing these data was beyond the scope of this thesis and remains pending.
- *Prediction of success rates of lifestyle interventions*. Research predicting the success rates lifestyle interventions based on physical and psychological patient characteristics would be of significant value. Studies show that individual features, including physical factors such as genetics, age, metabolic baseline values and the gut microbiome(41, 42), but also psychological or behavioural factors such as fewer self-implemented weight loss attempts, greater exercise self-efficacy, greater dietary restraint, motivation and psychopathology are associated with successful outcomes in lifestyle interventions(42, 43). Combining these features, for example using machine learning(44), may lead to personalised recommendations for lifestyle interventions, which may enhance adherence and improve health outcomes in the future.

Conclusion

The findings from the studies presented in this thesis provide new insights into the role of structured intermittent and periodic fasting for individuals with T2D, specifically through an FMD programme for primary care in the Netherlands. The results from the FIT trial demonstrate that a 5-day monthly FMD programme can be safely integrated into primary care for individuals with T2D, who manage glycaemic control with either lifestyle advice alone or in combination with metformin. The FMD programme has shown effectiveness in improving both primary outcomes, HbA1c levels and glucose-lowering medication use. Additionally, the study found improvements in several secondary outcomes including anthropometrics, laboratory measurements, and measurements from MRI-data. The programme appears feasible within primary care, and healthcare providers could also leverage the programme as a 'teachable moment' to stimulate additional lifestyle changes, as individuals may become more aware of the impact of lifestyle on health. The FMD programme may potentially be cost-effective in the long term, factoring in savings from reductions in diabetic complications including cardiovascular disease.

References

1. Arnason TG, Bowen MW, Mansell KD. Effects of intermittent fasting on health markers in those with type 2 diabetes: A pilot study. World J Diabetes. 2017;8(4):154-64.
2. Bhandari V, Dureja S, Bachhel R, Gupta M, Sidhu R. Effect of intermittent fasting on various health parameters in obese type 2 diabetics: A pilot study. National Journal of Physiology, Pharmacy and Pharmacology. 2022;12(2):170-2.
3. Che T, Yan C, Tian D, Zhang X, Liu X, Wu Z. Time-restricted feeding improves blood glucose and insulin sensitivity in overweight patients with type 2 diabetes: a randomised controlled trial. Nutr Metab (Lond). 2021;18(1):88.
4. Kahleova H, Belinova L, Malinska H, Oliyarnyk O, Trnovska J, Skop V, et al. Eating two larger meals a day (breakfast and lunch) is more effective than six smaller meals in a reduced-energy regimen for patients with type 2 diabetes: a randomised crossover study. Diabetologia. 2014;57(8):1552-60.
5. Carter S, Clifton PM, Keogh JB. Effect of Intermittent Compared With Continuous Energy Restricted Diet on Glycemic Control in Patients With Type 2 Diabetes: A Randomized Noninferiority Trial. JAMA Netw Open. 2018;1(3):e180756.
6. Umphonsathien M, Rattanasian P, Lokattachariya S, Suansawang W, Boonyasuppayakorn K, Khovidhunkit W. Effects of intermittent very-low calorie diet on glycemic control and cardiovascular risk factors in obese patients with type 2 diabetes mellitus: A randomized controlled trial. J Diabetes Investig. 2022;13(1):156-66.
7. Sulaj A, Kopf S, von Rauchhaupt E, Kliemank E, Brune M, Kender Z, et al. Six-Month Periodic Fasting in Patients With Type 2 Diabetes and Diabetic Nephropathy: A Proof-of-Concept Study. J Clin Endocrinol Metab. 2022;107(8):2167-81.
8. Tang F, Lin X. Effects of Fasting-Mimicking Diet and Specific Meal Replacement Foods on Blood Glucose Control in Patients with Type 2 Diabetes: A Randomized Controlled Trial. Oxid Med Cell Longev. 2020;2020:6615295.
9. Rivera Regalado JA, García J, Ramirez I, Hermosilla P, Rascon J, Fausto Girón SJ. Exploring the Impact of Fasting and Fasting-Mimicking Diets on Type 2 Diabetes Management in Adults: A Systematic Review. Cureus. 2024;16(9):e70332.
10. Alblas G, Lamb HJ, Rosendaal FR, van Hoek B, Coenraad MJ, de Mutsert R. Prevalence of non-alcoholic fatty liver in the general Dutch population and in groups at increased risk. Nutr Metab Cardiovasc Dis. 2023;33(12):2497-507.
11. Leite NC, Salles GF, Araujo AL, Villela-Nogueira CA, Cardoso CR. Prevalence and associated factors of non-alcoholic fatty liver disease in patients with type-2 diabetes mellitus. Liver Int. 2009;29(1):113-9.
12. Zhao J, Bai M, Wei S, Li C, Lv Q, Chen Y. Improvement of Non-Alcoholic Fatty Liver Disease in Mice by Intermittent Use of a Fasting-Mimicking Diet. Mol Nutr Food Res. 2021;65(23):e2100381.
13. Abuelazm MT, Mohamed I, Naeem A, Khlidj Y, Tanashat M, Katamesh BE, et al. Intermittent fasting regimens for metabolic dysfunction-associated steatotic liver disease: a systematic review and network meta-analysis of randomized controlled trials. Eur J Gastroenterol Hepatol. 2024;36(4):371-81.
14. Merlotti C, Ceriani V, Morabito A, Pontiroli AE. Subcutaneous fat loss is greater than visceral fat loss with diet and exercise, weight-loss promoting drugs and bariatric surgery: a critical review and meta-analysis. Int J Obes (Lond). 2017;41(5):672-82.
15. Abe T, Song JS, Bell ZW, Wong V, Spitz RW, Yamada Y, et al. Comparisons of calorie restriction and structured exercise on reductions in visceral and abdominal subcutaneous adipose tissue: a systematic review. Eur J Clin Nutr. 2022;76(2):184-95.
16. Usui C, Asaka M, Kawano H, Aoyama T, Ishijima T, Sakamoto S, et al. Visceral fat is a strong predictor of insulin resistance regardless of cardiorespiratory fitness in non-diabetic people. J Nutr Sci Vitaminol (Tokyo). 2010;56(2):109-16.
17. Anyiam O, Abdul Rashid RS, Bhatti A, Khan-Madni S, Ogunyemi O, Ardavani A, et al. A Systematic Review and Meta-Analysis of the Effect of Caloric Restriction on Skeletal Muscle Mass in Individuals with, and without, Type 2 Diabetes. Nutrients. 2024;16(19).
18. Seimon RV, Roekenes JA, Zibellini J, Zhu B, Gibson AA, Hills AP, et al. Do intermittent diets provide physiological benefits over continuous diets for weight loss? A systematic review of clinical trials. Mol Cell Endocrinol. 2015;418 Pt 2:153-72.
19. Lee SA, Sypniewski C, Bensadon BA, McLaren C, Donahoo WT, Sibille KT, et al. Determinants of Adherence in Time-Restricted Feeding in Older Adults: Lessons from a Pilot Study. Nutrients. 2020;12(3).

20. Mathew R, Gucciardi E, De Melo M, Barata P. Self-management experiences among men and women with type 2 diabetes mellitus: a qualitative analysis. BMC Fam Pract. 2012;13:122.
21. Laranjo L, Neves AL, Costa A, Ribeiro RT, Couto L, Sá AB. Facilitators, barriers and expectations in the self-management of type 2 diabetes--a qualitative study from Portugal. Eur J Gen Pract. 2015;21(2):103-10.
22. Skoglund G, Nilsson BB, Olsen CF, Bergland A, Hilde G. Facilitators and barriers for lifestyle change in people with prediabetes: a meta-synthesis of qualitative studies. BMC Public Health. 2022;22(1):553.
23. Vilafranca Cartagena M, Tort-Nasarre G, Rubinat Arnaldo E. Barriers and Facilitators for Physical Activity in Adults with Type 2 Diabetes Mellitus: A Scoping Review. Int J Environ Res Public Health. 2021;18(10).
24. Cradock KA, ÓLaighin G, Finucane FM, Gainforth HL, Quinlan LR, Ginis KA. Behaviour change techniques targeting both diet and physical activity in type 2 diabetes: A systematic review and meta-analysis. Int J Behav Nutr Phys Act. 2017;14(1):18.
25. Habka D, Hsu WC, Antoun J. Economic Evaluation of Fasting Mimicking Diet Versus Standard Care in Diabetic Patients on Dual or Triple Medications at Baseline in the United States: A Cost-Utility Analysis. Value Health. 2025;28(1):51-9.
26. Tran L, Zielinski A, Roach AH, Jende JA, Householder AM, Cole EE, et al. Pharmacologic treatment of type 2 diabetes: oral medications. Ann Pharmacother. 2015;49(5):540-56.
27. Tran L, Zielinski A, Roach AH, Jende JA, Householder AM, Cole EE, et al. Pharmacologic treatment of type 2 diabetes: injectable medications. Ann Pharmacother. 2015;49(6):700-14.
28. Galindo RJ, Trujillo JM, Low Wang CC, McCoy RG. Advances in the management of type 2 diabetes in adults. BMJ Med. 2023;2(1):e000372.
29. Wing RR, Lang W, Wadden TA, Safford M, Knowler WC, Bertoni AG, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care. 2011;34(7):1481-6.
30. Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, Clark JM, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care. 2007;30(6):1374-83.
31. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. Lancet. 2018;391(10120):541-51.
32. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of Type 2 Diabetes Mellitus. Int J Mol Sci. 2020;21(17).
33. Koppold DA, Breinlinger C, Hanslian E, Kessler C, Cramer H, Khokhar AR, et al. International consensus on fasting terminology. Cell Metab. 2024;36(8):1779-94.e4.
34. Viera AJ, Bangdiwala SI. Eliminating bias in randomized controlled trials: importance of allocation concealment and masking. Fam Med. 2007;39(2):132-7.
35. Kristal AR, Andrilla CH, Koepsell TD, Diehr PH, Cheadle A. Dietary assessment instruments are susceptible to intervention-associated response set bias. J Am Diet Assoc. 1998;98(1):40-3.
36. Grajower MM, Horne BD. Clinical Management of Intermittent Fasting in Patients with Diabetes Mellitus. Nutrients. 2019;11(4).
37. Vinke PC, Navis G, Kromhout D, Corpeleijn E. Socio-economic disparities in the association of diet quality and type 2 diabetes incidence in the Dutch Lifelines cohort. EClinicalMedicine. 2020;19:100252.
38. Sezer B, Albers J, Meisters R, Schram MT, Köhler S, Stehouwer CDA, et al. Do poor psychosocial resources mediate health inequalities in type 2 diabetes mellitus? Findings from the Maastricht study. Eur J Public Health. 2024;34(6):1029-35.
39. Duan MF, Zhu Y, Dekker LH, Mierau JO, Corpeleijn E, Bakker SJL, et al. Effects of Education and Income on Incident Type 2 Diabetes and Cardiovascular Diseases: a Dutch Prospective Study. J Gen Intern Med. 2022;37(15):3907-16.
40. Kist JM, Smit GWG, Mairuhu ATA, Struijs JN, Vos RC, van Peet PG, et al. Large health disparities in cardiovascular death in men and women, by ethnicity and socioeconomic status in an urban based population cohort. EClinicalMedicine. 2021;40:101120.
41. Siebert JC, Stanislawski MA, Zaman A, Ostendorf DM, Konigsberg IR, Jambal P, et al. Multiomic Predictors of Short-Term Weight Loss and Clinical Outcomes During a Behavioral-Based Weight Loss Intervention. Obesity (Silver Spring). 2021;29(5):859-69.

42. Delahanty LM, Peyrot M, Shrader PJ, Williamson DA, Meigs JB, Nathan DM. Pretreatment, psychological, and behavioral predictors of weight outcomes among lifestyle intervention participants in the Diabetes Prevention Program (DPP). Diabetes Care. 2013;36(1):34-40.

43. Rotella F, Lazzeretti L, Barbaro V, Castellini G, Bigiarini M, Cresci B, et al. All roads bring to Rome: a different way for predicting success in the therapy of obesity through psychological features. J Endocrinol Invest. 2014;37(12):1187-94.

44. Irandoust K, Parsakia K, Estifa A, Zoormand G, Knechtle B, Rosemann T, et al. Predicting and comparing the long-term impact of lifestyle interventions on individuals with eating disorders in active population: a machine learning evaluation. Front Nutr. 2024;11:1390751.