Article

Healthy preconception nutrition and lifestyle using personalized mobile health coaching is associated with enhanced pregnancy chance

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KEY MESSAGE
Healthy nutrition and lifestyle are associated with an improved chance of conceiving. Mobile health can support infertile couples to improve these modifiable factors. These findings will stimulate the implementation of mobile health in preconception, pregnancy and reproductive care with beneficial effects on reproduction, pregnancy, and future health and healthcare costs.

ABSTRACT

Periconceptional nutrition and lifestyle are essential in pathogenesis and prevention of most reproductive failures, pregnancy outcome and future health. We aimed to investigate whether personalized mobile health (mHealth) coaching empowers couples contemplating pregnancy to increase healthy behaviour and chances of pregnancy. A survey was conducted among 1053 women and 332 male partners who received individual coaching using the mHealth programme 'Smarter Pregnancy' to change poor nutrition and lifestyle for 26 weeks, depending on pregnancy state and gender. Poor behaviours were translated into a total risk score (TRS) and Poisson regression analysis was performed to estimate associations with the chance of pregnancy adjusted for fertility status, age and baseline body mass index expressed as adjusted hazard ratio (aHR) and 95% confidence interval (95% CI). A lower (a)HR suggests a higher chance of achieving pregnancy. A higher TRS was significantly associated with a lower chance of pregnancy in all women (aHR 0.79, 95% CI 0.72–0.85) and (a)HR was lowest in women whose male partner participated (aHR 0.75, 95% CI 0.61–0.91). This survey shows that empowerment of couples in changing poor nutrition and lifestyle using personalized mHealth coaching is associated with an enhanced pregnancy chance in both infertile and fertile couples.

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Introduction

The worldwide increase of obesity and other nutrition and lifestyle-related non-communicable diseases (NCD) has increased the awareness of these detrimental behaviours on reproductive and pregnancy outcomes with health consequences in later life and next generations (Homan et al., 2007). Nevertheless, the prevalence of modifiable poor behaviours remains high, both in couples contemplating pregnancy and even in those undergoing medically assisted reproduction (MAR) (Domar et al., 2012; Gormack et al., 2015; Hammiche et al., 2011; van Dijk et al., 2016).

The estimated prevalence of infertility is approximately 9% worldwide, of which 42–76% of the couples seek specialized fertility care or treatment (Boivin et al., 2007). Successful reproduction is determined by the compliance with treatment as well as the complex interactions between individual maternal and paternal conditions and behaviours, of which some are modifiable (Evers, 2002; Hammiche et al., 2011; Sharma et al., 2013; Twigt et al., 2012). Poor periconception nutrition, lifestyle and environmental exposures are associated with failure of reproduction, MAR, impaired embryonic and fetal development, and long-term programming of offspring health (Lane et al., 2014; Steegers-Theunissen et al., 2013). Therefore, modifiable parental behaviours should be the specific targets of preconception care and interventions to improve the chance of pregnancy and pregnancy outcomes and to reduce healthcare costs, including MAR (Anderson et al., 2010).

Studies aiming to achieve behavioural changes and maintain healthy nutrition and lifestyle using electronic health (eHealth) and mobile health (mHealth) interventions that include personalized and individual feedback have shown promising results in the prevention of NCDs (Chow et al., 2015; Kroeze et al., 2006). We have already showed that the mHealth 'Smarter Pregnancy' programme (Dutch version available at: www.slimmerzwanger.nl, English equivalent available at: www.smarterpregnancy.co.uk/research), which contains personalized individual online coaching by SMS and e-mail messages during a period of 26 weeks, is an effective tool to increase intakes of vegetables, fruit and folic acid supplements, as well as to quit smoking and alcohol consumption (van Dijk et al., 2016).

Building on these findings we enlarged our study population with the aim of demonstrating associations between improvement of preconception nutrition and lifestyle using the mHealth 'Smarter Pregnancy' coaching programme and the chance of pregnancy in both fertile and infertile couples.

Materials and methods

Study population

All couples contemplating pregnancy who visited the outpatient clinics of the Department of Obstetrics and Gynecology at the Erasmus MC, University Medical Center, or participating midwifery practices in Rotterdam (the Netherlands), between January 2012 and September 2014 were invited to participate in a survey for which they received a brochure with information about a free subscription to the 'Smarter Pregnancy' coaching programme. All male partners were also invited to participate. Participants known to be receiving MAR at the time of enrolment were considered infertile and all others were considered fertile.

After registration and a baseline screening on fruit and vegetable intake, folic acid supplement use, and smoking and alcohol consumption, participants received personalized and individual online coaching by SMS and e-mail messages (maximum of three per week) over a period of 26 weeks. During this time online questionnaires, incorporated into the programme, were automatically sent every 6 weeks to monitor changes in the risk behaviour identified at baseline and to verify whether the pregnancy state changed during the previous 6 weeks. If so, the programme automatically adjusted its personalized individual coaching by using algorithms to meet the recommendations concerning nutrition and lifestyle based on the given answers and pregnancy status. Self-reported pregnancy was based on a positive pregnancy test or ultrasound confirmation. A detailed description of the programme has been provided before and can be found in the supplementary materials (van Dijk et al., 2016).

Risk scores

All identified poor nutrition and lifestyle factors were translated into risk scores for each behaviour, based on the Rotterdam Reproduction Risk score (R3 score), the Preconception Dietary Risk (PDR) score and other existing evidence of associations with reproductive and pregnancy outcome. As demonstrated by previous research, especially smoking, but also alcohol consumption, folic acid supplement use and daily fruit and vegetable intake, have a strong association with impaired reproduction and reproductive outcome (Anderson et al., 2010; Augood et al., 1998; Donnelly et al., 1999; Hammiche et al., 2011; Temel et al., 2008; Twigt et al., 2012). The total risk score (TRS) per individual was defined as the sum of all risk scores per behaviour (5 in women and 4 in men). A higher TRS denotes more unhealthy nutrition and lifestyle. 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 <200 g and a fruit intake of 1.5 to <2 pieces per day), taking into account 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 <150 g 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 whether participants had the intention to improve their behaviour 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 µg 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 with regard to 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. Initially, we decided that each risk factor would contribute equally to the TRS, but because the effect of smoking on reproduction and reproductive outcome is known to be very strong, we chose the extended range of 0 to 6 instead of the 0 to 3 range of all other risk factors.

Because of the lack of evidence of a recommendation for folic acid supplement use by men, the male participants neither received questions nor feedback and coaching with regard to folic acid supplementation, resulting in a maximum TRS of 15 in male and 18 in female participants.

Statistical analysis

Baseline general characteristics and risk factors of all non-pregnant women and male partners were divided according to fertility status and subsequently compared using chi-squared tests for categorical (including *P*-values for trend) and Mann–Whitney *U*-tests for continuous variables. These analyses, stratified by gender, were also performed to compare participants who completed the programme with those who dropped out prematurely.

We used an exponential survival model, equivalent to a Poisson model, to estimate the associations between the TRS and the chance of pregnancy, depicted as hazard ratios (HR) including 95% confidence intervals (95% CI). Because this model does not provide the opportunity to include an estimate of the probability of conceiving for each cycle, we assumed this estimate to be constant during the 26 weeks of coaching. The estimated survival should therefore be considered an abstraction. An alternative would be to estimate a discrete time survival model, but this model should also be considered an abstraction as the scheme by which we asked for the pregnancy status did not run parallel to the cycle of the women.

We created a separate record in the data file for each individual and for every 6-week interval for which we have a measurement of the risk score. The response is an indicator variable that is 0 if the woman did not get pregnant or 1 if the women did get pregnant. The risk score was used as an explanatory variable. Whenever a woman became pregnant we assumed that this happened (on average) in the middle of each 6-week interval. This means the exposure time for these women was shorter. To account for this the logarithm of the time in the interval where the woman was at risk of becoming pregnant is included as an offset (i.e. a variable for which the coefficient is not estimated but fixed at 1) (McCullagh and Nelder, 1989). We included an indicator variable in the model to study whether the relationship between the risk score and the probability of a pregnancy was different between couples defined as fertile or infertile. Finally, we adjusted the model for baseline body mass index (BMI) and age. In men, we used the indicator variable of the corresponding woman per individual man.

We analysed all women as one group, all men as one group and the participating women as two separate subgroups, namely those who participated alone and those who participated with their male partner as a couple. In addition, we performed analyses discriminating between participants who completed the programme or dropped out prematurely. We used the IBM SPSS 21 software package (IBM Corp., Armonk, NY, USA). *P*-values <0.05 were considered statistically significant for all analyses.

Ethical approval

All data were anonymously processed. This survey was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving patients were approved by the Medical Ethical and Institutional Review Board of the Erasmus MC, University Medical Center, Rotterdam, the Netherlands (MEC-2011–524, approved on 22 December 2011). Digital informed consent was obtained from all participants to use the anonymous data for analysis.

Results

The flow chart of the study population of the survey is depicted in **Figure 1**, showing a total cohort of 1652 non-pregnant participants, of whom 267 (16.2%) were excluded because of incomplete registration or data entry after subscribing to the programme. We analysed a preconception cohort of 1385 participants at baseline of which 891 (64.3%) completed the programme. The baseline characteristics of the study population are presented in **Table 1** (women) and **Table 2** (men) and were classified according to gender and subdivided into a fertile and infertile group. In addition, comparison between the baseline characteristics of women who completed the programme and those who dropped out prematurely showed a higher percentage of infertility (63.7% versus 56.2%) and greater age (31.6 versus 30.8 [**Supplementary Table S1**]). In men, no significant differences were observed.

Compared with the infertile couples, we observed a significantly higher percentage of women with an inadequate vegetable intake ($P < 0.001$). We considered becoming pregnant as an event, therefore the (adjusted) HR should be interpreted as the risk of remaining non-pregnant, in which a lower (a)HR suggests a higher chance of becoming pregnant.

Table 3 shows a significant association between the TRS of all women and the chance of pregnancy (adjusted HR 0.79, 95% CI 0.72–0.85), indicating that a higher TRS (per point) was associated with a lower chance of pregnancy. The TRS of men-only was not significantly associated with the chance of pregnancy (adjusted HR 0.98, 95% CI 0.87–1.10). Subgroup analyses showed that a higher TRS remained significantly associated with a lower chance of pregnancy in women who participated without their partner (women-only: adjusted HR 0.81, 95% CI 0.73–0.89) and the association was the strongest in women whose partners also participated (women, couples: adjusted HR 0.75, 95% CI 0.61–0.91), as these women had the highest chance of achieving pregnancy. The correlation coefficient (*r*) between the TRS of women and men was 0.457. Associations between TRS and chance of pregnancy were comparable for participants who completed the programme and those who dropped out prematurely (data not shown).

Figure 2 shows mean TRS over time (per 6 weeks), subdivided according to gender. Both groups showed a mean TRS at baseline of approximately 4 and 5 for women and men, respectively. The largest reduction of the TRS was observed during the first 6 weeks of coaching in all groups, and was more evident in women than in men and more pronounced in those who became pregnant. The chances of pregnancy over time are shown in **Table 4**. The incidence of pregnancy in fertile and infertile couples was 19.0% and 9.2%, respectively. The mean change per risk factor over time, stratified by gender, is depicted in **Supplementary Figure S1**.

Discussion

This survey shows that empowerment of women and men to change poor nutrition and lifestyle using personalized mHealth coaching over a time span of 26 weeks is associated with an increased chance of pregnancy. Although our programme was not tailored to fertility status, these associations were shown in both infertile and fertile couples. These findings also support our previous studies and those of others,

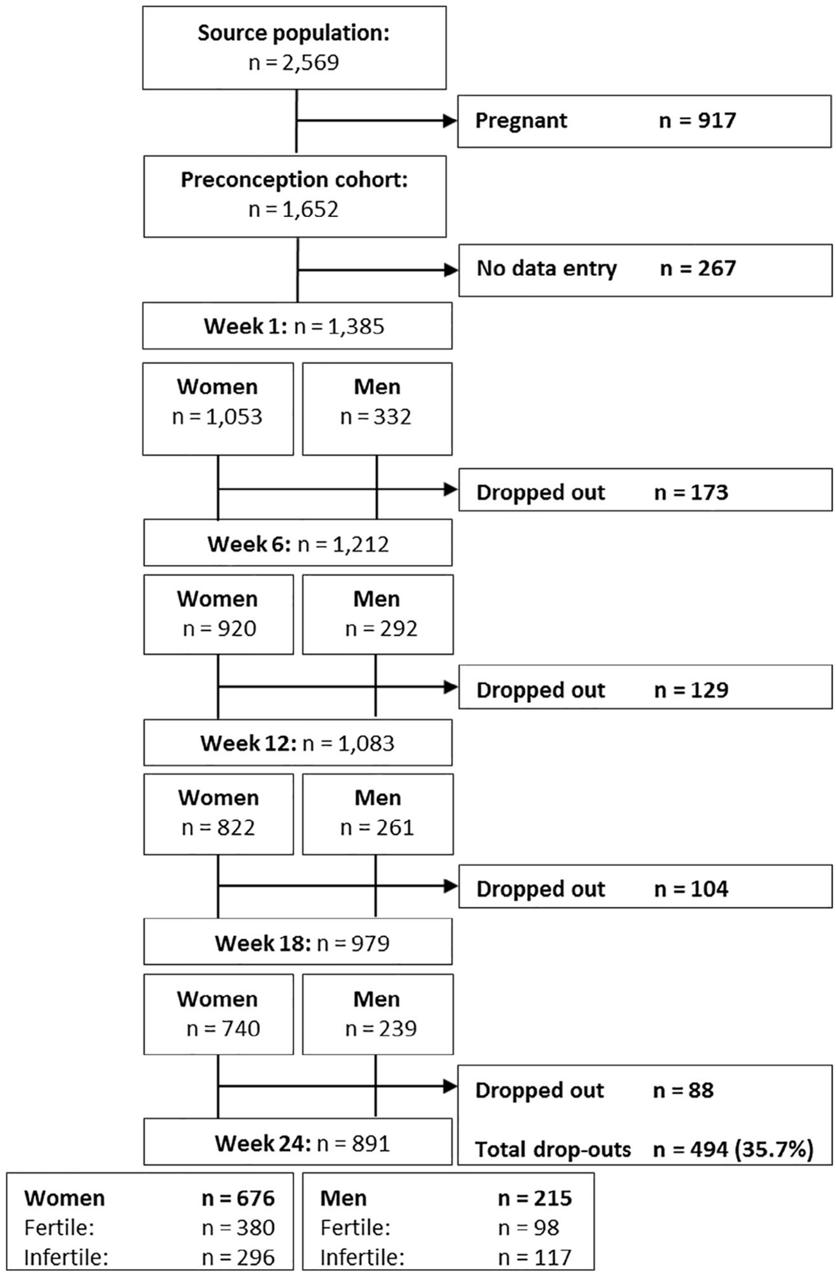

Figure 1 – Flow chart of source population and total cohort of participants in the 'Smarter Pregnancy' programme. Percentage based on total participants (*n* = 1385) in week 1.

which suggest that improvement of poor nutrition and lifestyle enhances fertility in fertile and infertile populations (Homan et al., 2007; Lintsen et al., 2005; Twigt et al., 2012). It also corresponds with the results of recent studies suggesting that the development and use of new technologies, such as mHealth applications in general, can indeed be useful and effective to improve general health (Irvine et al., 2013; Spring et al., 2012; van Dijk et al., 2016).

Obesity is a feature of a poor dietary pattern, characterized by high caloric and relative low vitamin intakes in combination with a sedentary lifestyle, which detrimentally affect metabolism, endocrine functions and the oxidative state of the microenvironment of the gametes. These derangements can subsequently alter the epigenome with consequences for not only reproduction and pregnancy but also for health and disease in later life (Lane et al., 2014; Steegers-Theunissen et al., 2013; Twigt et al., 2012; Younglai et al., 2005). Adopting preconception healthy behaviours to also achieve a healthy weight will therefore be beneficial for women and men regarding short- and long-term health of parents and their offspring (Godfrey et al., 2010; Hodgetts et al., 2015; Jaddoe et al., 2014; McPherson et al., 2014; Sinclair and Watkins, 2013; Stuppia et al., 2015). Our previous study showed that, although the prevalence of participating men is relatively low, the behavioural change in women with a participating male partner is greater than women who participate without a male partner (van Dijk et al., 2016). In this study, the prevalence of participating men was also relatively low (24%), but we observed a positive influence of male participation on the

Table 1 – Baseline characteristics and baseline risk scores of all women (total) and subdivided into a fertile and infertile group.

	Risk score	Total (*n* = 1053)	Fertile (*n* = 620)	Infertile (*n* = 433)	*P*-value
Age (years), median (IQR)		30.9 (7.3)	30.2 (6.5)	32.4 (4.3)	<0.001
Height (cm), median (IQR)		170.0 (10.0)	170.0 (10.0)	169.0 (11.0)	0.011
BMI (kg/m^2), median (IQR)		24.1 (5.9)	24.2 (5.7)	24.1 (6.5)	NS
Underweight (BMI <20), *n* (%)		96 (9.1)	55 (8.9)	41 (9.5)	
Normal (BMI ≥20 to <25), *n* (%)		517 (49.1)	304 (49.0)	213 (49.2)	
Overweight (BMI >25 to <30), *n* (%)		285 (27.1)	175 (28.2)	110 (25.4)	
Obese (BMI ≥30), *n* (%)		155 (14.7)	86 (13.9)	69 (15.9)	NS
Vegetables, g per day					
<150, *n* (%)	3	582 (55.3)	369 (59.5)	213 (49.2)	
150 to <200, not motivated, *n* (%)	2	19 (1.8)	10 (1.6)	9 (2.1)	
150 to <200, motivated, *n* (%)	1	229 (21.7)	120 (19.4)	109 (25.2)	
≥200, *n* (%)	0	223 (21.2)	121 (19.5)	102 (23.6)	<0.001
Fruit, pieces per day					
<1.5, *n* (%)	3	384 (36.5)	237 (38.2)	147 (33.9)	
1.5 to <2, not motivated, *n* (%)	2	21 (2.0)	15 (2.4)	6 (1.4)	
1.5 to <2, motivated, *n* (%)	1	127 (12.1)	81 (13.1)	46 (10.6)	
≥2, *n* (%)	0	521 (49.5)	287 (46.3)	234 (54.0)	0.045
Folic acid supplement use					
Inadequate, *n* (%)	3	241 (22.9)	154 (24.8)	87 (20.1)	
Adequate, *n* (%)	0	812 (77.1)	466 (75.2)	346 (79.9)	NS
Smoking, cigarettes per day					
>15, *n* (%)	6	22 (2.1)	15 (2.4)	7 (1.6)	
6–15, *n* (%)	3	74 (7.0)	33 (5.3)	41 (9.5)	
1–5, *n* (%)	1	45 (4.3)	21 (3.4)	24 (5.5)	
No smoking, *n* (%)	0	912 (86.6)	551 (88.9)	361 (83.4)	NS
Alcohol, beverages per day					
>2, *n* (%)	3	4 (0.4)	4 (0.6)	0 (0.0)	
1–2, *n* (%)	2	33 (3.1)	23 (3.7)	10 (2.3)	
<1, *n* (%)	1	289 (27.4)	176 (28.4)	113 (26.1)	
No drinking, *n* (%)	0	727 (69.0)	417 (67.3)	310 (71.6)	0.045
Total risk score, median (IQR)	0–18	4.0 (3.0)	4.0 (4.0)	4.0 (4.0)	<0.001

BMI = body mass index; IQR = interquartile range; NS = not statistically significant; SD = standard deviation.

Table 2 – Baseline characteristics and baseline risk scores of all men and subdivided into two groups: fertile and infertile. To improve readiness, a legend of the risk scores was added.

	Risk score	Total (n = 332)	Fertile (n = 158)	Infertile (n = 174)	P-value
Age (years), median (IQR)		34.0 (7.2)	32.7 (6.6)	35.0 (8.0)	<0.001
Height (cm), median (IQR)		184.0 (10.0)	184.0 (10.0)	183.0 (8.0)	NS
BMI (kg/m^2), median (IQR)		25.1 (4.0)	25.1 (3,9)	25.2 (4.2)	NS
Underweight (BMI <20), *n* (%)		8 (2.4)	4 (2.5)	4 (2.3)	
Normal (BMI ≥20 to <25), *n* (%)		146 (44.0)	74 (46.8)	72 (41.4)	
Overweight (BMI >25 to <30), *n* (%)		150 (45.2)	66 (41.8)	84 (48.3)	
Obese (BMI ≥30), *n* (%)		28 (8.4)	14 (8.9)	14 (8.0)	NS
Vegetables, g per day					
<150, *n* (%)	3	175 (52.7)	89 (56.3)	86 (49.4)	
150 to <200, not motivated, *n* (%)	2	7 (2.1)	2 (1.3)	5 (2.9)	
150 to <200, motivated, *n* (%)	1	77 (23.2)	34 (21.5)	43 (24.7)	
≥200, *n* (%)	0	73 (22.0)	33 (20.9)	40 (23.0)	NS
Fruit, pieces per day					
<1.5, *n* (%)	3	173 (52.1)	83 (52.5)	90 (51.7)	
1.5 to <2, not motivated, *n* (%)	2	5 (1.5)	5 (3.2)	0 (0.0)	
1.5 to <2, motivated, *n* (%)	1	33 (9.9)	14 (8.9)	19 (10.9)	
≥2, *n* (%)	0	121 (36.4)	56 (35.4)	65 (37.4)	NS
Smoking, cigarettes per day					
>15, *n* (%)	6	25 (7.5)	7 (4.4)	18 (10.3)	
6–15, *n* (%)	3	28 (8.4)	10 (6.3)	18 (10.3)	
1–5, *n* (%)	1	19 (5.7)	4 (2.5)	15 (8.6)	
No smoking, *n* (%)	0	260 (78.3)	137 (86.7)	123 (70.7)	NS
Alcohol, beverages per day					
>2, *n* (%)	3	11 (3.3)	7 (4.4)	4 (2.3)	
1–2, *n* (%)	2	36 (10.8)	21 (13.3)	15 (8.6)	
<1, *n* (%)	1	116 (34.9)	54 (34.2)	62 (35.6)	
No drinking, *n* (%)	0	169 (50.9)	76 (48.1)	93 (53.4)	NS
Total risk score, median (IQR)	0–15	5.0 (4.0)	5.0 (4.0)	5.0 (4.25)	NS

BMI = body mass index, IQR = interquartile range; NS = not statistically significant; SD = standard deviation.

Table 3 – Associations between total risk score and chance of pregnancy using all participants.

Participants		Crude model		Adjusted model	
	n	HR	95% CI	aHR	95% CI
Women, total	1053	0.79	0.73–0.86	0.79	0.72–0.85
Women, couples	332	0.75	0.63–0.89	0.75	0.61–0.91
Women-only	721	0.81	0.73–0.89	0.81	0.73–0.89
Men-only	332	0.91	0.81–1.02	0.98	0.87–1.10

Outcome of the Poisson regression model given as hazard ratio (HR) and 95% confidence intervals (CI). A lower HR suggests a higher chance of achieving pregnancy. The 'crude' model was adjusted for fertility status only, while the adjusted model (aHR) was adjusted for fertility status (fertile or infertile), baseline body mass index and age. 'Women, couples' is defined as women with a male partner who also participated in the programme. Consequently, 'women-only' did not have a participating male partner.

association between healthy behaviour (low TRS) and the chance of pregnancy of the corresponding woman. We believe that mutual motivation in couples and consequently mutual behavioural change improves adherence to a healthy lifestyle, resulting in a stronger association, despite the non-significant association in men. Thus, optimizing parental conditions through preconception empowerment targeting modifiable behaviours can be considered as a long-term investment in the health of current and future generations.

In general, the potential of mobile health is well accepted and is already used for many different purposes regarding healthcare delivery, including tools to increase awareness by providing information, e.g. regarding nutrition and lifestyle, to a specific target population (Dute et al., 2016; van Kerkhof et al., 2016). The current developments in mobile technology make women embrace mHealth as a way to anonymously control and self-manage information online for adopting healthy behaviours (Willcox et al., 2015). Online anonymity has been highly valued before because it provides a 'comfort zone' and encourages honest feedback (Valaitis and Sword, 2005). Online resources are also often used by young women who seek information regarding nutrition and lifestyle in relation to fertility and pregnancy (Hearn et al., 2014). Therefore, we believe that tailored mHealth programmes can contribute to not only improving awareness of the importance of nutrition and lifestyle as a part of preconception care, but can also support women and men contemplating pregnancy to improve their nutrition and lifestyle prior to conception.

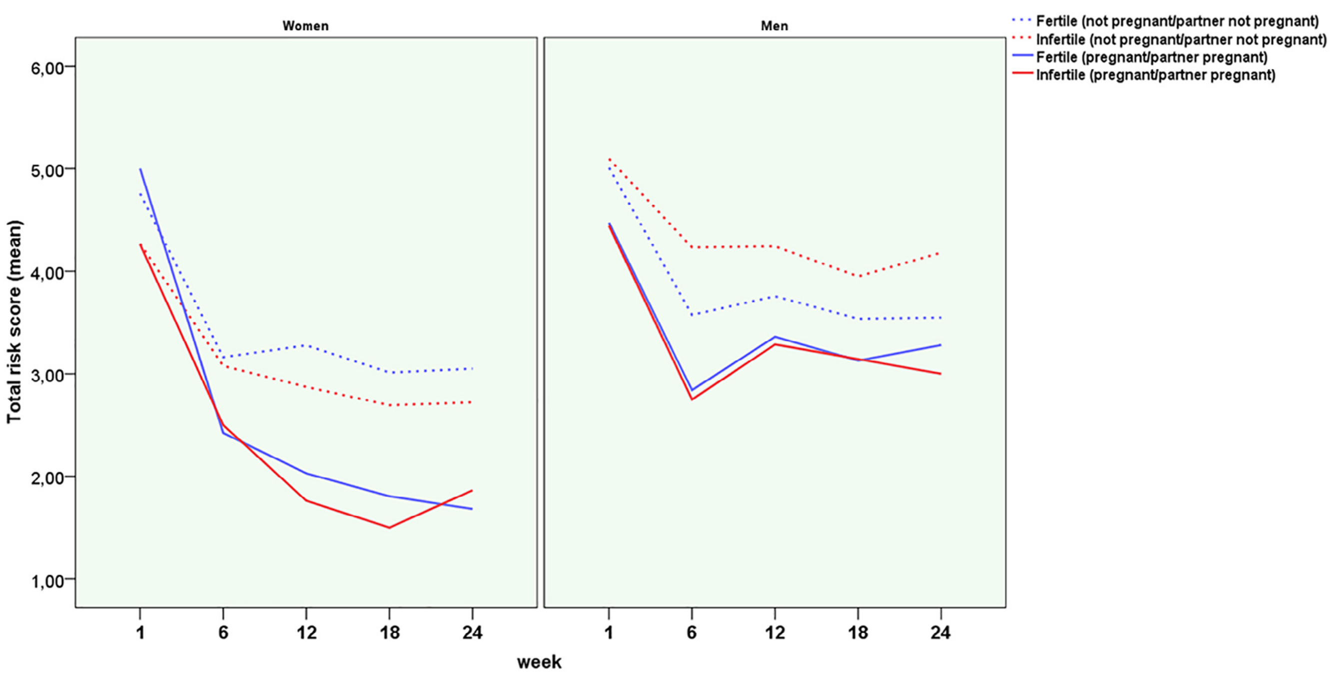

Figure 2 – Mean total risk score over time in women (left) and men (right) using the mHealth programme in the fertile and infertile population.

Table 4 – Number and cumulative number of pregnancies ('events') occurring while using the mHealth programme in the fertile and infertile population, including the percentages compared with the total per time point and the baseline total per group.

Parameter	Week 1	Week 6	Week 12	Week 18	Week 24	Cumulative
Total women	1053	920	822	740	676	–
Fertile women						
Total, *n*	620	543	476	421	380	–
Pregnant, *n* (%)	–	25 (4.6)	35 (7.4)	36 (8.6)	22 (5.8)	118 (19.0)
Infertile women						
Total, *n*	433	377	346	319	296	–
Pregnant, *n* (%)	–	5 (1.3)	14 (4.0)	14 (4.4)	7 (2.4)	40 (9.2)

Strengths of our study are its large sample size, the high compliance of 64% completion of the 26-week intervention, the use of serial measurements, the involvement of a subgroup of men, and the stratification of the study group into fertile and infertile couples. Inherent to a survey is the absence of a control group and the fact that residual confounding cannot be excluded. Other limitations are missing data on the source population, parity, ethnicity and socioeconomic status. This survey comprises a large cohort, however the sizes of the subgroups per inadequate behaviour were too small to determine the single behavioural effects on the chance of pregnancy. We realize that couples who are contemplating pregnancy unsuccessfully, but are not (yet) diagnosed as infertile, are more motivated to participate in this intervention, especially as time passes. This may explain the relatively low incidence of 19% of pregnancies in the group that was considered to be fertile.

We are aware of the fact that all (composite) risk scores are debatable, especially when comprising a combination of elements regarding behavioural change and risk factors for impaired reproduction and reproductive outcome. The use of this TRS can be considered a first step towards designing a comprehensive outcome measure comprising behavioural change regarding nutrition and lifestyle in women and men. We considered an alternative approach, by means of using dietary patterns, but these patterns are less easy to address and to inventory and therefore less suitable regarding our mobile health approach.

In conclusion, we show that women, and especially couples, contemplating pregnancy can improve their chance of pregnancy by improving individual nutrition and lifestyle. The mHealth 'Smarter Pregnancy' coaching programme can support these women. Further development of this programme, including the tailoring of language, cultural, social and economic features, will also stimulate its implementation in preconception, pregnancy and reproductive care with beneficial effects on reproduction, pregnancy, and future health and healthcare costs.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.rbmo.2017.06.014.

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