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First effective mHealth nutrition and lifestyle coaching program for subfertile couples undergoing in vitro fertilization treatment: a single-blinded multicenter randomized controlled trial

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Objective: To study compliance and effectiveness of the mHealth nutrition and lifestyle coaching program Smarter Pregnancy in couples undergoing in vitro fertilization (IVF) treatment with or without intracytoplasmic sperm injection (ICSI).
Design: Multicenter, single-blinded, randomized controlled trial, conducted from July 2014 to March 2017.
Setting: IVF clinics.
Patient(s): A total of 626 women undergoing IVF treatment with or without ICSI and 222 male partners.
Interventions(s): Couples were randomly assigned to the light (control group) or regular (intervention group) Smarter Pregnancy program. Both groups filled out a baseline screening questionnaire on nutrition and lifestyle behaviors, and the intervention group received coaching tailored to inadequate behaviors during the 24-week period.
Main Outcome Measure(s): Difference in improvement of a composite dietary and lifestyle risk score for the intake of vegetables, fruits, folic acid supplements, smoking, and alcohol use after 24 weeks of the program.
Result(s): Compared with control subjects, women and men in the intervention group showed a significantly larger improvement of inadequate nutrition behaviors after 24 weeks of coaching. At the same time, the women also showed a significantly larger improvement of inadequate lifestyle behaviors.
Conclusion(s): The mHealth coaching program Smarter Pregnancy is effective and improves the most important nutritional and lifestyle behaviors among couples undergoing IVF/ICSI treatment. International multicenter randomized trials are recommended to study the effect of using Smarter Pregnancy on pregnancy, live birth, and neonatal outcome.
Netherlands Trial Register Number: NTR4150 (Fertil Steril® 2020;114:945–54. ©2020 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Telemedicine, artificial reproductive techniques, risk reduction, preconception, pregnancy

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Poor nutrition and lifestyle behaviors are still very common risk factors for many noncommunicable diseases, including reproductive disorders, with an estimated 49 million couples coping with subfertility worldwide (1, 2). Nowadays, assisted reproductive techniques, such as in vitro fertilization (IVF) treatment with or without intracytoplasmic sperm injection (ICSI), show highly acceptable cumulative ongoing pregnancy rates (fresh plus frozen-thawed) per initiated cycle (36.2% ongoing pregnancies in 2017 in the Netherlands, 33.4% ongoing pregnancies in 2016 in the United States) (3, 4). However, these rates may be improved by adopting healthier nutritional and lifestyle behaviors (5). Unfortunately, most couples contemplating pregnancy, including subfertile couples for whom a clinical pregnancy has not occurred after $\geq$ 12 months of regular unprotected intercourse, as well as health professionals, are usually not aware of the impact of nutritional and lifestyle behaviors on reproductive outcomes. Raising awareness by providing information and motivating these couples to change behaviors remains challenging (6).

As stated by Barker et al. (7), there are four preconception action phases (i.e., children and adolescents, adults with no immediate intention to become pregnant, adults with intention to become pregnant, and adults with intention to become pregnant again) in relation to the goal to become a parent, each with its own features and intervention strategies. A modern and potentially effective intervention strategy to initiate behavioral changes is the mobile phone with internet access, called mHealth (8–10). In reproductive and obstetrical health care, existing mHealth interventions mainly target weight loss or monitor glucose concentrations (11–13). Moreover, based on the scientific evidence on the impact of nutrition and lifestyle behaviors (e.g., maternal smoking, alcohol, and folic acid supplement use) on reproduction, and the absence of an mHealth tool to support healthy nutrition and lifestyle behaviors tailored for couples contemplating pregnancy, we developed the web-based coaching program called Smarter Pregnancy in English (www.slimmerzwanger.nl) (14, 15). This program was first launched in 2011 and developed based on evidence of the effectiveness of nutrition and lifestyle interventions, educational programs using mobile phones (16, 17), our experiences with a Dutch preconception counseling clinic (18, 19), and three theoretical models for behavioral change (20–22).

In our survey, including more than 2,000 (sub)fertile couples, we already showed that compliance to the regular Smarter Pregnancy program is high (65%). Moreover, we observed a significantly positive association between the improvement of nutrition (intake of fruit and vegetables) and lifestyle behaviors (alcohol consumption and smoking cessation) and pregnancy rate (23, 24). Inherent to the design of a survey, a control group was not included. As a next step toward implementation, we conducted a multicenter, single-blinded, randomized controlled trial to investigate the compliance and effectiveness of Smarter Pregnancy on the improvement of inadequate nutrition and lifestyle behaviors in couples undergoing IVF/ICSI treatment, while pregnancy rate was, among others, studied as a tertiary outcome (25).

MATERIALS AND METHODS

Study Design and Participants

We performed a multicenter, single-blinded, randomized controlled trial in six IVF centers located in the Netherlands. A detailed protocol of the study has been published previously (25). Briefly, from July 2014 to March 2017, women with an indication for IVF treatment with or without ICSI were informed about the study before their upcoming treatment. Thereafter, they were contacted by a researcher and invited to participate in the trial. Eligible women were 18–45 years of age, had a sufficient knowledge or understanding of the Dutch language, and were to start their IVF/ICSI treatment within the next 3 months. Women were excluded in case of oocyte donation or adherence to a specific diet (e.g., vegan). Male partners were also invited to participate if they were not on a specific diet. All participants gave written and digitally informed consent.

Ethical Approval

All procedures involving participants were approved by the Medical Ethical and Institutional Review Board of the Erasmus Medical Center, University Medical Center, Rotterdam, The Netherlands (MEC no. NL40414.078.12), and subsequently by all participating centers. The trial was registered with the Netherlands Trial Register (NTR4150; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4150).

Randomization and Masking

Participating women were randomly assigned to the intervention (regular version of Smarter Pregnancy) or control group (light version of Smarter Pregnancy) in a 1:1 ratio by computer and stratified according to the study center from which they had been recruited. Permuted blocking ensured that the number of women and men from the different study centers was balanced between the treatment groups. Allocation concealment was used to ensure that researchers did not know the order of group assignment at recruitment and randomization. Moreover, researchers were blinded to the allocation of the participants. When a woman and her partner participated together, they were both randomized into the same group.

Intervention

A detailed description of the intervention has been published previously (25). In short, at study entry, all participants completed the short online questionnaire to record baseline characteristics as well as nutritional (vegetables, fruits, folic acid supplement use) and lifestyle (smoking, alcohol) behaviors. Participants assigned to the intervention group subsequently received tailored coaching based on sex, pregnancy status, and behaviors identified as inadequate at the baseline screening. At 6, 12, 18, and 24 weeks of coaching, participants were invited to complete a short online questionnaire to monitor changes in their identified risk behaviors and to assess pregnancy status. The results from the questionnaires were used by the algorithm of the program to adjust the

content of the coaching program where necessary. The results were presented on a personal online page to show the participant's progress and to stimulate compliance. The tailored coaching included a maximum of three e-mails or text messages per week that contained tips, recommendations, vouchers, seasonal recipes, feedback on progress, and additional questions addressing pregnancy status and adequacy of the inadequate behaviors identified at baseline.

Participants assigned to the control group were offered the "light" version of Smarter Pregnancy. At baseline and 12 and 24 weeks, those participants filled out the same online questionnaire on baseline characteristics and nutritional and lifestyle behaviors, but did not receive feedback on identified inadequate behaviors. Similarly to the intervention group, participants of the control group were asked to adjust their pregnancy status every 6 weeks if applicable.

To validate the Smarter Pregnancy coaching program at baseline and 12 and 24 weeks, blood samples were collected from a subset of participants in the intervention and control group. Samples were kept at −20°C for a maximum of 4 hours (25). The serum was analyzed for folate levels to validate vegetable and fruit intake and use of folic acid supplements. To this end, the hemolysate was prepared by diluting 0.1 mL full blood in 0.9 mL fresh 1.0% ascorbic acid. After the haemolysate was centrifuged at 1,000*g* for 5 minutes at 18°C, serum folate levels were measured by means of an electrochemiluminescence immunoassay (Modular E170; Roche).

A follow-up questionnaire was sent out 12 weeks after completion of the program (i.e., 36 weeks after enrollment), with questions about nutritional and lifestyle behaviors and to record whether or not these behaviors had changed after completing the coaching. Moreover, 52 weeks after the start of the program a follow-up questionnaire was sent out to collect information on whether or not a pregnancy had occurred within the preceding 52 weeks. In case of nonresponse, participants were contacted by phone and e-mail.

Outcomes

The primary outcome of the study was improvement of inadequate nutritional behaviors based on a reduction of dietary risk score (DRS) 24 weeks after starting the Smarter Pregnancy program (18, 19, 23). Vegetable and fruit intake were subdivided into risk scores of 0, 1.5, and 3, where 0 represents an adequate daily intake (≥200 g of vegetables, ≥2 pieces of fruit). A score of 1.5 represents a "nearly adequate" intake (150–200 g of vegetables, 1.5–2 pieces of fruit). A score of 3 represents an inadequate daily intake (<150 g of vegetables, <1.5 pieces of fruit). Folic acid supplement use was considered to be adequate (score 0) or inadequate (score 3) when the recommended dose of 400 μg/d was either met or not (26). For male participants, folic acid supplement use was not taken into account. The DRS was calculated as the sum of the scores of vegetable, fruit, and folic acid supplement intake and ranged from 0 to 9 for women and 0 to 6 for men. A higher risk score reflects more inadequate nutritional and lifestyle behaviors.

Secondary and tertiary outcomes were improvement of nutritional and lifestyle behaviors 36 weeks after starting the Smarter Pregnancy program according to the DRS and the lifestyle risk score (LRS) (5, 18). Risk score for smoking was based on average daily use: no smoking (score 0) and daily smoking of 1–5 (score 1), 6–14 (score 3), or ≥15 (score 6) cigarettes. Because smoking has a profound effect on reproduction, this score carries more weight than the scores for other risk factors. Risk scores for alcohol consumption were based on average weekly use:, no alcohol use (score 0) and 1–7 (score 1), 8–14 (score 2), or ≥15 (score 3) alcoholic beverages (glasses) per week. The LRS was calculated as the sum of the scores of smoking and alcohol use and ranged from 0 to 9 for both women and men. Other secondary and tertiary outcomes investigated were the compliance to complete the 24 weeks of the coaching program and the impact of participation as a couple, overweight/obesity, and pregnancy on the primary outcome. Also, cumulative pregnancy rates at 52 weeks after the start of the Smarter Pregnancy coaching program were evaluated in both the intervention and the control groups.

Statistical Analysis

The sample size for the trial was based on the estimated reduction in DRS as primary outcome measure (a difference of 0.5 DRS points) in the intervention group compared with the control group (25). Considering alpha = 0.05, power = 0.80, and a drop-out rate of 10%, we needed to include 1,000 women (2 arms of 500 each) in total.

Compliance was calculated as the percentage of participants who completed the 24 weeks of the Smarter Pregnancy coaching program. Comparison between the intervention and control group was carried out with the use of chi-square tests. The DRS and LRS were calculated at baseline, after 24 weeks of coaching, and 12 weeks after completion of the program (36 weeks of follow-up). Our analyses included all participants who activated the program and either completed the program or resigned prematurely (intention-to-treat analysis). Missing data were handled with the use of the last-observation-carried-forward method. A linear regression model based on the difference-in-differences principle was used to analyze differences in improvement of DRS and LRS between groups, adjusted for baseline values of DRS and LRS. The obtained beta coefficient represents the difference in improvement between the intervention and control groups. Because participants in the intervention group received coaching only regarding inadequate behavior, regression analyses were performed only on those participants who showed inadequate behavior at baseline.

Explorative analyses were performed by including an interaction term in the regression model to test whether participation by the male partner, overweight/obesity (body mass index [BMI] ≥25 kg/m^2), or pregnancy influenced the primary outcome. We used a bootstrap method for all analyses because residuals of the linear regression analyses were not normally distributed (27). *P* values of <.05 were considered to be statistically significant. We controlled for the probability of type 1 error on a test-by-test basis. All analyses were performed with the use of Statistical Package for the Social Sciences software

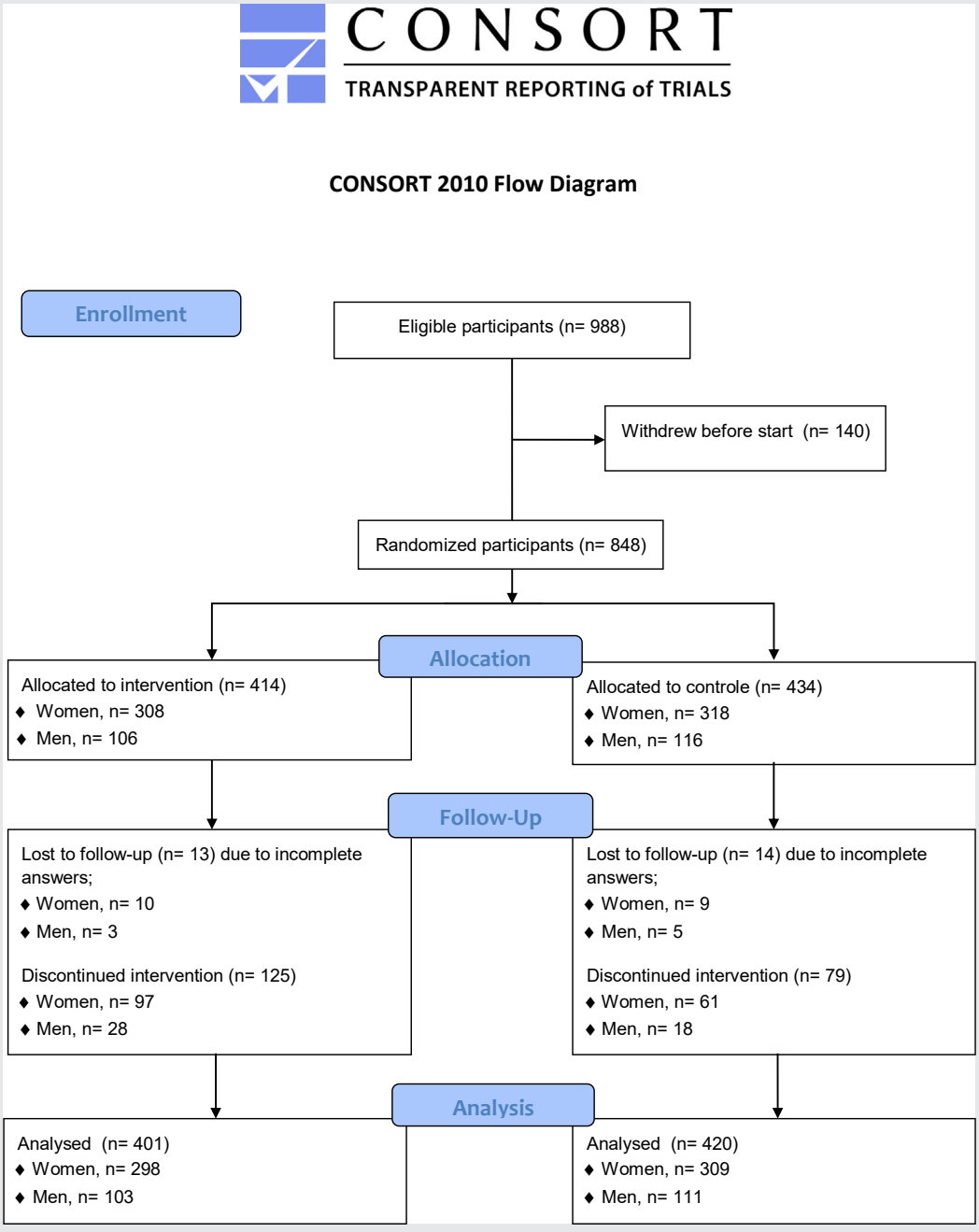
(version 21.0 for Windows; IBM) and R (version 3.1.3 2015 for Windows; R Core Team).

RESULTS

From July 1, 2014, to March 31, 2017, 988 participants (women and men) were recruited (Fig. 1). A total of 140 participants withdrew before the start, leaving 848 participants for randomization. The intervention group consisted of 414 participants (308 women and 106 men) and the control group 434 participants (318 women and 116 men). Baseline characteristics of the study population, stratified by sex, are presented in Table 1. Women in the study had a median age of 33 (interquartile range [IQR] 30–36) years and a median BMI of 23.8 (IQR 21.6–27.0) kg/m^2. The median age and BMI of men were 35 (IQR 31–39) years and 25.2 (IQR 23.0–27.8) kg/m^2, respectively. A majority of participants were of Dutch origin and highly educated.

Of the 626 randomized women, 468 completed the program, resulting in an overall compliance of 74.8%: 211 in the intervention group (68.5%) and 257 in the control group

FIGURE 1



CONSORT (Consolidated Standards of Reporting Trials) flow diagram showing recruitment of participants, exclusions, and dropouts.

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TABLE 1

Baseline characteristics and nutritional and lifestyle behaviors of all participating women and men in the multicenter study population (total n = 848).

	Women		Men	
Characteristic	**Intervention (n = 308)**	**Control (n = 318)**	**Intervention (n = 106)**	**Control (n = 116)**
Age, y	33 (29–37)	33 (30–36)	35 (31–39)	35 (31–41)
Body mass index, kg/m^2	23.7 (21.6–26.7)	23.8 (21.6–26.3)	25.1 (22.7–26.9)	25.2 (23.2–28.3)
Underweight (<20)	35 (11.4)	31 (9.7)	4 (3.8)	4 (3.4)
Normal (≥20 to 25)	165 (53.6)	172 (54.1)	46 (43.4)	50 (43.1)
Overweight (≥25 to 30)	68 (22.1)	81 (25.5)	45 (42.5)	49 (42.2)
Obese (≥30)	40 (13.0)	34 (10.7)	11 (10.4)	13 (11.2)
Missing	0	0	0	0
Geographic background				
Dutch	223 (79.6)	229 (78.7)	84 (95.5)	86 (90.5)
Western	13 (4.6)	21 (7.2)	2 (2.3)	4 (4.2)
Non-Western	44 (15.7)	41 (14.1)	2 (2.3)	5 (5.3)
Missing	28	27	18	21
Education				
Low	6 (2.1)	7 (2.4)	4 (4.5)	5 (5.3)
Intermediate	128 (45.7)	92 (32.1)	40 (45.5)	41 (43.2)
High	146 (52.1)	188 (65.5)	44 (50.0)	49 (51.6)
Missing	28	31	18	21
Adequate behavior at baseline				
Vegetable intake	76 (25.5)	90 (28.8)	29 (28.2)	29 (25.7)
Fruit intake	145 (48.7)	139 (45.0)	48 (46.6)	44 (39.6)
Folic acid supplement use	302 (98.1)	310 (97.5)	NA	NA
Adequate dietary risk score[a]	49 (19.7)	56 (18.1)	17 (16.5)	12 (10.8)
No smoking	275 (92.3)	286 (93.2)	88 (86.3)	92 (83.6)
No alcohol consumption	192 (64.4)	185 (60.5)	32 (31.7)	30 (27.5)
Adequate lifestyle risk score[b]	175 (58.7)	175 (57.2)	27 (26.7)	26 (23.9)
Compliance				
Program completed (24 wk)	211 (68.5)	257 (80.8)	78 (73.6)	98 (84.5)

Note: Values are presented as median (interquartile range) or n (%).
[a] Dietary risk score = sum of risk scores for vegetable intake, fruit intake, and folic acid supplement use.
[b] Lifestyle risk score = sum of risk scores for smoking and alcohol consumption.

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(80.8%; $P<.001$). Of the 222 randomized men, 176 completed the program, resulting in an overall compliance of 79.3%: 78 in the intervention group (73.6%) and 98 in the control group (84.5%; $P=.045$; Table 1).

Supplemental Table 1 (Supplemental Tables 1–4 are available online at www.fertstert.org) presents the distribution of adequate nutritional and lifestyle behaviors among the study population at baseline, 24 weeks, and 36 weeks. Both the intervention and the control group showed more adequate behavior after 24 weeks of coaching. These findings are supported by the results of the statistical analyses, which showed that DRS decreased (i.e., improved) in both the intervention and the control group. However, the decrease of DRS in the intervention group was significantly larger than in the control group (β = 0.779, 95% confidence interval [CI] 0.456–1.090 for women; β = 0.826, 95% CI 0.416–1.284 for men) after 24 weeks of coaching (Table 2; Fig. 2). For women, the decrease of the LRS in the intervention group was also significantly larger than in the control group (β = 0.108, 95% CI 0.021–0.203) (Table 2; Fig. 2).

Twelve weeks after completion of the program (i.e., 36 weeks after enrolment) the DRS and LRS of participants in both groups were still lower than the baseline scores (Fig. 2). At 36 weeks after enrollment, the decrease of DRS compared with baseline was larger in the intervention group than in the control group (β = 0.816, 95% CI 0.478–1.142 for women; β = 0.639, 95% CI 0.212–1.081 for men; Table 2).

Biomarker validation showed that 12 weeks after enrollment, serum folate levels of women in the intervention group (n = 50) were significantly higher than in the control group (n = 64): median 48.6 (IQR 28.8–64.1) nmol/L versus 30.1 (IQR 17.9–51.9) nmol/L (Supplemental Table 2). Compared with the rest of the study population, this subset of participants showed no statistically significant differences, except for improvement in DRS at the end of the program. Participants in the subset showed larger improvement in DRS of a median 1.5 (IQR 1.5–3.0) compared with the remainder of the study population (median 0, IQR 0–1.5).

Analyses of the secondary and tertiary outcomes showed that the results of the women were not significantly influenced by participation of their male partners. It also showed that improvement in nutritional and lifestyle behaviors after 24 weeks of coaching was similar between overweight/obese and normal-weight women. However, subgroup analyses showed that improvement of fruit intake in overweight/obese men was significantly different from that observed in men of normal weight after 24 weeks of coaching: interaction coefficient 0.745, 95% CI 0.167–1.312. The regression coefficient (β) for overweight/obese men was 1.001 (95% CI 0.582–1.439), whereas for normal-weight men it was five times

TABLE 2

Regression coefficients (β) for the difference in improvement of the individual inadequate behaviors and for the dietary risk score and lifestyle risk score between the intervention and control group 24 weeks after the start of the program and 12 weeks after completion of the program (i.e., 36 weeks of follow-up), stratified for women and men.

	24 wk		36 wk	
Variable	**Women**	**Men**	**Women**	**Men**
Vegetable intake				
β	0.781	0.376	0.620	0.439
95% CI	0.567 to 0.973	0.040 to 0.707	0.415 to 0.800	0.144 to 0.737
Fruit intake				
β	0.185	0.526	0.245	0.362
95% CI	−0.026 to 0.391	0.245 to 0.833	0.050 to 0.457	0.061 to 0.668
Folic acid supplement use				
β	−0.090	*NA*	0.006	*NA*
95% CI	−0.187 to −0.022		−0.121 to 0.120	
Dietary risk score				
β	0.779	0.826	0.816	0.639
95% CI	0.456 to 1.090	0.416 to 1.284	0.478 to 1.142	0.212 to 1.081
Smoking				
β	0.090	−0.047	0.065	0.007
95% CI	0.020 to 0.184	−0.287 to 0.110	−0.013 to 0.167	−0.225 to 0.151
Alcohol consumption				
β	0.037	0.122	0.016	0.055
95% CI	−0.034 to 0.111	−0.035 to 0.302	−0.057 to 0.091	−0.114 to 0.242
Lifestyle risk score				
β	0.108	0.109	0.067	0.086
95% CI	0.021 to 0.203	−0.106 to 0.300	−0.032 to 0.165	−0.131 to 0.277

Note: Number of women and men, respectively, with inadequate behavior at baseline for the different factors: vegetable intake: 442 and 156; fruit intake: 322 and 122; folic acid supplement use: 14; dietary risk score: 502 and 185; smoking: 46 and 33; alcohol consumption: 227 and 148; and lifestyle risk score: 254 and 157. CI = confidence interval; NA = not applicable.

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smaller (β = 0.247, 95% CI −0.132 to 0.669; Supplemental Table 3). This was also observed for smoking cessation at 12 weeks after completion of the program: interaction coefficient 0.213, 95% CI 0.010–0.541. The regression coefficient for overweight/obese men was 0.141 (95% CI −0.064 to 0.440), whereas for normal-weight men it was negative (β = −0.153, 95% CI −0.623 to 0.001; Supplemental Table 4).

After performing these analyses for pregnancy status, we observed a larger improvement in adequate nutritional behavior for pregnant women (β = 1.132, 95% CI 0.642–1.604) compared with nonpregnant women (β = 0.622, 95% CI 0.165–1.037; Supplemental Table 3), although it was not statistically significant. Pregnancy significantly influenced lifestyle behavior (interaction coefficient −0.219, 95% CI −0.409 to −0.052). The regression coefficient for pregnant women was 0.135 (95% CI −0.081 to 0.352), whereas for nonpregnant women it was three times higher (β = 0.445, 95% CI 0.206–0.750; Supplemental Table 3). This was mainly due to smoking cessation: interaction coefficient −0.107, 95% CI −0.255 to −0.001. The regression coefficient for smoking in pregnant women was 0.091 (95% CI 0.001–0.306), whereas for nonpregnant women it was three times higher (β = 0.248, 95% CI 0.086–0.517; Supplemental Table 3). This significant difference was still observed after 36 weeks: interaction coefficient 0.274, 95% CI 0.169–0.425.

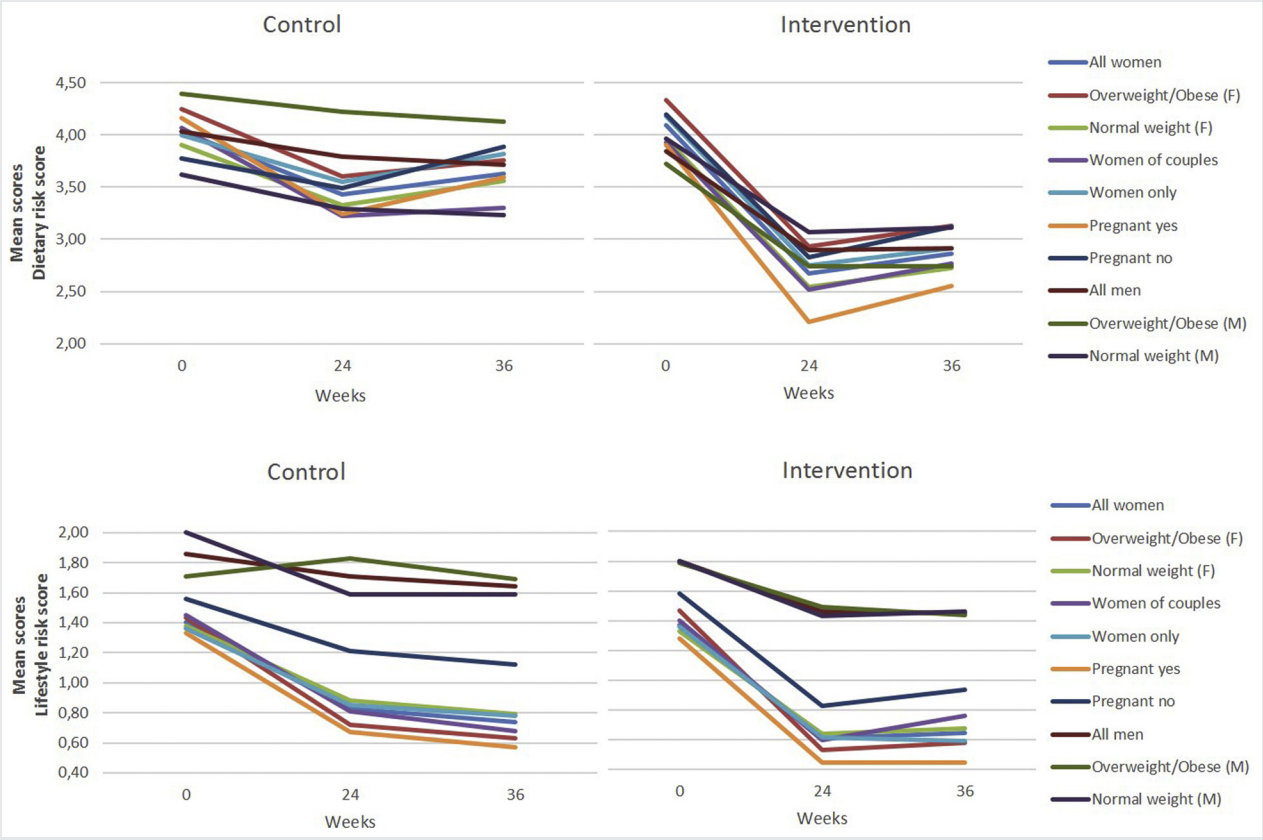
The pregnancy rates at 52 weeks after start of the coaching program were 62.5% and 67.3% in the intervention and control groups, respectively, but they were not significantly different between the groups (odds ratio 0.807, 95% CI 0.574–1.134).

DISCUSSION

This multicenter, single blinded, randomized controlled trial demonstrates that the Smarter Pregnancy coaching program is an effective mHealth tool to improve vegetable, fruit, and folic acid supplement intake and to reduce smoking and alcohol consumption in couples undergoing IVF/ICSI treatment. These effects were most pronounced for intakes of vegetables and fruits and were supported by higher serum folate levels in the intervention group. Regarding lifestyle behaviors, in the intervention group, reduction of smoking was more pronounced in women, whereas reduction of alcohol consumption was more pronounced in men compared with control subjects.

The high overall compliance to the Smarter Pregnancy coaching program (76%) indicates that participants indeed appreciate the personalized mHealth interventions tailored to a small set of a maximum of five of the most prevalent (vegetables, fruits, alcohol) and strongest (smoking, folic acid supplement use) inadequate behaviors. The compliance in this trial is even higher than shown in our previous survey (65%) and in line with the results of a previous focus group study in which most couples undergoing IVF/ICSI treatment indicated that they would be interested in tailored intervention programs on the mobile phone (23, 28). Interestingly, compliance to the light version of Smarter Pregnancy program was significantly higher than to the regular version. More individuals in the intervention group discontinued participation: 30.2% versus 18.2% in the control group. An explanation may be that

FIGURE 2



Mean risk scores after 24 weeks (end of the coaching) and 12 weeks after completion of the program (i.e., 36 weeks of follow-up) for (top) dietary and (bottom) lifestyle risk scores. F = female; M = male.

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participants in the intervention group (regular version) were overwhelmed by the intensity of the coaching, making them more likely than the control subjects (light version) to withdraw. Nevertheless, the effectiveness of the coaching program for those who maintained participation was still greater for the intervention group.

The finding that the improvement in nutritional behaviors is more pronounced than the improvement in lifestyle behaviors can be explained by the fact that the frequency of inadequate intake of nutrition (average 73%) and fruits (average 55%) was much higher than the frequency of smoking (average 11%). The detrimental effects of smoking and alcohol consumption on fertility and reproductive outcomes are widely acknowledged (29). Therefore, it is to be expected that, in particular, subfertile couples who are willing to stop smoking and drinking alcohol will already have done so. This leaves more room for improvement in the area of nutritional behaviors, the effects of which are unfortunately less widely known, as suggested by the high frequency of inadequate vegetable and fruit intakes.

The significant difference in improvement of fruit intake and smoking cessation between normal-weight and overweight/obese men was expected, because at baseline the overweight/obese men already displayed more inadequate behaviors than normal-weight men ($P<.01$; data not presented), leaving more room for improvement. This was not apparent in women, which could be due to the limited number of overweight/obese women in our study. This is also inherent to the guidelines of IVF/ICSI treatment in most clinics in the Netherlands, where a maximum BMI is set before treatment.

Although we did not find significant differences in pregnancy rates, they were similar to Dutch data for both the intervention and the control group (62.5% and 67.3%, respectively) (30). Besides the fact that this study was not powered to estimate differences in pregnancy rates, another explanation can be that the percentage of women with adequate vegetable and fruit intakes was still too small to show associations with pregnancy rate (i.e., in the intervention and control groups, respectively, an increase in adequate intake of vegetables from 25.5% to 41.5% and from 28.8% to 28.4% and an increase in adequate intake of fruit from 48.7% to 69.2% and from 45% to 58.5%). Other issues to be addressed are that either the dietary recommendations of 200 g of vegetables and 2 pieces of fruit per day is too low or that vegetables and fruits are contaminated with environmental toxins, e.g., pesticides, with detrimental effects on pregnancy rate (31). Thus, the improvement of inadequate behaviors following the Smarter Pregnancy coaching program possibly

contributes to reproductive health, regardless of using the extended or lean version. However, from these considerations it is clear that further studies on dietary recommendations and a safe fertility diet for subfertile women undergoing IVF treatment are needed.

In a subgroup analysis, pregnant women showed larger improvement of inadequate lifestyle behavior compared with nonpregnant women. This is in line with previous observational studies in which stronger adherence to a healthy dietary pattern and smoking cessation are associated with higher pregnancy rates (32, 33). On the other hand, one may argue that pregnancy renders women more willing to adopt healthier behavior, as suggested by our findings. Although not likely, it could have been possible that pregnant women received counseling regarding a healthy diet and lifestyle apart from the Smarter Pregnancy coaching program, which may have affected our results. Finally, women in the intervention group perhaps may have become pregnant at an earlier stage of their treatment. Data on the exact timing of their pregnancy were, however, not available.

Despite evidence of the importance of healthy nutrition and lifestyle regarding reproduction, the low prevalence of adequate fruit and vegetable intake and high percentage of alcohol consumption in our study group indicates that in the period before IVF/ICSI treatment couples continue to make poor lifestyle choices (5, 29, 34–36). This emphasizes also that health care providers should take implement nutritional and lifestyle care into preconception and reproductive care. We have demonstrated that one way of achieving this would be to increase the availability and applicability of the simple evidence-based mHealth tool Smarter Pregnancy. This is in line with the acceptance of user-friendly and effective mHealth tools in health care, particularly those supporting patients with specific conditions, such as diabetes and cardiovascular diseases (13, 37). In line with the aforementioned preconception action phases, we have shown that the Smarter Pregnancy coaching program satisfies many of the features of these action phases for a successful implementation in the earliest life course.

The present study has several strengths. Besides the large number of women and men included in this trial, its multicenter design makes the results applicable to various IVF/ICSI settings. Moreover, the results of the self-administered questionnaires are supported with biomarker validation of nutritional behavior by measurement of serum folate, a sensitive marker of short-term folate status. Finally, the DRS and LRS are validated risk scores based on previous studies.

However, there are also some limitations. First, we did not achieve our estimated sample size of 500 women and 300 men in each group, mainly owing to a slower participation rate than expected, which reduced the power to show significance of our secondary and tertiary outcomes. However, differences in effect estimates (betas) between the intervention and control group were still higher than expected and demonstrated a statistically significant effect of the Smarter Pregnancy program regarding the improvement of nutrition and lifestyle behaviors. Secondly, the majority of our study population was highly educated, which may reduce generalization of our findings. Also, it is unclear whether or not this affected our results. The study by Gootjes et al. (38) showed that participants living in deprived neighborhoods, in which the majority were lower educated, show larger improvement of inadequate behavior compared with participants living in nondeprived neighborhoods. This indicates that in the present study there might have been larger improvement of inadequate behavior when educational level was well balanced, with possible different outcomes in pregnancy rates. Third, the Smarter Pregnancy coaching program was available only in the Dutch language, thereby excluding non–Dutch speakers, which gives rise to selection bias. The Smarter Pregnancy program has recently become available in the English language (www.smarterpregnancy.co.uk), which means that this limitation has been resolved. Finally, participants completed self-administered questionnaires, which are susceptible to desirable answers and recall bias. However, they were validated by the biomarkers and we expect that the degree of such bias would be similar between the intervention and control groups.

CONCLUSION

We demonstrated that users of the Smarter Pregnancy coaching program significantly improved inadequate nutritional and lifestyle behaviors. Therefore, we encourage wider implementation of the Smarter Pregnancy coaching program, in the Netherlands as well as other countries, to make preconception nutritional and lifestyle care more accessible to patients and health care providers. Future studies will focus on the effects of improvement of inadequate nutritional and lifestyle behaviors on pregnancy outcomes, such as live birth, preterm birth, and low birth weight. Last but not least, we emphasize that every approach of improving nutrition and lifestyle behaviors in an early period of life is an investment that eventually will contribute to the health of current and future generations.

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Primer programa de coaching en nutrición y estilo de vida para parejas subfértiles sometidas a tratamiento de fecundación in vitro: Ensayo controlado multicéntrico aleatorizado simple ciego.

Objetivo: Estudiar el cumplimiento y la eficacia del programa de coaching mHealth nutrición y estilo de vida Smarter Pregnancy en parejas sometidas a tratamiento de fecundación in vitro (IVF) con o sin inyección intracitoplasmática de espermatozoides (ICSI).

Diseño: Ensayo controlado aleatorizado multicéntrico, simple ciego, realizado entre julio de 2014 y marzo de 2017.

Entorno: Clínicas de FIV.

Paciente(s): Um total de 626 mujeres sometidas a tratamento de FIV com o sin ICSI y 222 parejas masculinas.

Intervención(es): Las parejas fueron assignadas de manera aleatoria a ligero (grupo control) o regular (grupo de intervención) del programa Smarter Pregnancy. Ambos grupos cumplimentaron un cuestionario basal de screening sobre conductas de nutrición y estilo de vida y el grupo de intervención recibió entrenamiento individual para las conductas inadecuadas durante un periodo de 24 semanas.

Resultado(s) principal(es): Diferencias en la mejoría de la composición de la dieta y en la tabla de riesgo del estilo de vida para la ingesta de verduras, frutas, suplementos de ácido fólico, tabaco y alcohol después del programa de 24 semanas

Resultado(s): Cuando se compararon con los sujetos control, los hombres y mujeres en el grupo de intervención mostraron una mejoría significativa en las conductas de nutrición inadecuada después del entrenamiento de 24 semanas. Al mismo tiempo, las mujeres mostraron también una significativa mejoría en las conductas de estilo de vida inadecuadas.

Conclusión: El programa mHealth de entrenamiento Smarter Pregnancy es efectivo y mejora las conductas de nutrición y de estilo de vida más importantes en las parejas sometidas a tratamiento de FIV/ICSI. Se recomienda realizar ensayos aleatorizados multicéntricos internacionales para estudiar el efecto del uso del programa Smarter Pregnancy sobre el embarazo, nacido vivo y resultados neonatales.