Effectiveness of the MyFertiCoach lifestyle app for subfertile couples: a single center study

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Abstract

Background: Many couples who undergo fertility treatment have multiple lifestyle risk factors that reduce their chances of becoming pregnant. The MyFertiCoach (MFC) app was developed as an integrated lifestyle program with modules on healthy weight, nutrition and exercise, and quitting smoking, alcohol, drugs, and reduction of stress. We hypothesized an improvement in lifestyle.

Objective: The primary outcome is the change in Total Risk Score (TRS) at three- and six-months follow-up. The TRS per individual is defined as the sum of all risk scores per behavior (i.e., based on vegetable/fruit/folic acid intake, smoking, and alcohol use after three and six months). The higher the TRS, the unhealthier the nutrition and lifestyle habits that are present, and the lower the chance of pregnancy. The secondary endpoints are changes in BMI, activity score, preconception dietary risks (PDR) score, Distress-score (e.g., burden), smoking habits, alcohol intake, and program adherence.

Methods: This was a retrospective, observational, single-center study including patients between the 1st of January 2022 and the 31st of December 2023. We invited subfertile female patients, and their partner, aged 18-43 with a referral to a gynecologist to follow the online lifestyle coaching via the MFC app. Relevant lifestyle modules were chosen by the gynaecologist using the results of the integrated screening questionnaires. We used (hierarchical) linear mixed-models (LMMs) to estimate the change in outcomes. Where the pattern of missing data was MNAR (missing not at random), we deployed joint modelling. Statistical significance was set at p?0.05 considering methods to retain the same false-positive rate.

Results: A total of 1805 patients received an invitation to participate in this study, of which on average 737 (40.8%) filled out a screenings questionnaire at baseline. For the TRS score, we included 798 (44.2%) patients at baseline, of which 517 (64.8%) patients included their partner. An average of 282 patients (37.9%) sent in at least one follow-up questionnaire. Patients rated the app above average (N=137, median=7 on a 1-10 scale) at days 7 and 14. The TRS scored decreased 1.5 points (P<.001) on average at T3 and T6 compared to baseline, which is clinically relevant. All secondary outcomes changed significantly (statistically) in a positive direction for patients who used a relevant lifestyle module. Most of the gains were achieved at three months yet remained statistically significant at six months (except for alcohol). These findings are similar across LMMs and joint models.

Conclusions: Our results show the immediate benefit of a m-health application for women wanting to become pregnant. However, to maintain and even improve these results there is a need to further tailor the patient-specific programs.

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Keywords: fertility, m-health, pregnancy, lifestyle, application

Abstract

Background: Many couples who undergo fertility treatment have multiple lifestyle risk factors that reduce their chances of becoming pregnant. The MyFertiCoach (MFC) app was developed as an integrated lifestyle program with modules on healthy weight, nutrition and exercise, and quitting smoking, alcohol, drugs, and reduction of stress. We hypothesized an improvement in lifestyle. **Objective:** The primary outcome is the change in Total Risk Score (TRS) at three- and six-months follow-up. The TRS per individual is defined as the sum of all risk scores per behavior (i.e., based on vegetable/fruit/folic acid intake, smoking, and alcohol use after three and six months). The higher the TRS, the unhealthier the nutrition and lifestyle habits that are present, and the lower the chance of pregnancy. The secondary endpoints are changes in BMI, activity score, preconception dietary risks (PDR) score, Distress-score (e.g., burden), smoking habits, alcohol intake, and program adherence. **Methods:** This was a retrospective, observational, single-center study including patients between the 1st of January 2022 and the 31st of December 2023. We invited subfertile female patients, and their partner, aged 18-43 with a referral to a gynecologist to follow the online lifestyle coaching via the MFC app. Relevant lifestyle modules were chosen by the gynaecologist using the results of the integrated screening questionnaires. We used (hierarchical) linear mixed-models (LMMs) to estimate the change in outcomes. Where the pattern of missing data was MNAR (missing not at random), we deployed joint modelling. Statistical significance was set at $p \leq 0.05$ considering methods to retain the same false-positive rate. **Results:** A total of 1805 patients received an invitation to participate in this study, of which on average 737 (40.8%) filled out a screenings questionnaire at baseline. For the TRS score, we included 798 (44.2%) patients at baseline, of which 517 (64.8%) patients included their partner. An average of 282 patients (37.9%)

sent in at least one follow-up questionnaire. Patients rated the app above average (N=137, median=7 on a 1-10 scale) at days 7 and 14. The TRS scored decreased 1.5 points (*P<.001*) on average at T3 and T6 compared to baseline, which is clinically relevant. All secondary outcomes changed significantly (statistically) in a positive direction for patients who used a relevant lifestyle module. Most of the gains were achieved at three months yet remained statistically significant at six months (except for alcohol). These findings are similar across LMMs and joint models. **Conclusions:** Our results show the immediate benefit of a m-health application for women wanting to become pregnant. However, to maintain and even improve these results there is a need to further tailor the patient-specific programs.

Introduction

Many couples who undergo fertility treatment have multiple lifestyle risk factors, like obesity, unbalanced nutritional habits and smoking, that reduce their chances of becoming pregnant[1] [2-4]. Hence, reducing any or all these lifestyle factors prior to pregnancy, or assisted reproductive technology treatment, contributes to the improvement of their reproductive health[5-9]. In summary, the more negative lifestyle factors, the less chance of becoming pregnant and the longer the time until pregnancy[10].

For instance, by improving dietary patterns during the preconception period the risk of several adverse birth outcomes decrease, such as fetal growth restriction and babies born small or large for gestational age. Maternal complications, like gestational diabetes, hypertensive disorders and premature delivery, seem to decrease as well[11, 12].

Moreover, cognitive behavior therapy and psychological support during fertility treatment is suggested to lead to significantly more viable pregnancies versus routine care[13-15].

While the evidence on the importance of improving and maintaining a healthy lifestyle is abundantly clear, our habits and behaviors are difficult to change [16]. Health-compromising behaviors are hard to stop, and health-promoting behaviors are challenging to adopt, making a behavior change particularly challenging. Since healthcare budgets are increasingly under pressure due to non-communicable diseases associated with an aging population, scarcity in the workforce, and rising costs of novel medical technologies, it is key that lifestyle interventions are cost-effective, for instance by use of online programs and apps[17].

Several lifestyle intervention programs for women actively seeking medical support in achieving pregnancy showed high attrition and small effects[18]. However,
mobile health applications have the potential to overcome these obstacles by providing individual, tailored, and repeated information [19, 20]. Indeed, evidence is accumulating that mobile technology can effectively improve inadequate nutrition, lifestyle, and medication adherence[21, 22].

There are many lifestyle apps currently available on the market, but only a very few are specific for couples wishing to have children. To provide guidance for both the patients and healthcare provides, we developed the MyFertiCoach (MFC) app which is a 6-months integrated lifestyle program with modules on healthy weight, nutrition and exercise and quitting smoking, alcohol, drugs and stress.

MFC offers support in modifying unhealthy dietary and lifestyle habits of couples wishing to have children and pregnant women. The healthcare provider can use MFC to help patients improve his/her lifestyle. Based on demographic parameters and the questioning of nutrition and lifestyle habits, a screening takes place and a personal coaching program, consisting of lifestyle modules, is prepared. Interactive elements, visual support and motivational interviewing will be used as much as possible, and at various times during the program, we will measure whether the lifestyle of the

different domains has improved.

This prospective, observational, single center study will be the first time to assess changes in lifestyle habits by using the MFC app.

Methods

This is a prospective, single center study performed at the Elisabeth TweeSteden hospital in Tilburg, The Netherlands. The use of the app was found to be GDPR compliant. The study design was checked by the medical ethical commission. The retrospective nature and the fact that patients gave their consent for the use of anonymous data did not necessitate further actions.

The MyFertiCoach (MFC) app

The MFC app is a coaching program that focuses specifically on lifestyle change developed by Ferring Pharmaceuticals B.V. in combination with a multidisciplinary team of healthcare professionals, and advice from patients' association Freya and patients who participated in the test phase.

The healthcare provider can support the patient and any partner while actively monitoring the (pre) active treatment phase. While patient and possible partner are motivated within the domains that are important to them, the changes and results are visualized in the dashboard. Data that is important for the next steps in the treatment and can also be used for evaluations and scientific research.

The MFC app focuses for 6 months on lifestyle change through motivation (use of motivational interviewing techniques), information (on the different domains), and relaxation (by introducing game elements in the application). The focus is on seven domains: healthy weight,

healthy diet, healthy exercise, stopping smoking, stopping alcohol, quitting drugs/anabolic steroids, and stress reduction with mindfulness. These domains were determined by the study group, and based on literature that shows which domains influence the likelihood of a healthy pregnancy.

During the registration process, baseline demographic parameters and questionnaires about dietary and lifestyle habits are completed to screen patients on various parameters including BMI (Body Mass Index), smoking, nutrition, alcohol use and stress will provide insights into the habits of the patients. This is to determine which domains deserve attention / intervention, and these are then presented in order of importance to the patient. To assess a patients' knowledge, skills and confidence in being able to manage one's own health or illness, both patient and partner are asked to fill out the Patient Activation Measure (PAM)[23] questionnaire. This will provide HCPs with more insights into how and to what extent patients themselves believe they can improve their health, so that the method of motivational interviewing and the level of coaching can be adjusted accordingly.

At the first consultation, based on the outcomes of the screening, the HCP will decide with the patient on which aspects of their lifestyle to work on and will activate the relevant modules: healthy weight, healthy eating, healthy activity, stop smoking, stop alcohol, stop drug and stress reduction with mindfulness. Once the modules are activated, the patient receives module specific questionnaires and general patient reported outcome measures (PROM) monthly. Patients are free to complete the questionnaire at their earliest convenience but need to provide a baseline screening measure to be included in the study. The program length is set at six months.

Using the diary page, each patient has access to all functionalities which allow them to record their mood per day and receive motivating messages. They can also send messages to their HCP asking questions (e.g., about nutrition or other lifestyle factors). The HCP is free to react when possible. Progress for each patient is made visible to the HCP via the MFC platform using domain-specific visualizations. Patients can track their progress using the app.

Recruitment and data collection

All women that come to the fertility clinic were signed up for the MFC app, after providing written consent and prior to their first appointment with the HCP. Data extraction took place on February 1ste, 2024 and included all patients from January 1st, 2022, until December 31st, 2023 that completed the screening and had at least one activated module. Patient ID's were coded using the MFC ID number, so no direct association could made to patient information. In case the healthcare provider required the patients ID, he or she could request this at 23G, the company that stores and coded the data. Patients received a push notification and an e-mail 1 month after the previous questionnaire. Those patients that did not provide a baseline score for and at least a single follow-up score for an outcome score (regardless of time) were excluded from further analysis of that particular outcome.

Outcomes

To properly evaluate the MFC app, several outcome measures have been defined to evaluate the effectiveness of our lifestyle programThe primary outcome is the change in Total Risk Score (TRS) [10] at three- and six-months follow-up. Secondary endpoints are changes in BMI, activity score, Preconception Dietary Risk Score (PDR) [24], Distress score[25], smoking habits, alcohol intake, and program adherence.

Total Risk Score

The TRS is based on the Rotterdam Reproduction Risk score (R3 score), the PDR score and other existing evidence of associations with reproductive and pregnancy outcome. The TRS per individual

is defined as the sum of all risk scores per behaviour (i.e., based on vegetable/fruit/folic acid intake, smoking, and alcohol use after three and six months)[10].

Vegetable and fruit intake were both subdivided into a risk score of 0, 1, 2 or 3, in which 0 represents an adequate daily intake (≥200 g per day and ≥2 pieces per day, respectively). Score 1 and 2 both represent a 'nearly adequate' intake (vegetable intake of 150 to <200g and a fruit intake of 1.5 to <2 pieces per day), considering the presence (score 1) or absence (score 2) of the intention of the participant to change this risk factor. Score 3 represents an inadequate daily intake (vegetable intake <150g and a fruit intake of <1.5 pieces). If a participant had a score of 1 or 2, an additional question regarding their intrinsic motivation was asked to determine where [participants had the intention to improve their behavior regarding this risk factor.

Folic acid supplement use was considered adequate (score 0) or inadequate (score 3) if a participant did or did not meet the recommendations of using a folic acid supplement of 400 g daily during the periconceptional period. There is no evidence or recommendation for folic acid supplement use after 12 weeks of pregnancy. Therefore, pregnant women that passed the first 12 weeks of pregnancy received score 0 for folic acid supplement use.

Risk scores about smoking and alcohol consumption were based on the average daily use: no smoking (score 0), smoking 1–5 (score 1), 6–14 (score 3) or ≥15 (score 6) cigarettes and no drinking (score 0), drinking <1 (score 1), 1-2 (score 2) or ≥2 (score 3) alcoholic beverages (glasses) per day. An important distinction to make is that the TRS are calculated separately for females and their partners (male/female).

The higher the TRS, the unhealthier the nutrition and lifestyle habits that are present, and the lower the chance of becoming pregnant [10]. Considering previous results, in which a 1-point increase in TRS decreases the chance of becoming pregnant by 21%, we considered a 1-point drop in TRS clinically relevant.

Other scores

We considered a BMI (which is weight divided by length squared) between 18,5 and 25 to represent a ‘normal’ weight[26]. A BMI ≥ 29 is associated with a lower chance of getting pregnant, and every increase above 29 is associated with a 4% drop in fertility[2]. As such, we considered a 1-point drop in the high BMI group clinically relevant.

To determine the activity score, we followed the Dutch physical activity guidelines which stated that adults need to be physically active for at least 30 minutes a day for at least five days a week. They can meet this target by playing sports, walking, cycling or doing strenuous household chores. To compute a score, we devised two sets of three questions: the first set is about the number of active minutes (i.e., 75, 75 to 150 and ≥ 150 minutes), and the second set is about the amount of muscle-and bone enhancing activities (i.e., never, once a week, or at least twice a week). As the scores go from one to three, the sum of possibilities can reach two – six.

The level of distress was measured using the Distress score, which is designed to get a general impression of the problems couples experience in five different areas: practical problems, family/social problems, emotional problems, religious/spiritual problems and physical problems[27]. Couples are also asked, separately, to grade the level of distress they experience using a ‘Thermometer’ which ranges from 0 to 10. The physician can then explore with the couple where the greatest concerns lie and what options are available to address or reduce any symptoms or concerns as much as possible. If the patient scores a 5 or higher on the thermometer, a serious "burden" is present. We only used the thermometer in our analysis.

The PDR score was based on six nutritional questions designed to cover the intakes of the main food groups, based on the dietary recommendations of the Netherlands Nutrition Centre. The

current guidelines state that a person should eat at least four slices of whole wheat bread daily (or comparable servings of cereals), use monounsaturated or polyunsaturated oils, and consume ≥200 g of vegetables daily, ≥2 pieces of fruit daily, ≥3 servings of meat or meat replacers weekly and ≥1 servings of fish weekly. For each recommendation that was met, the patient received a single point. Thus, the maximum PDR score was six and represented highly adequate nutrition according to recommendations of the Netherlands Nutrition Centre.

The smoking and alcohol score followed the number of cigarettes or alcoholic beverages consumed per day. Adherence was measured by the number of active patients over time.

Statistical Analysis

Descriptives and transformations

We used descriptive statistics (descriptives) for each of the outcomes of interest: the number of patients, the number of observations, the mean and 95% confidence interval. For each outcome, we also calculated the number and percentage of response per time-point as well as the mean and standard deviation of the response time. Some outcomes are known composites of aggregated parameters (e.g., BMI) whilst others are transformations based on the specific manual of the questionnaire. We followed each manual on how to deal with missing data when transforming/aggregating the specific items of the questionnaire.

Missing data

There is no official cut-off on what constitutes an acceptable or non-acceptable level of missingness. In addition, it is seldom clear why the data is missing, except for when someone has died. Hence, we conducted a missing pattern analysis to collect for each parameter separately the amount of

missing and ascertain how often multiple parameters are missing together. We will look for missing patterns across all items in the dataset and try to classify them in three accepted types of missing data patterns: missing completely at random (MCAR), missing at random (MAR) or missing not at random (MNAR)[28]. Of the three possible patterns, the MNAR is the most problematic[29, 30], because the missingness in MNAR is missing for a reason, which has to do with the actual score someone could have provided but did not.

Power

Since this study was exploratory in nature, we did not conduct a formal power analysis to estimate numbers needed to achieve a particular effect size and level of statistical significance. Statistical significance is an estimate which does not contain a zero in its 95% confidence interval.

Statistical models used

The main objective of the study is to investigate the effect of following the MFC app program on the change in Total Risk Score (TRS) after three and six months. We analysed the secondary outcomes (i.e., BMI, activity score, PDR score, Distress score, smoking habits, alcohol intake) like the primary outcome, except for program adherence which can be depicted using descriptives.

To estimate change, we focused in our primary analysis on those patients for which the intended module was made available. As a result, we used the following combinations: Activity score for users of the activity module; Alcohol score for users of the alcohol module; BMI scores for users of the weight module; Last scores for users of the mindfulness module; PDR for users of the nutrition module, and smoking for users of the smoking module. TRS scores were analysed for all responders that participated in the study.

Using a maximum of seven measurements per patient (one baseline measurement and six follow-up measurement), and in the absence of a clinically relevant cut-off-value, we estimated the change in TRS using a (hierarchical) linear mixed-model (LMM)[31]. Linear mixed models are regression models that are designed to analyse clustered (longitudinal) data and can deal with MCAR and MAR[32] data.

An important note to make is that we will not conduct separate analyses for three and six months. We will build a single model from which the statistical significance of change can be derived at any moment in time until the last time observed. Hence, we built several LMMs with either a random intercept, random slope or random intercept and random slope[33].

Model selection

The primary explanatory factors to include in the models are time, partner, age, active number of modules, and the specific module connected to an outcome (e.g., the nutrition module for PDR). To properly include time we will use linear, polynomial, or natural cubic splines[34].

To assess the appropriateness of these inclusions, we will consecutively drop parameters from a fully specified fixed-effects model using the Chi-squared test. This means including both main effects and interaction effects. Assessment of each model for accuracy and parsimony will be done using the F-test (ANOVA) and the Aikaki Information Criterion (AIC – lower is better). Model assumptions will be tested by use of graphs and visualizations. An important note to make is that we will not conduct separate analyses for three and six months. We will build a single model from which the statistical significance of change can be derived at any moment in time until the last time observed.

The above stated analysis of the primary and secondary outcome(s) will lead to several different models. This raises issues in terms of spurious results, as all have the same 5% false-

positive included when determining statistical significance. To safeguard against spurious results, it is important to assess if the seven outcomes are correlated at any given time-point. Therefore, we will first create a correlation matrix using a Spearman rank correlation (since many outcomes are ordinal in nature). If correlations are found to be consistently higher than 0.50 between outcomes and across time, we will include correlated outcomes as predictors in the original LMM models. For instance, if there is a correlation between Distress and BMI, the outcome model of Distress will now not only include time, but also the secondary outcome BMI as a predictor.

Multiple imputation in case of MNAR

Although it could very well be that patients show intermittent missingness (which is most likely the case in a MAR situation and thus tackled by use of a MAR model or multiple imputation model), a sudden stop (i.e., monotone missingness or drop-out) is a strong indication for a MNAR response. Which is problematic for our analysis if it happens before three- or six-months follow-up. Hence, we will create a joint model, which is a combination of a LMM and a survival model[35, 36] which is accepted as a viable replacement of older models such as pattern-mixture modelling[37]. One of the authors has used this method successfully in the past when analysing Quality-of-Life changes in a population of palliative pancreas patients[38]. The end-result of a joint model is (1) a survival model on program adherence, which lends information from the LMM model, and (2) the LMM model which adjusts its estimates based on the survival model. For each joint model, we used the Markov Chain Monte-Carlo using 4 chains, and 100 thousand iterations of which ten thousand were used as a burn-in. Each model was assessed for fit using trace and density plots.

Statistical package used

All analyses were performed using R Statistical Software (v4.1.2; R Core Team 2021) which is a widely known and accepted software program. For the LMM, we used the *lme4* package. For the joint models, the *JMbayes2* was used in conjunction with the *nlme* package for building the LMM part of the joint model. The *survival* package was used for building the Cox Proportional Hazards part of the joint model.

Results

Patient characteristics

Table 1 shows the response during the study period, and the response time which differs per questionnaire (Figure S4) and across time (Figure S2). In total, we invited 1815 patients to participate, of which 818 (45%) responded. The mean age of those invited was 34.1 (5.46). A split between those who did and did not respond revealed similar age distributions: 33 (5.03) vs. 35.1 (5.63) (Figure S1).

Of the 818 patients who accepted, 532 (65%) also included a partner. The ratio partner/no partner was different compared to those who did not accept the invitation (65% / 35% vs 33% / 67% - X^2 =190.81, p <0.0001).

When we split the age distribution by presence of a partner the results remained the same: 34 (4.59) vs 35.6 (6.02) for those not included who did or did not have a partner, and 32.1(4.22) vs 34.7(4.22) for those included.

In the end, we included data on 798 patients (43.9%) who had a mean age of 33 (5.04) years and of whom 517 (64.7%) included their partner. Of the 784 (98.2%) patients who presented their

education history, the majority (54%) had higher professional or university degree. The higher the education, the higher the percentage of follow-up (Figure S5).

MFC programs and grading by patients

Patients had a diverse range of personal programs: 693 patients included a nutrition module, compared to 130 who included a smoking module. In total, we included 113 patients with one active module, 271 patients with two active modules, and 289 with three active modules. Four, five and six active modules were attached to 89, 33 and three patients respectively. When asked to grade the MFC app on the seventh and fourteenth day of using the app (Figure S6), 115 and 68 patients, respectively, give a median score of 7 (interquartile range = 3).

Patient response and response time

The percentage of patients who had both a baseline score and at least one single follow-up score (Figure S11) ranged from 84 patients (11%) for the Distress score to 579 patients (76.1%) for the smoking score (regardless of module included). Across questionnaires, we received an average follow-up response of 37.9% (or 282 out of 737 patients). When compared to patients who did not return a follow-up questionnaire (Figures S13, S14, and S16) those who did differed in their median baseline scores for BMI (29.4 vs 24.3), exercise (3 vs 5), last (6 vs 2), and alcohol (2 vs 0.1). The median scores for TRS (3), PDR (4) and smoking (0) did not differ by follow-up. The percentage follow-up did not significantly differ between those who did and those who did not include a partner (Figure S8). When we included the number of active modules, the graphs showed a somewhat different pattern (Figures S7, S8 and S10), but the cells became too sparse for any additional statistical analysis.

At baseline, the percentage of response ranged from 41.8% to 43.6% regardless of active module, and from 91.5% to 99% per active module. These percentages dropped with each time-point until they reached between 8.5% for the smoking module and 2.4% for the alcohol module at the last time-point (Figure S15). The average response time did not coincide with the envisioned response time. Although all patients filled out their questionnaire at the baseline date, the average response time for the first follow-up point regardless of module included ranged between 20 days (smoking score) and 65.7 days (Distress score). When only including patients with active modules, the response time changed to 16.4 and 66.4 days for the smoking and Distress score, respectively. As time progressed, the differences between the actual response time and the envisioned response time increased. At the fifth time-point, which is on average at five months follow-up, the response time (regardless of active module) ranged from 220 days for the Distress score to 114 days for the smoking score. The longest response time was for the BMI as it took on average 226 days to send in a response for the six-month follow-up.

Sensitivity analyses

Although secondary outcomes did show correlations per time-point, none were consequently higher than 0.5 (Figures S24 and S25). Hence, we did not use any of the secondary outcomes to explain each other.

When we created new time categories which are more in line of the envisioned return of questionnaires (e.g., T3 is defined as 90 days +- 14 days, T6 as 180 days +- 14 days) we significantly decreased our effective sample size (Figure S3) but did not significantly change the distribution of values across the outcomes (S14). Hence, we used the analysis of the Tx categories for our LMM models (main analysis), whilst using the actual time until the questionnaire was returned for our

joint models in which we also include our missing data.

Missing data pattern analysis

The missing data pattern analysis revealed a monotone pattern (Figures S31-S36) which means that once a patient stops sending back a questionnaire, the patient drops out altogether. This is an example of a potential MNAR pattern. Hence, we successfully fitted joint models for TRS (Figure S19), activity (Figure S26), alcohol intake (Figure (S27), BMI (Figure S29), PDR(Figure S30), and smoking habits (Figure S29). These results coming from the joint-model are in line with the outcomes of the LMM models, but somewhat less easy to interpret because of the splines included. We therefore reported the output of the LLM models which followed the original questionnaire sampling better. A joint model for Distress would not converge. In summary, the MNAR analysis via joint modelling did not warrant additional analysis.

Results for the primary and secondary outcomes

The model selection results (Figures S17 – S23) shows 14 models for alcohol intake, BMI, activity, and the Distress score. For PDR and smoking habits, we created 15 models whilst for TRS we included 13 different models. In almost all selection procedures, the AIC was lowest for a model including a main effect of time (as a dummy variable), partner, age, and number of active modules.

Figure 1 and Table 2 shows the results for the primary and secondary outcomes at baseline, three- and six-month follow-up. The number of patients and observations included ranged from 424 patients (and 1040 observations) for the TRS score to 83 patients (and 272 observations) for the Distress score. For all outcomes, the change in score compared to baseline was statistically significant at three months at the 5% level, and deemed positive (e.g., BMI was lower, smoking was

lower, nutrition was better). These changes remained statistically significant compared to baseline at six months, except for alcohol and the level of distress. For alcohol, part of the initial positive response (Δ -2.79) disappeared at six months (Δ -1.16). For distress, differences changed from a statistically significant change (Δ-1.69) to a positive trend (Δ -1.62). BMI was the only outcome that kept improving for six months (30.1 vs 29.6 vs 29.1). For the TRS score, the changes were also clinically relevant at three and six months. For BMI, this was only the case at six months.

When we split the longitudinal analysis by presence of a partner (Figure 1 and Table 3), we maintained statistical significance at three months, except for BMI which was no longer significant in the group including a partner (30.4 vs 30.2 vs 29.9). However, the group with no partner showed an even great decrease in BMI (29.8 vs 29.1 vs 28. 4). Regardless of partner, the change remained non-significant for alcohol intake.

When we split the analysis per partner and time-point (Table 4), we received lower scores for alcohol (Δ-2.2; *P<.001*) and higher for PDR (Δ.256; *P = .028*) in patients who did include their partner. These were both main effects. For BMI, however, we estimated an interaction effect showing a stronger decline in BMI at six months (Δ-1.555; *P = .043*) in those patients who did not include their partner.

Discussion

Principal Results

Our findings show that the introduction of a lifestyle app can immediately improve several lifestyle factors associated with subfertility and the success for fertility treatment. Our findings, via assessment of the TRS score, show that use of the app leads to a clinically relevant improvement. The peak of the intervention seems to be in the third month after which improvements made did

not further increase, except for BMI which was considered clinically relevant at six months.

The MFC app was designed using input from both patient and health-care professionals so it would offer a good starting-point in those life-style domains deemed useful. As such, the MFC app was aimed to be more than just a digital summary of sub-optimal lifestyle behavior. Via shared decision making, both patient and HCP contributed to a final selection of active modules which made it part of the larger treatment plan. Hence, from a preventive medicine point of view, the app contributed to a good start and efficient care as it is an inexpensive way to attempt to influence lifestyle. This can also be seen in the data, where most of the effects follow immediately.

However, it seems that not everyone is keen to start an intervention (of this type). Although we cannot say for certain why someone did not participate, we did find lower levels of participation in those at a lower level of education, and with no partner. It is unclear if the partner played a significant role in the acceptance process of this study, but if better follow-up led to a more desired effect of the app, partner participation often did not contribute to its effectiveness.

On an individual basis, it remains unclear what it was that made patients stop (or not even start) using the app, but one plausible explanation would be that parts of the group could not identify with the app even after extensive screening and discussion. Another plausible explanation is that the design and handling of the app did not appeal to everyone, but we do not have any data on this.

In summary, we do believe that MFC app is a cost-effectiveness addition to a larger treatment plan helping sub-fertile women and their partners tackle necessary lifestyle changes. Financial costs are low, and there is little time-investment required from the HCP. This means that although the app only seems to attract the attention of a particular group (high-education, partner included) for a longer period, the app does change important lifestyle factors.

Limitations

Related to the nature of our study design, we were unable to account for all known and unknown confounders. Despite conducting several sensitivity analyses, we cannot rule out that temporal differences (not) found between patients, and those who did include their partner, are related to things other than patient characteristics or the app itself. Then there is the pattern of missingness which cannot be formally assessed in a quantitative manner meaning that we do not know why patients dropped out when they did. We also did not include a formal comparative group, which means that we do not how the outcomes would develop in a group that did not receive guidance through the app.

Many things remain unclear. For instance, we do not know why patients dropped out, nor do we have full transparency on the exact selection process. Although modules were chosen based on shared decision making, it remains unclear if the actual choice was made based on motivation alone. This does not mean that any lack of improvement is due to a lack of motivation or sub-optimal care. It could very well be the case that the interventions by themselves did not support the patient sufficiently in improving sub-optimal lifestyle factors.

Comparison with Prior Work

In the Netherlands, there are two other groups that are busy developing apps to support treatment: the international LIFESTYLE study in which the Medical University of Groningen participates [6, 7, 39], and the Smarter Pregnancy platform at Erasmus Medical Center [40]. However, these are mostly hands-on interventions making them financially expensive and time intensive, but with better and more stable responses. Therefore, it seems that to ensure that patients stay motivated a

similar investment must be expected from the health-care professionals.

Lifestyle changes are notoriously difficult to achieve and maintain. Eating, drinking and smoking are all habits which provide immediate gratification, and only long-term side effects. Psychological stressors are also difficult to change and heavily dependent on the type of stressor: losing a loved one, for instance, is different than having persistent money problems. As such, our results of immediate but not long-lasting change mirror what has been extensively documented before.

Patients, in general, differed quite a bit in their personal trajectory which made us observe patients who did very well, those who improved marginally, and those who showed no benefit at all but nevertheless tried to. Analyzing heterogenous data often leads to marginal main effects which, even after reaching statistical significance, are considered sub-optimal clinical change. Any effort to include interactions between factors such as partner, number of active modules, and age did nothing to obtain a more clear view on why some patients did well whilst other did not.

However, the goal of the app and the setting of our research make our drop-out levels not surprising considering that we tried to reach lifestyle changes in an environment of largely working-class people with limited health-literacy. This does not mean that these patients cannot be helped, or do not wish to be treated, but it does mean that extra efforts need to be made if long-lasting change is the goal. As such, the evaluation of any m-health app should not only be accompanied by questionnaires, but also assessed via in-depth follow-up interviews which we will conduct in future stages of development.

Conclusions

Our results show an immediate and clinically relevant benefit of a m-health application for women

wanting to become pregnant.

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Conflicts of Interest

ES works at Ferring B.V. The rest of the author declare no conflict of interest.

Abbreviations

BMI	=	Body Mass Index
HCP	=	Healthcare professional
MFC	=	MyFertiCoach
AIC	=	Akaike Information Criterion
TRS	=	Total Risk Score
PDR	=	Preconception Dietary Risks Score
PAM	=	Patient Activation Measure
MAR	=	Missing at Random
MCAR	=	Missing Completely at Random
MNAR	=	Missing not at Random
LMM	=	Linear Mixed Model

PROM = Patient Reported Outcome Measure

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Table. 1 Number and percentage of responses, and the mean and standard deviation of the response time

Questionnaire		Measurement moments							
		Screening	T0	T1	T2	T3	T4	T5	T6
TRS		1815 (100%)	546 (30.1%)	270 (14.9%)	148 (8.2%)	91 (5%)	50 (2.8%)	36 (2.0%)	21 (1.2%)
Activity	regardless of active module	1815 (100%)	758 (41.8%)	235 (12.9%)	139 (7.7%)	85 (4.7%)	50 (2.8%)	34 (1.9%)	20 (1.1%)
			0 (0)	55.6 (40.9)	89.6 (25.1)	120.6 (23.5)	154.1 (26.3)	186.3 (24.0)	220.3 (27.8)
	only active module exercise	444 (100%)	438 (99%)	233 (52.5%)	138 (31.1%)	85 (19.1%)	50 (11.2%)	34 (7.6%)	20 (4.5%)
			0 (0)	55.8 (41.0)	89.7 (25.1)	120.6 (23.5)	154.1 (26.3)	186.3 (24.0)	220.6 (27.8)
Alcohol	regardless of active module	1815 (100%)	761 (41.9%)	210 (11.6%)	113 (6.2%)	61 (3.4%)	38 (2.1%)	23 (1.3%)	7 (0.4%)
			0 (0)	34.4 (23.7)	62.0 (24.0)	92.2 (26.2)	130.9 (31.9)	158.6 (31.2)	196.3 (45.6)
	only active module alcohol	209 (100%)	199 (95.2%)	95 (45.5%)	42 (20.1%)	26 (12.4%)	14 (6.7%)	11 (5.3%)	5 (2.4%)
			0 (0)	46.2 27.2)	76.2 (27.1)	104.3 (28.4)	154.5 (38.4)	177.4 (35.2)	211.8 (45.5)
BMI	regardless of active module	1815 (100%)	792 (43.6%)	209 (11.5%)	115 (6.3%)	73 (4.0%)	45 (2.5%)	32 (1.8%)	19 (1.0%)
			0 (0)	57.9 (43.5)	93.3 (30.1)	125.9 (27.7)	154 (25.2)	187.1 (25.3)	225.8 (27.6)
	only active module weight	420 (100%)	416 (99%)	207 (49.3%)	115 (27.4%)	73 (17.4%)	45 (10.1%)	32 (7.6%)	19 (4.5%)
			0 (0)	57.9 (43.5)	93.3 (30.1)	125.9 (27.7)	154.0 (25.2)	187.1 (25.3)	225.8 (27.6)
Last	regardless of active module	1815 (100%)	764 (42.1%)	84 (4.6%)	42 (2.3%)	27 (1.5%)	17 (0.9%)	13 (0.7%)	7 (0.4%)
			0 (0)	65.7	115.5	160.8	203.8	220.0	223.9

				(64.5)	(89.9)	(110.3)	(135.5)	(108.2)	(28.7)
	only active module mindfulness	157 (100%)	153 (97.5%)	83 (52.9%)	42 (26.8%)	27 (17.2%)	17 (10.1%)	13 (8.3%)	7 (4.5%)
			0 (0)	66.4 (64.5)	115.5 (89.9)	160.8 (110.3)	203.8 (135.5)	220.0 (108.2)	223.9 (28.7)
PDR	regardless of active module	1815 (100%)	783 (43.1%)	380 (20.9%)	218 (12%)	131 (7.2%)	80 (4.4%)	56 (3.1%)	32 (1.8%)
			0 (0)	55.2 (42.3)	87.8 (34.6)	123 (42.5)	155.7 (50.2)	192.6 (58.1)	222.9 (26.9)
	only active module nutrition	693 (100%)	680 (98.1%)	379 (54.7%)	218 (31.5%)	131 (18.9%)	80 (11.5%)	56 (8.1%)	32 (4.6%)
			0 (0)	55.3 (42.3)	87.8 (34.6)	123 (42.5)	155.7 (50.2)	192.6 (58.1)	222.9 (26.9)
Smoking	regardless of active module	1815 (100%)	761 (41.9%)	579 (31.9%)	375 (20.7%)	262 (14.4%)	191 (10.5%)	131 (7.2%)	94 (5.2%)
			0 (0)	20 (20.4)	44.4 (24.5)	71.7 (32.6)	88.6 (40.0)	114.1 (41.9)	129.6 (51.6)
	only active module smoking	130 (100%)	119 (91.5%)	82 (63.1%)	53 (40.8%)	42 (32.3%)	28 (21.5%)	18 (13.8%)	11 (8.5%)
			0 (0)	16.4 (16.5)	41.4 (20.5)	63.9 (29.6)	85.0 (34.8)	105.8 (33.2)	126.2 (40.5)

TRS: ;BMI: ;PDR:

Table.2 Results following the MFC App at three- and six-months follow-up.[a]

Questionnaire			Measurement moments									
			T0		T3				T6			
	N	Obs	Mean	95% CI	Mean	95% CI	Δ	p-value	Mean	95% CI	Δ	p-value
TRS	424	1040	3.81	(3.43; 4.19)	2.34	(1.87; 2.81)	-1.47	<.001	2.35	(1.65; 3.06)	-1.46	<.001
Activity	230	786	3.41	(3.25; 3.57)	4.18	(3.97; 4.40)	0.77	<.001	4.33	(3.95; 4.7)	0.92	<.001
Alcohol	94	286	5.43	(4.71;6.14)	2.64	(1.55; 3.72)	-2.79	<.001	4.26	(2.10; 6.42)	-1.16	0.531
BMI	207	698	30.1	(29.4; 30.8)	29.6	(28.9; 30.3)	-0.47	<.001	29.1	(28.4; 29.9)	-0.95	<.001
Distress	83	272	5.53	(4.94; 6.12)	3.84	(2.99; 4.70)	-1.69	<.001	3.91	(2.45; 5.37)	-1.62	0.073
PDR	265	375	3.42	3.30;3.55	4.28	4.11;4.45	0.86	<.001	4.23	3.93;4.53	0.81	<.001
Smoking	313	81	9.95	8.89;11.02	5.38	4.03;6.75	-4.75	<.001	5.22	2.87;7.56	-4.74	<.001

[a]Results are based on the most optimal model following an extensive model selection procedure. TRS: Total Risk Score; BMI: Body Mass Index ;PDR: Preconception Dietary Risk Score

Table.3 Results following the MFC App at three- and six-months follow-up.[a]

Questionnaire				Measurement moments									
				T0		T3				T6			
	Partner	N	Obs	Mean	95% CI	Mean	95% CI	Δ	p-value	Mean	95% CI	Δ	p-value
TRS	Yes	424	1040	3.56	(3.35; 3.77)	2.1	(1.74; 2.44)	1.47	<.001	2.1	(1.47; 2.73)	1.46	<.001
	No			4.07	(3.34; 4.79)	2.59	(1.82; 3.37)	1.47	<.001	2.6	(1.67; 3.54)	1.46	<.001
Activity	Yes	230	786	3.33	(3.17; 3.50)	4.1	(3.89; 4.33)	-0.77	<.001	4.26	(3.87; 4.64)	-0.9	<.001
	No			3.49	(3.23; 3.75)	4.26	(3.96; 4.56)	-0.77	<.001	4.41	(3.98; 4.84)	-0.9	<.001
Alcohol	Yes	94	286	4.33	(3.44; 5.21)	1.5	(0.32; 2.75)	2.79	<.001	3.2	(0.93; 5.39)	1.2	0.531
	No			6.52	(5.51; 7.54)	3.7	(2.44; 5.03)	2.79	<.001	5.4	(3.09; 7.63)	1.2	0.531
BMI	Yes	207	698	30.4	(29.6; 31.2)	30.2	(29.3; 31.0)	-0.23	.073	29.9	(29.0; 31.0)	-0.5	0.073
	No			29.8	(28.6; 31.0)	29.1	(27.9; 30.3)	-0.71	<.001	28.4	(27.0; 29.7)	-1.4	<.001
Distress	Yes	83	272	5.70	(5.14; 6.26)	4.01	(3.18; 4.84)	1.69	<.001	4.08	(2.62; 5.54)	1.62	.073
	No			5.36	(4.40; 6.32)	3.67	(2.53; 4.82)	1.69	<.001	3.74	(2.11; 5.37)	1.62	.073
PDR	Yes	1265	375	3.55	(3.42; 3.69)	4.41	(4.23; 4.59)	-0.86	<.001	4.36	(4.06; 4.66)	-0.81	<.001
	No			3.30	(3.10; 3.49)	4.15	(3.92; 4.38)	-0.86	<.001	4.10	(3.77; 4.44)	-0.81	<.001
Smoking	Yes	313	81	9.29	(8.03; 10.54)	4.72	(3.23; 6.20)	-4.75	<.001	4.55	(2.13; 6.97)	-4.74	<.001
	No			10.64	(9.09; 12.14)	6.04	(4.29; 7.80)	-4.75	<.001	5.88	(3.28; 8.47)	-4.74	<.001

[a]Results are based on the most optimal model following an extensive model selection procedure. TRS: Total Risk Score; BMI: Body Mass Index ;PDR: Preconception Dietary Risk Score

Table 4. Results following the MFC App at three- and six-months follow-up.[a]

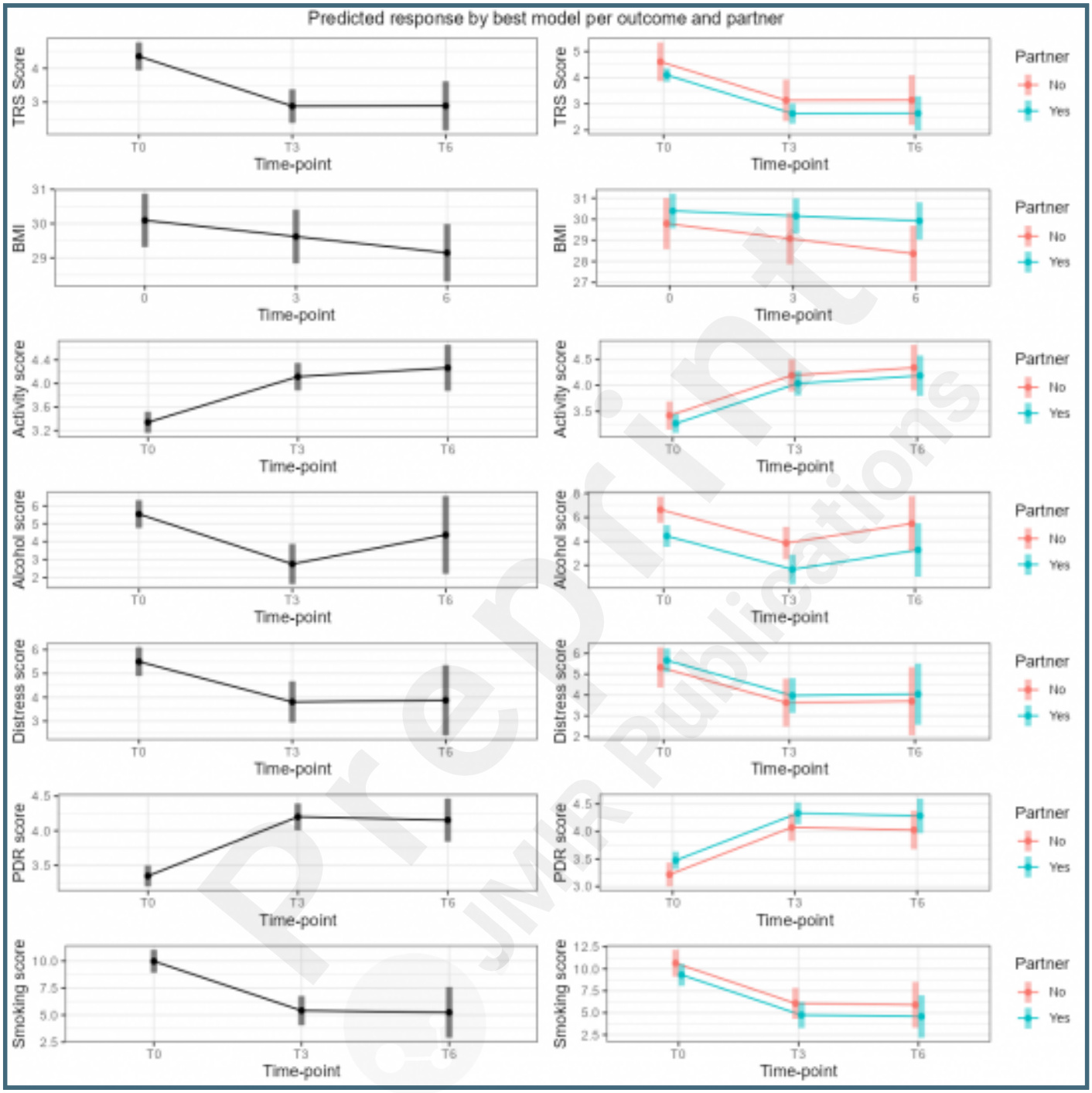
Questionnaire				Measurement moments								
				T0			T3			T6		
	Partner	N	Obs	Mean	Δ 95% CI	Δ p-value	Mean	Δ 95% CI	p-value	Mean	Δ 95% CI	p-value
TRS	Yes	424	1040	3.56	0.505 (-0.244; 1.25)	.189	2.1	0.505 (-0.244; 1.25)	.189	2.1	0.505 (-0.244; 1.25)	.189
	No			4.07			2.59			2.6		
Activity	Yes	230	786	3.33	0.154 (-0.135; 1.051)	.294	4.1	0.154 (-0.135; 1.051)	.294	4.3	0.154 (-0.135; 1.051)	.294
	No			3.49			4.3			4.4		
Alcohol	Yes	94	286	4.33	2.2 (0.922; 3.47)	<.001	1.5	2.2 (0.922; 3.47)	<.001	3.2	2.2 (0.922; 3.47)	<.001
	No			6.52			3.7			5.4		
BMI	Yes	207	698	30.4	-0.599 (-1.96; 0.767)	.388	30.2	-1.077 (-2.46; 0.3021	.125	29.9	-1.555 (-3.06; -0.0518)	.043
	No			29.8			29.1			28.4		
Distress	Yes	83	272	5.70	-0.339 (-1.37; 0.691)	.514	4.01	-0.339 (-1.37; 0.691)	.514	4.08	-0.339 (-1.37; 0.691)	.514
	No			5.36			3.67			3.74		
PDR	Yes	1265	375	3.55	-0.256 (-0.484; -0.028)	.028	4.41	-0.256 (-0.484; -0.028)	.028	4.36	-0.256 (-0.484; -0.028)	.028
	No			3.30			4.15			4.10		
Smoking	Yes	313	81	9.29	-0.909 (-0.485; 1.458)	.149	4.72	-0.909 (-0.485; 1.458)	.149	4.55	-0.909 (-0.485; 1.458)	.149
	No			10.64			6.04			5.88		

[a]Results are based on the most optimal model following an extensive model selection procedure. TRS: Total Risk Score; BMI: Body Mass Index ;PDR: Preconception Dietary Risk Score

Supplementary Files

Figures

Predicted Response by best model per outcome and partner.



Multimedia Appendixes

Supplementary figures.
URL: http://asset.jmir.pub/assets/3e65be4a266c0a3d94617eecb13df86c.zip