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

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Chapter 11

Cost-effectiveness of a periodic fasting-mimicking diet programme in patients with type 2 diabetes: a trial-based analysis and a lifetime model-based analysis

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Abstract

Background

The prevalence of type 2 diabetes continues to rise worldwide, which is associated with a decrease in quality of life and an increase in healthcare costs. The aim of this study was to determine cost-effectiveness of a one year monthly 5-consecutive day fasting-mimicking diet (FMD) programme for patients with type 2 diabetes treated with lifestyle advice only or lifestyle advice plus metformin, compared to usual care.

Methods

A trial-based cost-utility analysis with quality-adjusted life-years (QALYs) and healthcare costs was performed. These results were extrapolated to a lifetime horizon using the United Kingdom Prospective Diabetes Study Outcomes Model, predicting cardiovascular events and mortality. Cost-effectiveness acceptability curves were assessed, representing the probability of the FMD programme being cost-effective compared to usual care across a range of willingness-to-pay (WTP) thresholds per QALY.

Results

In the trial-based analysis (n=92), QALYs were insignificantly lower (-0.04, 95% CI -0.10 to +0.03), while healthcare costs were significantly higher (+€2241, 95% CI +182 to +2660) in the FMD group. In contrast, from a lifetime horizon, QALYs were insignificantly higher in the FMD group (+0.16, 95% CI -1.16 to +1.48) and costs were insignificantly higher as well (+€1336, 95% CI -753 to +3425), yielding an incremental cost-effectiveness ratio of €8369/QALY. Thus, in the lifetime analysis the probability of cost-effectiveness of the FMD programme was around 0.6 as compared to usual care at most WTP thresholds.

Conclusions

The FMD programme does not appear to be cost-effective over the first year of its application in the context of the Dutch healthcare system. However, this conclusion should be interpreted with caution due to the small sample size. In the extrapolations of 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.

Trial registration

ClinicalTrials.gov: NCT03811587. Registered 22 January 2019.

Background

The prevalence of type 2 diabetes continues to rise worldwide. The number of people suffering from it surpassed 536 million people in 2021 and is projected to reach an estimated 783 million by 2045, affecting approximately 11% of the world's population(1). The prevalence of type 2 diabetes related complications, which are associated with a significant decline in quality of life, is increasing as well(1-3). As a consequence, the costs involved in disease management rise, since complications are responsible for most healthcare costs associated with type 2 diabetes(4-7). Adopting a healthy lifestyle can improve glycaemic control, may positively influence quality of life, and may decrease costs as it is associated with a lower risk of complications(8-11).

Various dietary interventions effectively improve metabolic parameters in patients with type 2 diabetes(12, 13). However, as increasing healthcare costs threaten economic stability worldwide, it is imperative to any medical intervention to be cost-effective as well, particularly in the long term. The Fasting In diabetes Treatment (FIT) trial revealed clinical benefits of 12 monthly cycles of a so called fasting-mimicking diet (FMD) programme as an adjunct to usual care of patients with type 2 diabetes treated with lifestyle advice and/or metformin as the only glucose-lowering drug(14, 15). FMD programmes comprise cycles of low protein-, low sugar/starch food, mimicking the physiological effects of water-only fasting, while still allowing light meals to be consumed(16, 17). Here we present the results of two cost-effectiveness analyses of an FMD programme as deployed in the FIT trial: one evaluating short-term effects using trial data only, and another estimating long-term effects based on United Kingdom Prospective Diabetes Study Outcomes Model (version 2.2)(18).

Methods

Clinical trial design

The FIT trial was a randomised, controlled, assessor-blinded intervention trial, which investigated the effectiveness and costs of twelve monthly, 5-consecutive-days FMD cycles as an adjunct to usual care in patients with type 2 diabetes(14). The trial was conducted at the Leiden University Medical Centre (LUMC) in the Netherlands, between 20 November 2018 and 5 August 2021. The trial was performed according to the principles of the Declaration of Helsinki, in accordance with the Medical Research Involving Human Subjects Act, and to the standards of Good Clinical Practice. The Medical Research Ethics Committee of the LUMC approved the protocol and amendments. All participants provided written informed consent before entry into the study. The study was registered at ClinicalTrials.gov: NCT03811587. Registration was

initiated prior to the start of the trial, but due to a delay within the registration process, online publication occurred after the start of the trial.

Participants and intervention

Participants were recruited from general practice centres. They could be included if they were diagnosed with type 2 diabetes, had a BMI ≥ 27 kg/m^2, were aged >18 years and <75 years, and treated with lifestyle advice alone, while their HbA1c was above 48 mmol/mol, or with lifestyle advice plus metformin as the only glucose-lowering drug regardless of their HbA1c. After randomisation, participants in the FMD group received twelve 5-consecutive-days meal-replacement FMD cycles every month for one year as an adjunct to usual care by their primary care providers. The control group received usual care only. The FMD consisted of complete meal replacement products, which included mainly soups, bars and snacks. The first day provided approximately 4600 kJ (1100 kcal; 10% protein, 56% fat and 34% complex carbohydrate); days 2-5 were identical and provided approximately 3150 kJ (750 kcal; 9% protein, 44% fat, 47% complex carbohydrate). Further details of the study design, intervention and exclusion criteria can be found in the study protocol(14). One hundred patients with type 2 diabetes were enrolled in the FIT trial, and 92 participants completed baseline measurements(15). Data from these 92 participants is used for the cost-effectiveness analysis. Further details on enrolment, allocation, reasons for drop-out, follow-up and effects on metabolism and anthropometrics are described elsewhere(15).

Cost-effectiveness analysis

A cost-effectiveness analysis was performed of the FIT trial data, comprising two parts. Firstly, we conducted a trial-based analysis evaluating the costs and benefits of the FMD programme as an adjunct to usual care as compared to usual care alone over the trial period of twelve months. Second, the results of the FIT trial were extrapolated to estimate the lifetime cost-effectiveness of adding an FMD to usual care, using the United Kingdom Prospective Diabetes Study Outcomes Model version 2.2 (UKPDS-OM2.2)(18). The main analysis was performed from a healthcare perspective. Analyses were conducted using STATA version 17 for Windows. Figures were created in GraphPad Prism version 9.0.1 for Windows.

Trial-based analysis

A cost-utility analysis combined health outcomes and costs of care provided during the twelve-month follow-up of the FIT trial to yield short term results, which were compared between the two study arms.

Quality-adjusted life-years

Data on participants' quality of life was gathered at baseline, and after three, six, nine and twelve months follow-up, using the EQ-5D-5L questionnaire(19). The Dutch EQ-5D-5L tariff was used to calculate utility values at each measurement(20). These were used to calculate quality-adjusted life-years (QALYs) for the study duration by calculating the area under the utility curves for each individual patient.

Costs

Costs were calculated based on questionnaires filled out by participants at three, six, nine, and twelve months follow-up (Cost questionnaire in Supplementary Material). The self-designed questionnaire pertained to usage of healthcare services related to type 2 diabetes. Medication use was gathered at baseline, six and twelve months. The costs of the FMD programme per participant were calculated by multiplying the costs per day with the number of days that the FMD was actually consumed by that participant. Healthcare usage was valued using Dutch reference unit prices from the Dutch manual for costing research and consumer market prices(21). All prices were converted to 2023 values using the Dutch national consumer price index(22). Additional information on cost calculations can be found in the Supplementary Material (Additional Methods and **Table S1**).

Statistical analysis

All analyses were conducted following an intention-to-treat principle. For missing data, multiple imputations were performed with a total of 100 imputed datasets (Additional Methods in Supplementary Material). The 100 datasets were analysed separately, and estimates for utilities and costs were pooled using Rubin's rules(23).

Bootstrapping with 1000 replications was used to estimate the statistical uncertainty surrounding the cost-effectiveness after adjusting the healthcare costs and QALYs for baseline values, using seemingly unrelated regression, which accounts for the correlation between costs and effects. Variables were taken into account as a confounder, if the estimated regression coefficient for the cost or effect differences changed by 10% or more(24). Bootstrapped differences in cost and effect were plotted on cost-effectiveness planes. Subsequently, the cost-effectiveness of using the FMD (in addition to usual care) was compared to usual care only following a net benefit (NB) approach(21). An intervention is considered cost-effective if the NB is higher for a given willingness to pay (WTP) threshold. The NB estimate per group was calculated by multiplying the adjusted difference in mean QALYs with WTP per QALY, and then subtracting the adjusted difference in mean cost between FMD compared to usual care. For each WTP value, the fraction of the bootstrap replications for which the NB of the FMD group was higher than the control group is shown in the cost-effectiveness

acceptability curve. This curve reflects the probability of the intervention being cost-effective over a range of threshold values for willingness to pay for a QALY. A range of WTP values from 0 to 80,000 euros per QALY was used. At the probability of 0.5, there is no preference for either of the treatments.

The main analysis was performed from a healthcare perspective, using healthcare costs only and the QALYs calculated from the EQ-5D-5L. Two additional sensitivity analyses were performed: using QALYs calculated from the EQ-VAS instead of the EQ-5D-5L [1] and adopting a societal perspective instead of a healthcare perspective [2]. To this end, scores of the EuroQol Visual Analogue Scale (EQ-VAS), which was administered together with the EQ-5D-5L, were rescaled to a range of 0-1 and used to calculate QALYs using the area-under-the-curve method. For the societal perspective (regarding the second sensitivity analysis), costs consisted of healthcare costs, food costs and costs of productivity loss due to absence from work. Since the FMD is a meal replacement programme, total costs of food for the entire year were assessed. Food costs were determined with the presumed market price from the National Institute of Budget Education in the Netherlands, taking household sizes into account (Additional Methods in Supplementary Material)(25). Costs of productivity loss were based on patient reports of absenteeism from paid and unpaid work at three, six, nine and twelve months follow-up. Costs of absenteeism of paid work were estimated with the friction cost method, using a friction period of 12 weeks, and hourly wages according to the Dutch manual for costing research(21, 26). Costs of absence of unpaid work were assessed by multiplying the number of hours of unpaid labour lost by the average gross hourly wage of a domestic worker(21).

Lifetime model-based analysis

For the lifetime cost-effectiveness analysis from a healthcare perspective, the United Kingdom Prospective Diabetes Study Outcomes Model version 2.2 (UKPDS-OM2.2) was used(18). This model was used to extrapolate outcomes for individual FIT trial participants from end of trial (twelve months) until death (hereafter called post-trial results). The UKPDS-OM2.2 is based on data from the UKPDS trial and its ten-year post-trial monitoring(27). It can be used to predict the occurrence of diabetes-related complications over a lifetime as well as life expectancy, and estimate healthcare costs and QALYs(18).

To simulate outcomes and estimate costs beyond the trial period, participant data influencing cardiovascular risk was entered from the end of study follow-up into the UKPDS-OM2.2. Variables included were age, duration of type 2 diabetes, glycated haemoglobin (HbA1c) and history of cardiovascular disease among others (Additional Methods in Supplementary Material). Missing data was imputed in the within-trial

analysis, and the 100 imputed datasets were used as input in the UKPDS-OM2.2 model. In UKPDS-OM2.2, risk factors can be updated yearly, using the build-in equations that estimate risk factor progression over the years(28). The mean utility based on the EQ-5D-5L from the end of follow-up of the FIT trial was entered into the model. Yearly treatment costs for type 2 diabetes and costs for complications were based on literature data (**Table S2**). Costs were discounted at 4.0% per annum, and QALYs at 1.5% per annum according to the Dutch guideline for economic evaluations(21) to account for the fact that people generally value future costs and effects less than current costs and effects. All prices were converted to 2023 values using the Dutch national consumer price index(22). When running the UKPDS-OM2.2 model, uncertainty was taken into account by running 1000 Monte Carlo loops to reduce first order uncertainty and 100 sets of parameter estimates to address second order uncertainty.

Within-trial results on healthcare costs and QALYs were added to the post-trial results on an individual participant level, resulting in lifetime estimations. Lifetime costs and QALYs for each combination of the 100 imputations and 100 parameter sets were analysed using seemingly unrelated regression adjusting for baseline values of risk factors in UKPDS-OM2.2 and Rubin's rules(23, 29). Variables were taken into account as a confounder, if the estimated regression coefficient for the cost or effect differences changed by 10% or more(24). Cost-effectiveness acceptability curves for values of the willingness to pay ranging from 0 to 80,000 euro per QALY were constructed by assessing the fraction of the 10,000 combinations of imputation and parameter sets for which the NB of the FMD group was higher than the control group.

Since there is no information on the long-term adherence and effects of following the FMD, two different scenarios in the post-trial analysis were used. In the base-case scenario participants stop using the FMD directly after the end of the trial and risk factor progression follows the build-in equations of the UKPDS-OM2.2 model. In the alternative scenario, FMD participants who were still adhering to the FMD at the end of follow-up continue to use the FMD programme until the end of life, but only 4 FMD cycles per year are used. The assumption was made that the change in weight, HbA1c and HDL-cholesterol observed in the FIT trial would similarly change in the same direction for one more year in these participants. These risk factors were chosen, since in the FIT trial a statistically significant difference between baseline and twelve months follow-up was found for these outcomes(15). After this one year onwards, the assumption was made that risk factors would follow the build-in equations of the UKPDS-OM2.2 model. For participants who were not adhering to the FMD at the end of follow-up after one year, risk factor progression follows the UKPDS-OM2.2 model directly from the end of the trial. As sensitivity analyses for both scenarios,

it was postulated that the price of the FMD programme is 50% lower due to frequent utilisation as an approved treatment. For a detailed description of the scenarios and sensitivity analyses, see Additional Methods in Supplementary Material.

Results

Trial-based results

Utilities and QALYs

In general, utilities measuring quality of life calculated from the EQ-5D-5L remained stable during the follow-up period of twelve months (**Figure 1**). Though unadjusted differences in QALYs were not statistically significant, QALYs were lower in the FMD group compared to the control group. QALYs for the total study duration calculated from the EQ-5D-5L using the area under the utility curves were 0.86 in the FMD group and 0.90 in the control group (unadjusted mean difference -0.04, 95% CI -0.10 to 0.03). Also, differences in QALYs at separate timepoints were not statistically significant (**Table S3**).

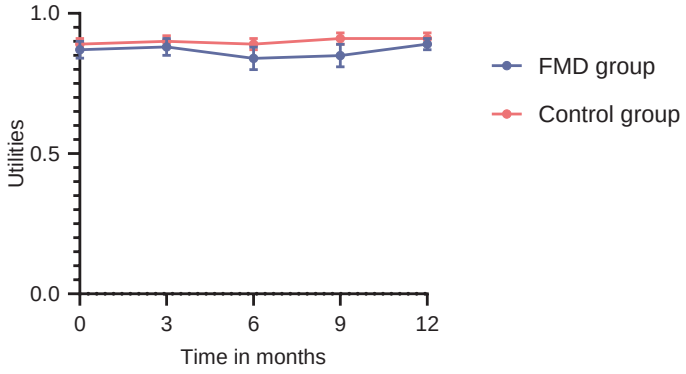

Figure 1. Utility curves over twelve months of follow-up calculated from the EQ-5D-5L.

Values are means ± SEM at baseline, 3 months, 6 months, 9 months and 12 months.
FMD = Fasting-mimicking diet. SEM = standard error of the mean.

Costs

The unadjusted total healthcare costs per patient in the FMD group were significantly higher compared to the control group (+€2241, 95% CI of +1821 to +2660; **Table 1**). This difference is mainly explained by the costs of the FMD programme (+€2043, 95% CI +1775 to +2311). The costs for visits to the nurse practitioner in general practice were also significantly higher in the FMD group compared to the control group (+€30, 95% CI +2 to +58). No other significant differences between groups were observed.

	Volume (%)		Mean costs in € (SE)		Difference	Confidence interval
	FMD	Control	FMD	Control		
Healthcare costs						
FMD	98	0	2043 (127)	0 (0)	2043	1775 to 2311
General practitioner	33	48	36 (11)	50 (13)	-14	-47 to 19
Nurse practitioner	94	87	94 (11)	63 (9)	30	2 to 58
Diabetes nurse	33	44	20 (5)	16 (4)	3.7	-10 to 17
Dietician	22	40	26 (9)	51 (12)	-25	-55 to 5
Physiotherapist	10	5	81 (41)	32 (26)	49	-51 to 149
Podiatrist	10	8	20 (12)	10 (6)	10	-17 to 37
Occupational physician	2	5	13 (13)	19 (15)	-6	-46 to 33
Outpatient visits	12	8	19 (9)	32 (23)	-13	-60 to 33
Other care providers	4	3	5 (4)	1 (1)	4	-4 to 12
Home care	4	0	112 (96)	0 (0)	112	-93 to 316
Medication	100	98	193 (46)	179 (34)	14	-102 to 131
Out of pocket healthcare costs	24	24	54 (23)	20 (8)	33	-17 to 84
Total healthcare costs			**2715 (187)**	**475 (73)**	**2241**	**1821 to 2660**
Non-healthcare costs						
Food costs	100	100	2150(44)	2493 (48)	-343	-473 to -214
Absence from paid work	2	4	47.2 (47)	486 (353)	-439	-1108 to 229
Absence from unpaid work	0	2	0 (0)	61 (61.0)	-61	-175 to 53
Total non-healthcare costs			**2197 (65)**	**3041 (393)**	**-844**	**-1591 to -97**
Societal costs			**4913 (200)**	**3515 (449)**	**1397**	**457 to 2337**

Table 1. Percentage of participants who have used resources and unadjusted average cost per participant for resource use during twelve-month follow-up (in 2023 euro).

FMD = Fasting-mimicking diet. SE = standard error.

Cost-effectiveness analysis

The uncertainty in the adjusted difference in costs and QALYs between both groups is shown in the cost-effectiveness plane (**Figure 2**). No relevant confounders for costs were found. QALYs were adjusted for age, white blood cell count, a history of stroke, a history of heart failure, and EQ-5D-5L at baseline. Since the majority of bootstrap replications fall in the north-west quadrant of the cost-effectiveness plane (**Figure 2**), indicating that following an FMD programme will cost more and result in an incremental QALY loss, it was not very likely that following an FMD programme was cost-effective compared to usual care in the within trial period. This is also illustrated in the cost-effectiveness acceptability curve (**Figure S1**).

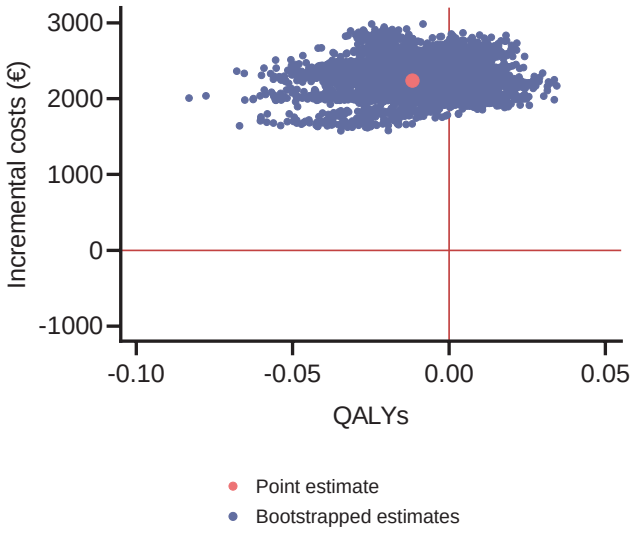

Figure 2. Cost-effectiveness plane of the healthcare costs in the trial-based analysis.

Incremental QALYs are based on the EQ-5D-5L. Point estimate: adjusted incremental QALYs -0.01, 95% CI -0.04 to 0.02; adjusted incremental costs €2241, 95% CI +1702 to +2552.
QALY = quality-adjusted life-years.

Sensitivity analyses

For the first sensitivity analysis, which was adjusted for the same confounders as the main analysis, QALYs were calculated from the EQ-VAS: 0.79 in the FMD group and 0.82 in the control group, with an adjusted mean difference of -0.02 (95% CI -0.05 to +0.01; **Figure S2**). The cost-effectiveness plane shows that it was not very likely that adding the FMD programme to usual care was cost-effective compared to usual care alone (**Figure S3a**).

For the second sensitivity analysis, the societal perspective was calculated which included healthcare costs, food costs and productivity costs due to absence from work. The (unadjusted) mean food costs were lower in the FMD group compared to the control group (-€343, 95% CI -473 to -214; **Table 1**). Moreover, the (unadjusted) total non-healthcare costs were lower in the FMD group compared to the control group (- €844 per patient, 95% CI -1591 to -97; **Table 1**). Combining the healthcare and the non-healthcare costs, the adjusted societal costs per patient were higher in the FMD group (+€1397, 95% CI -36 to +2100). Indeed, the majority of bootstrap replications fall in the north-west quadrant of the cost-effectiveness plane (**Figure S3b**), and the cost-effectiveness acceptability curve shows that it was not very likely that adding the FMD programme to usual care was cost-effective compared to usual care alone from a societal perspective either (**Figure S1**).

Lifetime model-based analysis

Base-case scenario

In the lifetime model-based analysis of the base-case scenario, in which participants do not continue following the FMD after the trial, both the adjusted QALYs and costs in the FMD group were non-significantly higher compared to the control group (respectively +0.16 and €1336; **Table 2**), resulting in an incremental cost-effectiveness ratio (ICER) of €8369/QALY. The probability of cost-effectiveness of the FMD programme was around 0.6 as compared to usual care at most WTP thresholds (**Figure 3**, **Figure S4**).

	ΔCost (CI)	ΔQALY (CI)	ΔCost/ΔQALY
Primary analyses			
Base-case scenario	1336 (-753 to 3425)	0.16 (-1.16 to 1.48)	8369
Alternative scenario	5619 (2332 to 8907)	0.45 (-0.89 to 1.81)	12230
Sensitivity analyses			
Base-case scenario with 50% price reduction of FMD programme	337 (-1737 to 2412)	0.16 (-1.16 to 1.48)	2102
Alternative scenario with 50% price reduction of FMD programme	2376 (307 to 4446)	0.47 (-0.97 to 1.91)	5050

Table 2. Lifetime results on difference in total costs and QALYs between FMD and usual care for the different scenarios and sensitivity analyses. Costs are in euros (2023).

Base-case scenario: Cost analysis was adjusted for the following confounders: age, history of stroke, history of myocardial infarction, and HDL at baseline. Analysis of the QALYs was adjusted for age, history of stroke, history of heart failure, history of myocardial infarction, and EQ-5D-5L, HbA1c, HDL, white blood cell count and eGFR at baseline.
Alternative scenario: Cost analysis was adjusted for the following confounders: age, history of stroke, and HDL at baseline. Analysis of the QALYs was adjusted for age, history of stroke, history of heart failure, history of myocardial infarction, and EQ-5D-5L, HbA1c, HDL, white blood cell count and eGFR at baseline.
Base-case scenario with 50% price reduction of FMD programme: Cost analysis was adjusted for the following confounders: age, history of stroke, history of myocardial infarction, and HDL at baseline. Analysis of the QALYs was adjusted for age, history of stroke, history of heart failure, history of myocardial infarction, and EQ-5D-5L, HbA1c, HDL, white blood cell count and eGFR at baseline.
Alternative scenario with 50% price reduction of FMD programme: Cost analysis was adjusted for the following confounders: age, history of stroke, history of myocardial infarction, and HDL at baseline. Analysis of the QALYs was adjusted for age, history of stroke, history of heart failure, history of myocardial infarction, and EQ-5D-5L, HbA1c, HDL, white blood cell count and eGFR at baseline.
CI = Confidence interval. QALY = quality-adjusted life-years.

Alternative scenario

In the alternative scenario, in which FMD participants who were adherent at twelve months continued to use the FMD programme for four cycles per year until the end of life, costs were significantly higher for following the FMD programme compared to usual care (+€5619), but QALYs were also higher (+0.45 QALY) though this was not statistically significant (**Table 2**). This gives an estimated ICER of €12,230/QALY. In this scenario, the probability of following the FMD programme being cost-effective is even more favourable (**Figure 3**, **Figure S4**).

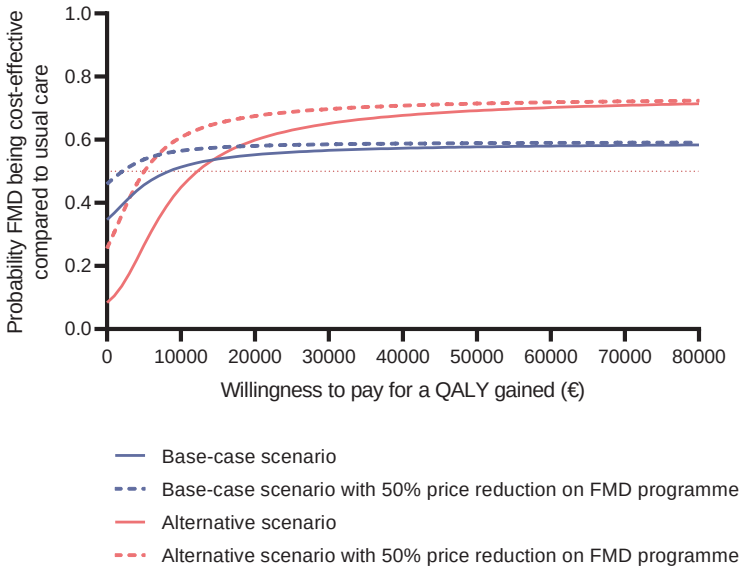

Figure 3. Cost-effectiveness acceptability curves based on the lifetime model-based analysis, showing how the probability that following the FMD programme is cost-effective compared with usual care varies with each willingness to pay threshold.

In the base-case scenario participants stop using the FMD directly after the end of the trial. In the alternative scenario, it was postulated that FMD participants who were adherent at twelve months continued to use the FMD programme for four cycles per year until the end of life. In the sensitivity analyses, it was postulated that the price of the FMD programme is 50% lower due to frequent utilisation as an approved treatment.

Sensitivity analyses

In the sensitivity analyses, it was postulated that the price of the FMD programme is 50% lower due to frequent utilisation as an approved treatment. When applied to the base-case scenario, costs remained non-significantly higher for following the FMD compared to usual care, with an estimated ICER of €2102/QALY (**Table 2**). The probability of the FMD programme being cost-effective increased compared to the base-case scenario (**Figure 3**, **Figure S4**). When applying 50% cost reduction of the FMD programme in the alternative scenario, costs remained higher for following the FMD programme compared to usual care, with an estimated ICER of €5050/QALY (**Table 2**). The probability of the FMD programme being cost-effective compared to usual care increased to about 0.7 at most WTP thresholds (**Figure 3**, **Figure S4**).

Discussion

Our trial-based cost-effectiveness analysis of the FIT trial, which evaluated the impact of periodic use of an FMD programme as an adjunct to usual care for patient with type 2 diabetes using lifestyle advice and/or metformin as the only glucose-lowering drug for glycaemic control, indicated that the intervention is not likely to be cost-effective within a year in this particular patient population. The lack of cost-effectiveness, despite clear clinical benefits(15), was largely because the costs of the FMD programme were not offset by lower costs of reduced medication in participants using the FMD, given the low costs of metformin. Furthermore, QALYs were slightly lower in the FMD group compared to the control group. The lack of cost-effectiveness should be interpreted with caution, given the small sample size and relatively short study duration. An additional analysis, incorporating societal consequences of distinct disease management, did not reveal short-term benefits from a societal perspective either. In contrast, similar analyses with a lifetime horizon, using the UKPDS-OM2.2 show that adding an FMD programme to usual care for patients with type 2 diabetes improves the probability of the intervention being cost-effective in the long run, even when applied in this relatively 'cheap' early-stage of disease. In the base-case as well as the alternative scenario, the likelihood of the intervention to be cost-effective compared to usual care was above 0.5-0.7 at all thresholds for willingness to pay per QALY in the Netherlands (between 20,000 and 80,000)(30). In addition, the sensitivity analyses showed that the probability of the intervention being cost-effective in the long term can be further improved by reducing the price of the FMD programme.

To our knowledge, this is the first study examining cost-effectiveness of an FMD programme in addition to usual care, compared to usual care alone in patients with type 2 diabetes treated in primary care. Like the FIT trial, two other trials also revealed benefits of an FMD programme in terms of glycated haemoglobin, fasting plasma glucose and bodyweight in patients with type 2 diabetes(31, 32). However, the cost-effectiveness of their FMD programme as compared to control was not reported. In general, there is not much known about the cost-effectiveness of dietary interventions in patients with type 2 diabetes. Intensive nutritional counselling by a dietitian has been found to be cost-effective compared with less intensive nutritional counselling(33-35). Furthermore, some low-calorie diet programmes were shown to be cost-effective in comparison with usual care(36, 37). Our study cannot be directly compared to these studies because of the heterogeneity of interventions and settings in which they were applied. Indeed, the context in which a medical intervention is used should always be taken into account when measuring its impact on clinical outcomes and costs of care. Although the present study suggests that an FMD programme as an adjunct to usual care is not cost-effective in its first year of application in 'early stage' patients with type 2 diabetes treated with

lifestyle advice and/or metformin as the only glucose-lowering drug, this conclusion should be interpreted with caution due to the small sample size. However, the cost-effectiveness estimates improve when long-term health effects are incorporated using the life-time extrapolations from the UKPDS-OM2.2.

It seems important to emphasize that the probability of cost-effectiveness of the FMD programme improves in the long run, even though we assumed that patients stopped using the diet immediately after the end of the trial in our base-case scenario. This finding may have to do with "metabolic memory" or the "legacy effect" of short term changes in glycaemic control on long term complications, which has been observed in various clinical trials in type 1-(38) and type 2 diabetes(27). The mechanism underlying this remarkable phenomenon remains to be fully explained, but epigenetic modifications brought about by various levels of glycemia are probably involved(39). Whatever the mechanism, short-term amelioration of hyperglycaemia may reduce diabetic complications in the long run, and thereby limit healthcare costs.

This cost-effectiveness study has several strengths and limitations. The UKPDS-OM2.2 model, including its build-in risk factor progression equations, is a reliable tool to simulate long term evolution of type 2 diabetes, which is frequently used to extrapolate trial outcomes to estimate associated costs of care(18, 27, 28). However, when extrapolating data, uncertainties have to be taken into account. The relatively short duration of follow-up may have prevented further benefits of longer-term use of the diet in terms of metabolic control, thereby potentially underestimating long term cost-effectiveness. For future research another trial with a larger sample size and longer study duration might help to analyse differences in QALYs. Additionally, a larger sample size would allow for subgroup analysis: results may differ between disease duration or age groups. In the FIT trial, the use of self-reported costs was the most practical approach, as it would not have been feasible to collect data from all healthcare facilities involved in regular patient care (e.g., general practice centres, hospitals, home care). Obtaining data directly from these facilities might have provided a more robust measure of healthcare costs. Furthermore, in theory, the cost-effectiveness of periodic cycles of an FMD could be further improved by using natural food of similar composition instead of a meal-replacement formula as in the FIT trial.

Regarding the generalizability, the results of our (and any other) cost-effectiveness analysis are applicable only in the context of the study: in primary care of patients with type 2 diabetes treated with lifestyle advice and/or metformin as the only glucose-lowering drug. Cost-effectiveness may be quite different in more advanced patients using far more expensive medication or in a hospital setting. Also, obviously, as

calculations were done using Dutch reference unit prices, the data are applicable to the Dutch healthcare system only.

Conclusions

An FMD programme in addition to usual primary care for patients with type 2 diabetes using lifestyle advice and/or metformin as the only glucose-lowering drug does not appear to be cost-effective over the first year of its application in the context of the Dutch healthcare system. However, this conclusion should be interpreted with caution due to the small sample size. In the extrapolations of 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.

Declarations

Ethics approval and consent to participate

The Fasting In diabetes Treatment (FIT) trial protocol and amendments were approved by the Medical Research Ethics Committee of the LUMC (identifiers NL63892.058.18 and P18.049). All study participants provided informed consent.

Availability of data and materials

The datasets generated during and/or analysed in the current study are available upon reasonable request. Requests should be sent to the FIT trial corresponding email (fit@lumc.nl). All proposals requesting data access will need to specify how the data will be used, and all proposals will need approval of the trial co-investigator team before data release.

Competing interests

HJL has received consulting fees from Royal Philips and was member of the board of trustees of the Society for Cardiovascular Magnetic Resonance and European Union of Medical Specialists Radiology section without payment. The remaining authors declare that they have no competing interests.

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Authors' contributions

ELvdB, PGvP, MPS, HJL, MEN, HP and MEvdA-vM contributed to the study protocol of the FIT trial. ELvdB and MPS conducted the trial. ELvdB, MPS, ACE and MEvdA-vM accessed and verified the data and performed the data analysis. ELvdB prepared the first draft of the manuscript. PGvP, HP and MEvdA-vM edited the manuscript. All authors reviewed the manuscript and had final responsibility for the decision to submit for publication. MEvdA-vM 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.

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QR-code to article and supplementary information

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