mHealth

An innovative approach in periconception care

Matthijs Reinoud van Dijk

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"Cars, like people, break down for one of two reasons,
either because they're poorly made or because they are driven on rough roads.
Rolls Royce cars don't break down no matter where they are driven."

David Barker
Southampton, 2013

CONTENTS

Chapter 1

General introduction and aim

The periconception window is defined as the 14 weeks prior to conception up to 10 weeks thereafter. This crucial period in reproduction comprises a timespan covering gametogenesis, conception embryogenesis and placental development[1]. During the preconception period, the gametes are exposed to both genetic and environmental factors that affect the microenvironment of oocytes in women and semen in men[2,3]. Poor nutrition and lifestyle are individual but modifiable risk factors that are associated with increased reproductive risks, such as subfertility and adverse maternal pregnancy and neonatal outcomes that contribute to maternal and perinatal morbidity and mortality[2-7]. Small for gestational age (SGA), preterm birth (PTB) and congenital malformations are defined as the 'Big 3 complications' and explain at least 85% of perinatal deaths in the Netherlands[8]. The evidence is overwhelming that mothers, who suffered from cardiovascular and metabolic pregnancy complications and experienced SGA or PTB outcome, as well as their children have increased risks of developing non-communicable diseases (NCDs) later in life[9-12]. These NCDs include obesity, diabetes, cancer, cardiovascular and respiratory diseases and are an increasing global health problem. During the last three decades, the prevalence of NCDs and their mortality rate increased tremendously. Of all deaths worldwide, 60% occurs due to NCDs[13]. The four leading risk factors for NCDs are the same as for adverse reproductive outcome, i.e. poor nutrition, smoking, alcohol consumption and obesity[14]. These modifiable risk factors derange metabolic, endocrine and several other pathways that can induce obesity, and raised blood pressure and cholesterol levels[14]. The distribution of these harmful behaviors differs between high-, middle- and low-income countries. For example, in high-income countries there is a higher prevalence of alcohol consumption, while smoking and poor nutrition are more common in low-income countries. Without interventions, the burden of NCDs is expected to continue to increase significantly in the 21st century[14].

Developmental origins of health and disease

The concept that environmental factors, including nutrition and lifestyle, influence the intra-uterine environment and subsequent health in later life is known as the paradigm of the developmental origins of health and disease (DOHaD). So far, the investigations involving the DOHaD paradigm have focused on the second half of pregnancy and on newborns. However, most adverse reproductive and pregnancy outcomes originate in the periconception window, a period in life which has been largely neglected in medical care and research. Since 2016, the periconception period has been recognized by the DOHaD society due to the overwhelming evidence that this period in life is crucial[1]. The mechanism of epigenetic programming can explain the associations observed between adverse pregnancy outcome and increased risks of early features of NCDs in later life. Therefore, the periconception period should be the earliest window of opportunity for interventions to reduce modifiable risk factors and, consequently, to prevent adverse maternal pregnancy and neonatal outcomes. To achieve the greatest impact regarding the prevention of these adverse outcomes, interventions should focus on the identification and change of modifiable risk factors for which adolescents, adults and health care professionals should be empowered[15].

Periconception care

The importance of interventions during the periconception period, preceded by early identification of risk factors, has been widely acknowledged as a part of general preconception care. However, the barriers to implement this type of preventive medicine appear to be hard to overcome. Aspects such as (public) awareness, responsibility and financing play important roles regarding the accessibility and uptake of preconception care[15]. The current situation in the Netherlands is that women or couples only receive preconception care when they have subfertility problems, known medical risk factors, a previous adverse pregnancy or neonatal outcome or upon a woman's own request. This implies that non-pregnant women or couples without a medical history are unfairly considered to be at low risk for these adverse outcomes. Moreover, most pregnant women enter antenatal care around 9 or 10 weeks gestation, through which the opportunity of pre- or periconception care is largely missed. This is likely the result of mutual unawareness and lack of knowledge of the couples contemplating pregnancy themselves as well as of health care professionals. Worrisome is that consequently the prevalence of in particular modifiable risk factors remains high in the reproductive population[16-18].

Mobile health

Mobile health (mHealth) has been defined in 2000 as 'unwired e-med' as a new approach in health care delivery[19]. Over time, mHealth became an area of electronic health (eHealth) characterized by a broad range of functions using mobile devices (e.g. smartphones and tablets or handheld computers)[20].

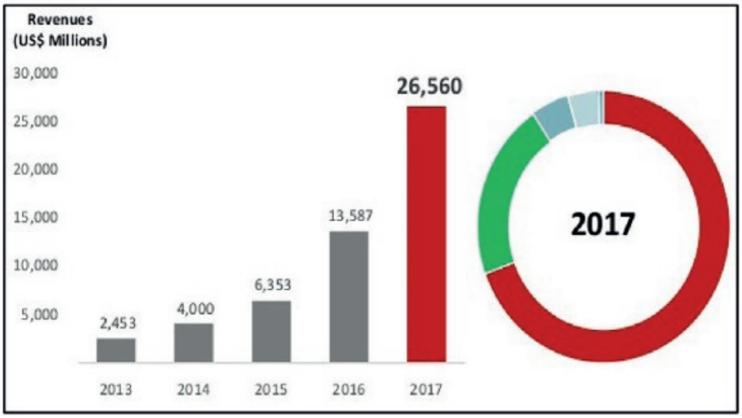

Figure 1 | Growth of the global mHealth market revenues (USD) during this thesis. Red: services (69%), Green: device sales (21%), Blue: paid downloads (5%), Grey: transaction (4%), Other: advertisement (1%). *Adapted from: research2guidance*

Due to the rapid growth and developments in the field of mHealth (Figure 1), new possibilities arise in the context of prevention strategies, bio-feedback and diagnostic tools[20,21]. Based on the massive adoption of smartphones worldwide, including low-income countries, the World Health

Organization emphasized the potential of mHealth in health care delivery on a large scale[22]. mHealth is an innovative approach to empower target groups to change and improve nutrition and lifestyle as part of personalized care. Since nearly all women and men of reproductive age have Internet access and own a smartphone, it will be very interesting to investigate the potential role and opportunities of mHealth regarding periconception care.

Main aim of this thesis

The main aim of this thesis is to investigate the benefits, barriers and effectiveness of the Smarter Pregnancy mHealth program regarding the adoption of healthy periconception nutrition and lifestyle and its impact on early reproductive and pregnancy outcome. To this main aim the following studies have been conducted:

PART I

1. Investigation of the feasibility, usability and first effectiveness of the Smarter Pregnancy mHealth program in a survey (Chapter 2, 3 and 4).
2. Exploring the perceptions and experiences of patients and health care professionals regarding mHealth and preconception care (Chapter 5).

PART II

3. Evaluation of the Smarter Pregnancy mHealth program in a randomized controlled trial (Chapter 6 and 7).
4. Investigation of the impact of periconception maternal nutrition and lifestyle on embryonic growth in a prospective periconception cohort (Chapter 8).

The ultimate goal of this thesis is that the new knowledge as described will further substantiate the awareness of patients and health care professionals regarding the importance of healthy periconception nutrition and lifestyle. Moreover, the opportunities provided by evidence-based personalized mHealth programs to empower these target groups will probably stimulate the accessibility and implementation of periconception care. Because periconception care is a form of preventive medicine in the earliest phase of life, it should be considered as the best investment in health of current and future generations[15].

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Part I

Chapter 2

Impact of an mHealth platform for pregnancy on nutrition and lifestyle of the reproductive population: a survey

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Van Dijk MR
Huijgen NA
Willemsen SP
Laven JSE
Steegers EAP
Steegers-Theunissen RPM

ABSTRACT

Background

Poor nutrition and lifestyle behaviors exert detrimental effects on reproduction and health during the life course. Therefore, lifestyle interventions during the periconceptional period can improve fertility, pregnancy outcome, and health of subsequent generations.

Objective

This survey investigates the compliance, usability, and initial effectiveness of the Web-based mHealth platform, Smarter Pregnancy.

Methods

A free subscription to the mHealth platform, Smarter Pregnancy, was provided to couples contemplating pregnancy (n=1275) or already pregnant (n=603). After baseline identification of inadequate nutrition and lifestyle behaviors, a personal online coaching program of 6 months was generated. Using multiple imputation and the generalized estimating equation model with independent correlations, we estimated the changes from inadequate to adequate nutrition and lifestyle behaviors over time. Subgroup analyses were performed for (1) overweight and obese women (body mass index (BMI) ≥25 kg/m^2), (2) pregnant women at the start of the program, and (3) couples.

Results

A 64.86% (1218/1878) compliance rate was observed and 54.7% (range 39.2-73.4%) of participants rated the program usability as positive or very positive. Adequate nutrition and lifestyle behaviors at baseline were 21.57% (405/1878) for vegetable intake, 52.61% (988/1878) for fruit intake, 85.44% (1303/1525) for folic acid use, 86.79% (1630/1878) for no tobacco use, and 64.43% (1210/1878) for no alcohol consumption. After 6 months of coaching, these lifestyle behaviors improved by 26.3% (95% CI 23.0-29.9) for vegetable intake, 38.4% (95% CI 34.5-42.5) for fruit intake, 56.3% (95% CI 48.8-63.6) for folic acid use, 35.1% (95% CI 29.1-41.6) for no tobacco use, and 41.9% (95% CI 35.2-48.9) for no alcohol consumption. The program showed the strongest effectiveness for participating couples.

Conclusions

This novel Web-based mHealth platform shows high compliance and usability, and users demonstrate improvements in nutrition and lifestyle behaviors. The next step will be further validation in randomized controlled trials and implementation.

INTRODUCTION

Worldwide, more than 45 million couples are contemplating pregnancy, of which around 22 million remain involuntarily childless. Moreover, of the more than 360 million pregnancies worldwide per year, at least 90 million end in miscarriage, 18 million result in congenital malformation, and 40 million result in children small for their gestational age. These reproductive and pregnancy failures largely originate in the periconceptional period, during which development and function of gametes, embryonic organs, and the placenta are programmed[1]. Poor periconceptional nutrition and lifestyle not only affect fertility and pregnancy outcome, but can also derange epigenetic programming with long-lasting health consequences[2]. Therefore, effective nutrition and lifestyle interventions in particular during this window of time will be an investment in healthy pregnancy and the health of current and future generations.

Currently, the most effective preconceptional interventions comprise weight loss, improvement of nutrition, use of folic acid supplements, and lowering the use of tobacco[3,4]. Unfortunately, women and men contemplating pregnancy or pregnant couples, as well as health care professionals, are often not aware of the detrimental effects of poor lifestyle behaviors[5-7]. These behaviors often accumulate not only in an individual, but also in couples, in particular among those with a low socioeconomic status, increasing the risk of a poor pregnancy outcome[8,9]. Therefore, it should be the responsibility of both health care professionals and patients to improve inadequate nutrition and lifestyle. To this aim, we previously developed and implemented a specific preconception outpatient clinic tailored to improve nutrition and lifestyle, which showed a 30% reduction of inadequate nutrition and lifestyle and a 65% increased chance of ongoing pregnancy after in vitro fertilization (IVF) treatment[6,10]. Obstacles of lifestyle counseling as part of periconceptional (clinical) care, however, require special expertise and time without reimbursement of costs.

Mobile health (mHealth) has the potential to transform health care delivery and to overcome obstacles by providing individual, tailored, and repeated information. Evidence is accumulating that mobile technology can effectively improve inadequate nutrition, lifestyle, and medication adherence[11]. Therefore, we developed the online, device-independent, Web-based coaching platform, Smarter Pregnancy[12]. This platform was based on scientific evidence of effective nutrition and lifestyle interventions, prevention and educational programs for noncommunicable diseases, and behavioral models, as well as our experience from the preconception outpatient clinic[6,13-15]. This mHealth platform aims to empower women, men, and health care professionals to improve inadequate nutrition and lifestyle. It also demonstrates the need for easily accessible, evidence-based interventions to improve the quality and effectiveness of periconceptional (clinical) care, the success of reproduction and pregnancy outcomes, as well as the prevention of disease during the life course[16,17].

Here we investigate the compliance, usability, and initial effectiveness of the Dutch version of this Web-based mHealth platform on changing inadequate nutrition and lifestyle behaviors in prepregnant women and their partners.

METHODS

Study Population

In 2012 and 2013, women and men contemplating pregnancy or pregnant couples living in Rotterdam, the Netherlands, visiting the Erasmus Medical Center (MC), University Medical Center, or midwifery practices in Rotterdam, were recruited to the study. Recruits were invited to sign up for a free subscription to the Web-based Smarter Pregnancy platform[12]. This included 6 months of coaching on the most prevalent inadequate nutrition and lifestyle behaviors (ie, vegetable, fruit, and alcohol intake) or the most strongly demonstrated associations of behaviors with fertility and pregnancy course and outcome (ie, tobacco and folic acid supplement use).

Adequate daily intakes are defined as at least 200 grams of vegetables and at least two pieces of fruit, a folic acid supplement of 400 µg, and no tobacco or alcohol use[18]. Men were screened on the same behaviors, except for folic acid supplement use. Evaluation of the results of the baseline survey and the four follow-up screening surveys are shown on each participant's personal page as lifestyle risk scores in graphs and text, accompanied by personal advice according to preconceptional recommendations and Dutch guidelines[18]. If a participant completes the final screening survey at 6 months, we consider this as maximum compliance. More details are described in the next paragraph.

Smarter Pregnancy

The coaching model developed for the Smarter Pregnancy platform is based on our research and expertise from the last 25 years on the impact of nutrition and lifestyle on reproduction as well as on pregnancy course and outcome[6,10,15,19,20]. In addition, we incorporated the following into the platform: results from the literature, Prochaska and Diclemente's transtheoretical model with a focus on the readiness for behavioral change, Bandura's social cognitive theory for self-efficacy, and Fogg's behavior model to include triggers to motivate and increase the ability to change[21-23]. Features of the attitude, social influence, and self-efficacy (ASE) model for coaching are applied; the ASE model has been frequently used for developing health education and prevention. Elements of this model comprise individual attitude, social influence, and self-efficacy aimed at the understanding and motives of people to engage in specific behavior[24].

The content of the individual coaching consisted of the baseline screening and follow-up screening at 6, 12, 18, and 24 weeks of the program. Coaching also included a maximum of three interventions per week comprised of short message service (SMS) text messaging and email messages containing tips, recommendations, vouchers, seasonal recipes, and additional questions addressing behavior, pregnancy status, body mass index (BMI), and adequacy of the diet. Every 6 weeks, participants were invited to complete a short, online, follow-up screening survey to monitor the change in their inadequate nutrition and lifestyle behaviors. Results from the screening session compared to the previous screening sessions were shown on their personal page (see Figure 1). This page also provided access to additional modules (ie, applications) to support physical activity, an agenda to improve the compliance of hospital appointments and intake of medication, and a module to monitor the safety of prescribed medication. A summary of all individual results were available to be obtained at any point by the participant, and to be handed over or sent by email to the health care professional for further evaluation and support of preconceptional and antenatal care. This mHealth platform complied with the highest rules of legislation for medical devices in Europe; therefore, it received the Conformité Européenne, classe 1 (CE-1), classification (2013) and can be used to improve the quality of medical care.

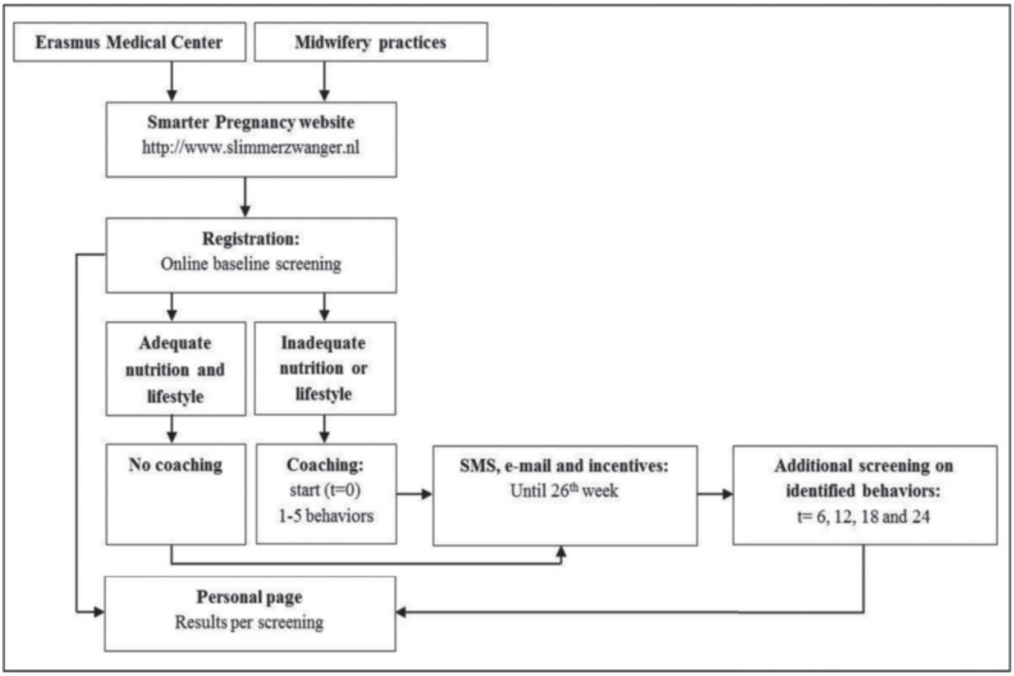

Figure 1 | Overview of the Web-based Smarter Pregnancy program: registration, identification of inadequate nutrition and lifestyle behaviors, and coaching. *SMS: short message service.*

Statistical Analysis

We analyzed all participants who completed or prematurely resigned from the platform. Compliance was defined by the percentage of participants who completed the 6-month program. Usability was assessed using a digital evaluation form containing 26 questions whose answers were scored using a 4-point Likert scale; the ratings were negative, neutral, positive, and very positive. This was used to report on participants' satisfaction with the platform, which was subdivided into three categories: (1) design and interface, (2) content and coaching, and (3) perception and personal benefit. General characteristics and lifestyle behaviors were compared using chi-square tests for proportions, and t tests and Mann Whitney U tests for continuous variables.

Using a generalized estimating equation (GEE) model with an independent working correlation matrix, we modeled the fraction that scored adequate at each of the follow-up time points. In order to minimize selection bias, we used multiple imputation models to handle missing data of the participants who prematurely resigned. Therefore, a separate model was built for each of the five lifestyle behaviors of interest using all available information on each of the time points, as well as the subgroup indicators to impute the missing values. For each nutrition and lifestyle behavior, we examined those individuals that scored inadequate at baseline.

Subgroup analyses were performed between (1) normal weight and overweight or obese women defined as having a BMI of <25.0 and ≥25.0 kg/m^2, respectively, (2) nonpregnant and pregnant women at the start of the program, and (3) women-only participants and couples, who were defined as the woman and her male partner who followed his own personal coaching program at the same time, which was also dependent on pregnancy status. To create the area under the curve (AUC) of the linear predictor as an overall measure of effectiveness of the program, we calculated the average of the log odds ratio at the specific time points. For each subgroup, this average was compared with that of its complement (eg, obese versus nonobese, pregnant versus nonpregnant, and couples versus women without a participating male partner). SPSS version 21.0 (IBM Corp, Armonk, NY) software package was used and the level of significance was set to .05 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. Digital informed consent was obtained from all participants, allowing us to use the data for analysis.

RESULTS

Compliance and Usability

Study compliance was 64.86% (1218/1878) among all participants who activated the program. Additional digital evaluation forms sent every 4 months to new participating women were received from 357 women out of 1878 (19.01%), of which 69.2% (247/357) were highly educated. The usability of the program was judged as positive or very positive by 54.7% of participants, and ranged from 39.2% (content and coaching) to 73.4% (design and interface) (see Figure 2).

Baseline Characteristics

We evaluated 1878 out of 2003 (93.76%) participants after exclusion of 125 (6.24%); these participants were excluded because of nonactivation due to incomplete registration or no data entry after subscribing to the application (see Figure 3). The baseline characteristics of the cohort (n=1878) who completed or prematurely resigned from the platform are depicted in Table 1. They are classified according to gender and further subdivided into groups that (1) completed the last screening and (2) resigned prematurely from the platform. No significant differences were observed in women and men that completed or resigned prematurely from the platform with regard to age, height, BMI, percentage of overweight and obesity, mean vegetable and fruit intake, percentage of inadequate folic acid supplement, and tobacco and alcohol use. The woman-to-man ratio of the participants was 4.3 to 1. Of the total group of 1525 registered women, 603 (39.54%) reported to be pregnant at baseline, of which 416 (69.0%) completed the program and 187 (31.0%) prematurely resigned (P=.04).

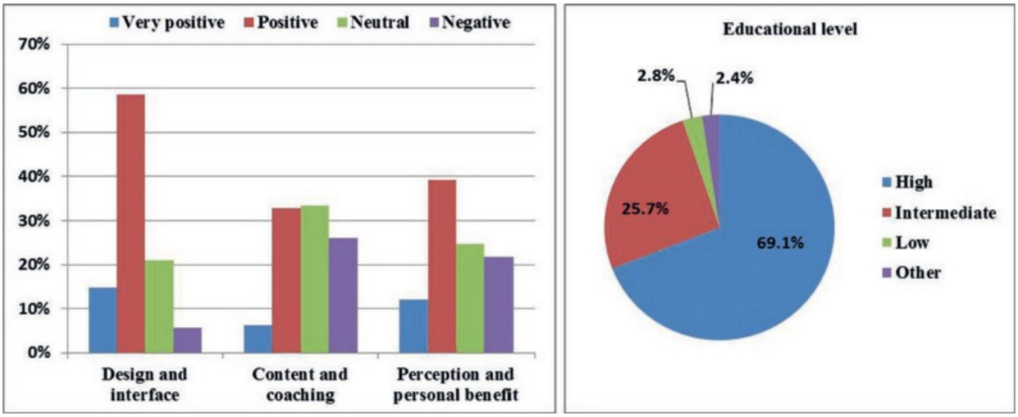

Figure 2 | Results of the evaluation of usability based on 357 evaluation forms. Usability of the Smarter Pregnancy program was subdivided into three program characteristics (left) and by participant educational levels (right).

Baseline Nutrition and Lifestyle Behaviors

Adequate nutrition and lifestyle behaviors at baseline were 21.57% (405/1878) for vegetable intake, 52.61% (988/1878) for fruit intake, 85.44% (1303/1525) for folic acid use, 86.79% (1630/1878) for no tobacco use, and 64.43% (1210/1878) for no alcohol consumption. The most prevalent inadequate behavior among both women and men was vegetable intake, which was 78.75% (1201/1525) and 77.1% (272/353), respectively. Inadequate fruit intake was observed in 43.21% (659/1525) of the women and 65.4% (231/353) of the men, whereas only 14.56% (222/1525) of the women reported no folic acid supplement use. Tobacco use was reported for 11.34% (173/1525) and 21.2% (75/353) of the women and men, respectively. Alcohol consumption was reported in 27.73% (423/1525) of all women and 69.4% (245/353) of all men. Women who resigned from the platform prematurely showed a significantly higher percentage of alcohol consumption of 31.6% (165/522) versus 25.72% (258/1003) (P=.02).

Effectiveness

Figure 4 depicts the changes in nutrition and lifestyle behaviors of the total and specific subgroups. Results at every follow-up screening point have been compared to baseline values. At baseline, vegetable intake was inadequate in 1473 out of 1878 participants (78.43%). An improvement of 20.9% (95% CI 18.5-23.5) was observed after 6 weeks and persisted to an increase up to 26.3% (95% CI 23.0-29.9) at 6 months (see Figure 4, A). Inadequate fruit intake was observed in 890 out of 1878 participants (47.39%) at baseline and improved by 36.1% (95% CI 33.0-39.3) and 38.4% (95% CI

34.5-42.5) at 6 weeks and 6 months, respectively (see Figure 4, B). The figures for inadequate folic acid supplement use observed in 222 out of 1525 women (14.56%) showed a decrease of 53.6% (95% CI 46.8-60.3) and 56.3% (95% CI 48.8-63.6) at 6 weeks and 6 months, respectively (Figure 4, C). At baseline, the prevalence of tobacco and alcohol use was 248 out of 1878 (13.21%) and 668 out of 1878 (35.57%), respectively. Tobacco and alcohol use were further reduced by 23.8% (95% CI 16.8-32.6) and 27.0% (95% CI 22.4-32.1) at 6 weeks and 35.1% (95% CI 29.1-41.6) and 41.9% (95% CI 35.2-48.9) at 6 months, respectively (Figure 4, D and E). All percentages are depicted in Multimedia Appendix 1.

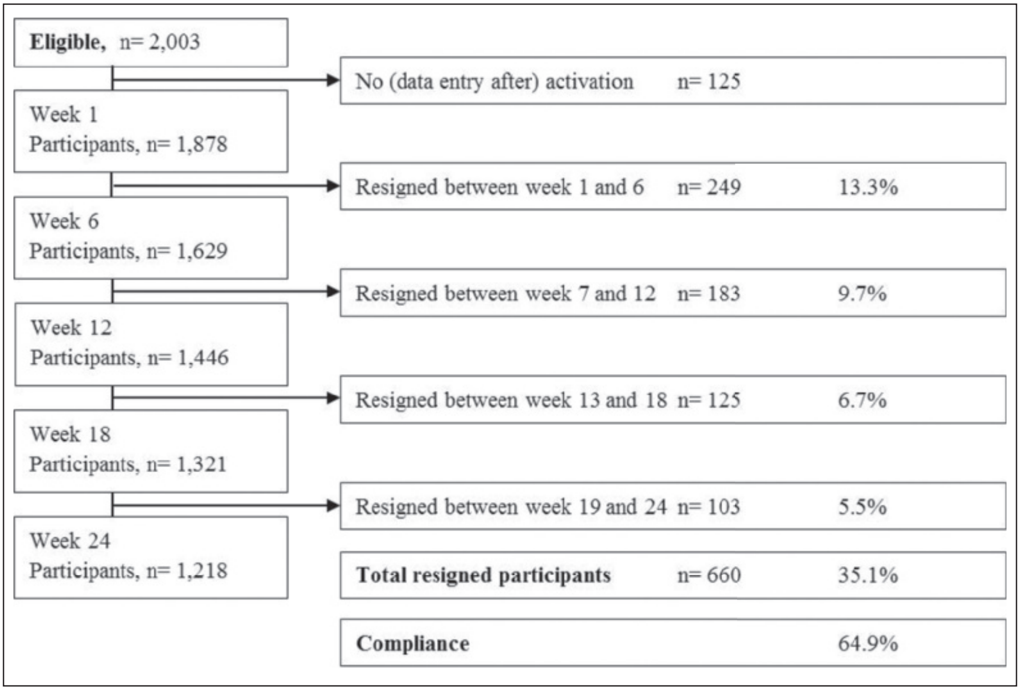

Figure 3 | Flowchart of the Smarter Pregnancy survey. Percentages are based on total participants (n=1878) in week 1.

Subgroup: Overweight and Obese Women

Baseline screening revealed 614 out of 1525 (40.26%) and 190 out of 353 (53.8%) overweight and obese women and men, respectively. Subgroup analysis showed patterns of inadequate nutrition and lifestyle behaviors in these women and men comparable to the total group (see Figure 4). The AUCs of the five inadequate lifestyle behaviors were comparable in overweight and obese (BMI ≥25 kg/m^2) and nonobese (BMI <25 kg/m^2) women and men (see Multimedia Appendix 1).

Table 1 | Baseline characteristics of all participants. *IQR: interquartile range. *Independent t test. **Pearson chi-square test. ***Mann Whitney U test.*

	Women (n= 1525)			Men (n= 353)		
	Completed (n=1003)	**Stopped (n=522)**	**p-value**	**Completed (n=215)**	**Stopped (n=138)**	**p-value**
Age (years), median (IQR)	31.2 (27.7-34.6)	31.5 (27.9-35.2)	.807*	33.7 (30.1-37.0)	34.6 (30.4-38.1)	.635*
Height (cm), median (IQR)	169.0 (164.0-174.0)	170.0 (165.0-175.0)	.525*	183.0 (179.0-190.0)	185.0 (181.0-188.0)	.160*
Pregnant (yes), % (n)	41.4 (416)	35.9 (187)	.036**	–	–	–
BMI (kg/m²)	24.0 (21.3-27.6)	24.0 (21.7-27.0)	.531*	25.2 (23.7-27.8)	25.3 (23.2-27.5)	.304*
Overweight (BMI 25-30), median (IQR)	27.1 (25.8-28.4)	26.7 (25.9-28.1)	.251*	26.6 (25.5-28.1)	27.2 (25.9-28.2)	.479*
Overweight in %, (n)	26.5 (266)	26.7 (139)		44.7 (96)	45.0 (62)	
Obese (BMI 30-60), median (IQR)	32.9 (31.3-35.8)	32.7 (31.2-36.1)	.521*	31.3 (30.8-35.1)	31.7 (30.3-35.1)	.424*
Obese in %, (n)	14.0 (141)	13.0 (68)		10.2 (22)	7.2 (10)	
Vegetables (gram/day), median (IQR)	135.7 (96.4-185.7)	142.9 (100.0-185.7)	.903*	142.9 (100.0-192.9)	150.0 (107.1-185.7)	.879*
Inadequate (<200), % (n)	78.2 (785)	79.9 (416)	.230**	75.3 (162)	79.7 (110)	.190**
Fruit (pieces/day), median (IQR)	2.3 (1.3-3.4)	2.1 (1.3-3.3)	.317***	1.4 (0.7-2.3)	1.4 (0.5-2.2)	.463***
Inadequate (<2), % (n)	42.5 (427)	44.6 (232)	.226**	64.7 (139)	66.7 (92)	.293**
Folic acid (no), % (n)	14.9 (150)	13.8 (72)	.592**	–	–	–
Smoking (yes), % (n)	11.9 (119)	10.3 (54)	.396**	22.3 (48)	19.6 (27)	.595**
Alcohol (yes), % (n)	25.7 (258)	31.7 (165)	.016**	70.2 (151)	68.1 (94)	.723**

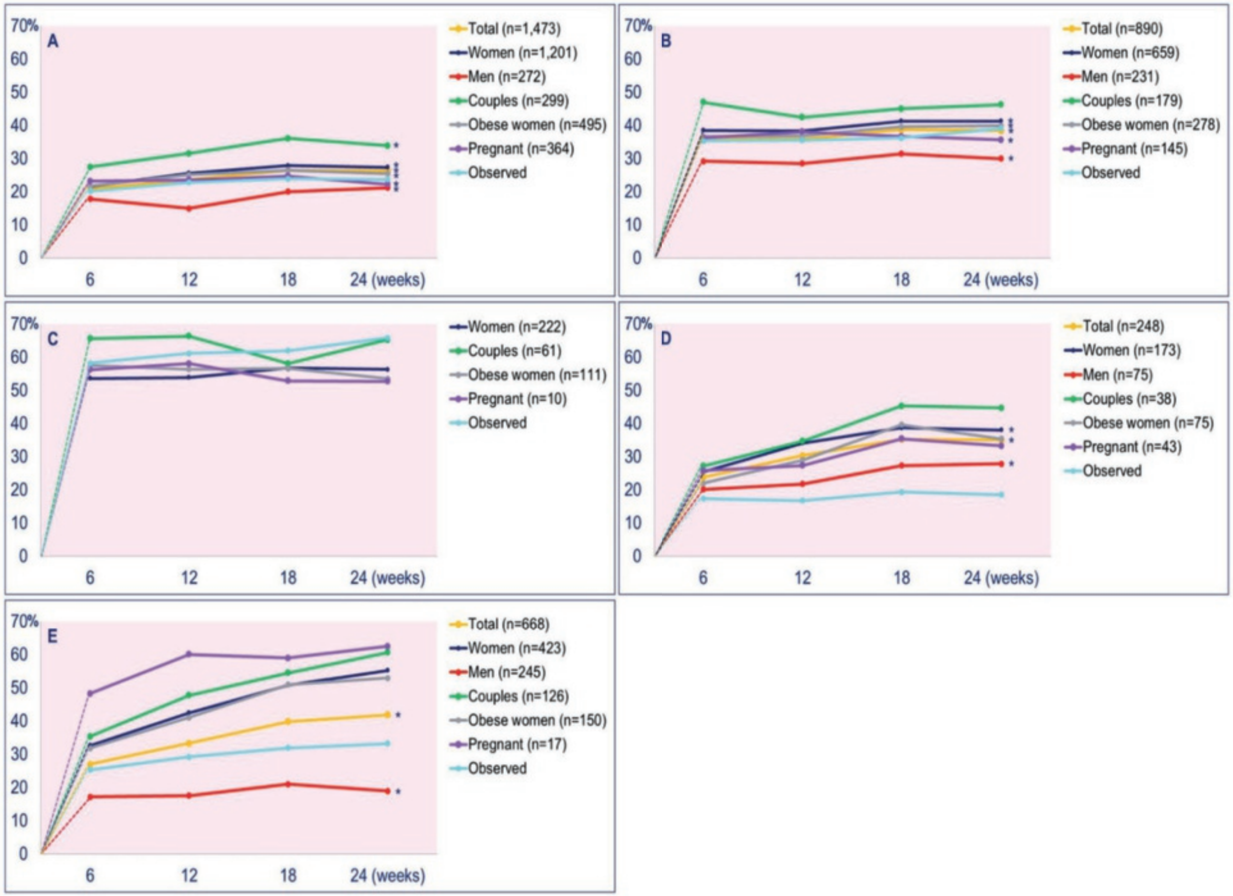

Figure 4 | Vegetable intake (A), fruit intake (B), folic acid use (C), tobacco use (D), and alcohol consumption (E) by participants. Improvement of behavior from inadequate at baseline to adequate at every screening point is shown as the percentage (y-axis) of the total group or subgroup. The dotted lines representing the change in relation to baseline are included to improve the interpretation of the graphs. **P*<.05 at all screening points. All percentages (per screening point) and areas under the curve, including P values, are included in Multimedia Appendix 1.*

Subgroup: Women Pregnant at Entry

A trend of comparable improvement of vegetable, fruit, and folic acid intake was shown in pregnant and nonpregnant women. Cessation of tobacco and alcohol use was higher in pregnant women although the groups were small (n=10 and n=17, respectively). The AUCs did not differ significantly (see Multimedia Appendix 1).

Subgroup: Couples

A total of 353 couples were coached, of which 215 (60.9%) completed the 6 months of coaching. The program was most effective on changing inadequate nutrition and lifestyle behaviors, except for tobacco use, when both the women and men used the program compared to the group of women only (see Figure 4).

DISCUSSION

Smarter Pregnancy is the first CE-1-certified, Web-based, personal mHealth platform tailored to convert inadequate to adequate nutrition and lifestyle behaviors in couples during the prepregnancy and pregnancy periods. This survey highlights the very high prevalence of inadequate intake of vegetables, fruit, and folic acid supplements, as well as tobacco and alcohol use in both women and men in the prepregnancy and pregnancy periods. Previous research by Hammiche et al and Vujkovic et al targeting the same period showed comparable results for inadequate vegetable and fruit intake (32.7-80.6%), inadequate folic acid supplement use (18.9-37.9%), tobacco use (11.3-31.0%), and alcohol use (35.5-66.0%)[6,25]. Screening tools and programs, such as ZwangerWijzer[26] and Healthy Pregnancy 4 All, have been developed and are being implemented[27,28]. However, routine preconceptional care is still only scarcely available. There is some evidence from other groups substantiating that eHealth and mHealth can support and enhance preventive preconceptional health care interventions.

The strengths of this survey are the high number of participants (n=1878), the high compliance of 64.86% (1218/1878) of participants to complete the 6 months of coaching, the positive feedback of the usability, participation of couples, and the analysis in which selection bias was limited by multiple imputation. The high appreciation of usability and initial effectiveness of this program on improving lifestyle behaviors suggests increased awareness and strong adherence to the given insights and recommendations. A possible explanation for these results is the multifunctional, interactive, and individual character of the coaching, which is distinctive compared to most eHealth and mHealth tools providing information only without taking individual conditions into account. Other strengths are the prospective and automatic data collection, as well as the subgroup analyses addressing the influence of pregnancy status, overweight and obesity, gender, and the participation of individuals or couples.

Our previous research has shown that a short self-administered risk score is a valid method to identify adequate or inadequate vegetable and fruit intake on both food group and nutrient levels[15]. Moreover, the percentages of these inadequate nutrition and lifestyle behaviors are in line with our data from the preconceptional outpatient clinic[6,10]. Limitations of this survey are the absence of validation by biomarkers and, inherent to the design of a survey, the absence of a control group. Moreover, using the Internet and a website in the Dutch language excludes groups using other languages and those having less access to the Internet.

In general, the endless opportunities of mHealth tools and knowing how to access them can be of unprecedented importance, especially with regard to health care. The rise of mobile technology by mobile phones, with more than one billion users worldwide, and other handheld devices also contributes to accessibility regarding online information and recommendations concerning healthy nutrition and lifestyle behaviors during the preconceptional period[29,30]. Couples contemplating pregnancy are often unaware of the availability and importance of these recommendations[5,6,19,31]. Unfortunately, health care professionals are often unfamiliar with up-to-date, evidence-based preconception care; it should be their responsibility to educate and increase patient awareness concerning healthy lifestyle behaviors in order to improve their chances to conceive and ensure a healthy prenatal environment for all couples[5]. Our findings contribute to previous research suggesting that both women and men should be involved in preconceptional care[32]. We demonstrated that the support of the partner by utilizing the same platform increases the effect of this intervention.

It is known that changing inadequate nutrition and lifestyle behaviors and maintaining healthy behavior is hard to accomplish, especially when there is a possibility that the goal to become pregnant will not be reached. Currently, only a small group of women that will not conceive spontaneously and those with a previous complicated pregnancy may receive preconceptional counseling by a health care professional (eg, general practitioner or gynecologist). Because the Smarter Pregnancy program has the potential as an mHealth platform to reach and educate a much larger population, including men, its use and implementation in health care is of interest to patients, health care professionals, and health care insurance companies to reduce health care costs in the future. The initial results of this survey were encouraging; this opens up the opportunity of implementation and conducting randomized controlled trials to further substantiate the findings on changing nutrition and lifestyle behaviors, and to further demonstrate the clinical effectiveness and cost-effectiveness of this mHealth platform in several target groups.

In conclusion, Smarter Pregnancy is a mHealth Web-based coaching platform that has the potential to improve and maintain healthy nutrition and lifestyle behaviors in women as well as men and, in particular, couples in the prepregnancy and pregnancy periods. These findings are important for further improvement of the quality and accessibility of preconceptional and pregnancy care, fertility, pregnancy course and outcome, and ultimately health from the earliest moment and throughout the life course.

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Multimedia Appendix 1 | Data are presented per risk factor per screening moment as percentage of improvement from inadequate into adequate behavior of the total (sub)group, including 95% confidence interval. Area-under-the-curve (AUC) is presented as log odds ratio: AUC-subgroup versus AUC-complement, difference and corresponding p-value.

	N	T=6	T=12	T=18	T=24	AUC –sub	AUC –compl	Diff.	p-value
Vegetables intake, % (95%CI)									
Observed	–	20.2	22.8	23.9	23.7	N/A	N/A	N/A	N/A
Total	1,473	20.9 (18.5-23.5)	23.6 (21.2-26.2)	26.5 (23.0-30.2)	26.3 (23.0-29.9)	-1.15	N/A	N/A	N/A
Women	1,201	21.6 (19.0-24.4)	25.6 (22.8-28.6)	27.9 (24.3-31.9)	27.4 (23.8-31.4)	-1.07	-1.56	0.49	.004
Men	272	17.8 (12.8-24.2)	15.0 (10.2-21.3)	20.0 (14.5-26.8)	21.2 (15.5-28.3)	-1.56	-1.07	-0.49	.004
Pregnant	364	23.2 (17.8-29.6)	23.6 (18.6-29.4)	24.7 (18.9-31.7)	22.2 (16.7-29.0)	-1.21	-1.02	0.19	.177
Overweight and obese	495	21.7 (18.1-25.7)	25.1 (20.7-30.0)	26.5 (21.4-32.3)	25.5 (20.0-31.9)	-1.12	-1.04	-0.08	.519
Couples	299	27.4 (22.4-33.0)	31.6 (25.5-38.3)	36.1 (29.5-43.3)	33.9 (27.8-40.5)	-0.74	-1.20	0.46	.0009
Fruit intake, % (95% CI)									
Observed	–	35.4	35.6	36.2	39.1	N/A	N/A	N/A	N/A
Total	890	36.1 (33.0-39.3)	35.8 (31.9-40.0)	38.7 (34.0-43.8)	38.4 (34.5-42.5)	-0.53	N/A	N/A	N/A
Women	659	38.5 (34.6-42.6)	38.4 (33.1-43.9)	41.3 (35.4-47.6)	41.3 (36.1-46.7)	-0.41	-0.88	0.47	.005
Men	231	29.2 (23.3-35.8)	28.6 (22.3-35.7)	31.5 (25.2-38.6)	30.0 (21.4-40.2)	-0.88	-0.41	-0.47	.005
Pregnant	145	36.3 (28.2-45.2)	38.1 (30.1-46.8)	36.7 (26.7-47.9)	35.7 (24.2-49.0)	-0.54	-0.38	0.17	.355
Overweight and obese	278	36.7 (29.9-44.0)	36.8 (28.5-46.0)	39.6 (30.6-49.3)	39.9 (30.0-50.7)	-0.48	-0.37	0.11	.482
Couples	179	47.0 (38.2-56.0)	42.5 (34.2-51.1)	45.0 (36.0-54.4)	46.3 (37.1-55.6)	-0.22	-0.49	0.27	.087
Folic acid sup. use, % (95% CI)									
Observed	–	58.2	61.1	61.9	65.8	N/A	N/A	N/A	N/A
Women	222	53.6 (46.8-60.3)	53.9 (46.5-61.1)	56.8 (48.7-64.5)	56.3 (48.8-63.6)	0.18	N/A	N/A	N/A
Pregnant	10	56.2 (2.3-98.6)	58.0 (3.0-98.4)	52.9 (8.9-92.8)	52.7 (7.6-93.8)	-0.72	0.21	-0.93	.577
Overweight and obese	111	57.5 (47.1-67.2)	56.4 (46.9-65.5)	56.6 (45.8-66.8)	53.5 (42.8-64.0)	0.27	0.09	0.18	.47
Couples	61	65.6 (52.0-77.0)	66.3 (50.1-79.5)	58.1 (43.9-71.0)	65.3 (52.5-76.2)	0.55	0.04	0.51	.099

Multimedia Appendix 1 | *Continued*

	N	T=6	T=12	T=18	T=24	AUC –sub	AUC –compl	Diff.	p-value
Smoking, % (95%CI)									
Observed	–	17.4	16.8	19.3	18.6	N/A	N/A	N/A	N/A
Total	248	23.8 (16.8-32.6)	30.4 (24.4-37.2)	35.3 (28.5-42.8)	35.1 (29.1-41.6)	-0.85	N/A	N/A	N/A
Women	173	25.4 (17.4-35.3)	34.1 (26.2-42.9)	38.7 (30.1-48.0)	38.1 (29.7-47.4)	-0.72	-1.18	0.46	.110
Men	75	20.2 (11.3-33.4)	21.8 (13.5-33.3)	27.4 (16.7-41.5)	27.9 (16.9-42.5)	-1.18	-0.72	-0.46	.110
Pregnant	43	25.8 (12.2-46.6)	27.4 (15.1-44.4)	35.5 (15.5-62.1)	33.3 (16.9-55.0)	-0.86	-0.68	-0.18	.617
Overweight and obese	75	22.0 (12.7-35.5)	29.0 (18.0-43.1)	39.7 (25.5-55.8)	35.4 (22.4-51.0)	-0.84	-0.65	-0.19	.552
Couples	38	27.2 (12.9-48.4)	34.7 (19.9-53.1)	45.3 (29.8-61.7)	44.7 (29.0-61.6)	-0.63	-0.75	0.12	.736
Alcohol consumption, % (95%CI)									
Observed	-	25.3	29.2	31.9	33.3	N/A	N/A	N/A	N/A
Total	668	27.0 (22.4-32.1)	33.3 (29.8-37.1)	39.8 (34.3-45.6)	41.9 (35.2-48.9)	0.63	N/A	N/A	N/A
Women	423	32.7 (27.2-38.6)	42.5 (37.0-48.0)	50.7 (44.3-57.1)	55.2 (46.1-63.9)	-0.22	-1.49	1.27	.031
Men	245	17.2 (12.3-23.5)	17.5 (12.7-23.7)	21.0 (14.6-29.2)	18.9 (13.7-25.5)	-1.49	-0.22	-1.27	.031
Pregnant	17	48.2 (25.9-71.3)	60.0 (35.5-80.4)	58.9 (31.8-81.5)	62.4 (35.5-83.3)	0.22	-0.24	0.46	.325
Overweight and obese	150	31.9 (24.1-40.8)	41.0 (33.3-49.3)	50.9 (42.0-59.8)	52.9 (37.6-67.7)	-0.25	-0.20	-0.05	.788
Couples	126	35.4 (26.4-45.5)	47.8 (36.0-59.8)	54.5 (41.1-67.2)	60.7 (50.1-70.3)	-0.04	-0.30	0.26	.207

Chapter 3

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

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Van Dijk MR
Koster MPH
Willemsen SP
Huijgen NA
Laven JSE
Steegers-Theunissen RPM

ABSTRACT

Periconceptional nutrition and lifestyle are essential in the pathogenesis and prevention of most reproductive failures, pregnancy outcome and health in later life. Therefore, we aim to investigate whether personalised mobile health (mHealth) coaching empowers couples contemplating pregnancy to improve healthy behaviour and their chance of pregnancy. A survey was conducted among 1,053 women and 332 male partners whom received individual coaching using the mHealth program 'Smarter Pregnancy' to change poor nutrition and lifestyle for 26 weeks dependent 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 higher TRS was significantly associated with a lower chance of pregnancy in all women (aHR 0.79, 95% CI 0.72-0.85) and in women with a participating male partner (aHR 0.75, 95% CI 0.61-0.91). This survey shows that empowerment of couples in changing poor nutrition and lifestyle using personalised mHealth coaching is associated with an enhanced pregnancy chance in both infertile and fertile couples.

INTRODUCTION

The worldwide increase of obesity and other nutrition and lifestyle-related non-communicable diseases (NCDs) has increased the awareness of these detrimental behaviours on reproductive and pregnancy outcomes with health consequences in later life and next generations[1]. Nevertheless, the prevalence of modifiable poor behaviours remains high, also in couples contemplating pregnancy and even in those undergoing medical assisted reproduction (MAR)[2-5].

The estimated prevalence of infertility is approximately 9% worldwide, of which 42-76% of the couples seek specialized fertility care or treatment[6]. Successful reproduction is determined by the compliance of treatment as well as the complex interactions between individual maternal and paternal conditions and behaviours of which some are modifiable[2,7-9]. Poor periconception nutrition, lifestyle and environmental exposures are associated with failure of reproduction, MAR, impaired embryonic and foetal development, and long-term programming of offspring health[10,11]. Therefore, the 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 health care costs including MAR[12].

Studies aiming to achieve behavioural changes and maintain healthy nutrition and lifestyle using electronic health (e-Health) and mobile health (mHealth) interventions that include personalised and individual feedback have shown promising results in the prevention of NCDs[13,14]. We already showed that the mHealth program 'Smarter Pregnancy' (Dutch version available on: www.slimmerzwanger.nl, English equivalent available on: www.smarterpregnancy.co.uk/research), which contains personalised 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[3].

Building on these findings we enlarged our study population with the aim to demonstrate associations between improvement of preconception nutrition and lifestyle using the mHealth coaching program 'Smarter Pregnancy' 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 Gynaecology at the Erasmus MC, University Medical Centre, 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 for a free subscription of the 'Smarter Pregnancy' coaching program. All male partners were invited to participate as well. Participants known to receive MAR at the moment 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 for a maximum of 3 per week during a period of 26 weeks. During this time window online questionnaires, incorporated into the program, were automatically sent every six weeks to monitor changes in the risk behaviour identified at baseline and to verify whether the pregnancy state changed during the previous six weeks. If so, the program automatically adjusts 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 program has been described before and can be found in the supplemental materials[3].

Risk scores

All identified poor nutrition and lifestyle were translated into risk scores for each behaviour, based on the Rotterdam Reproduction Risk score (R3-score), the Preconception Dietary Risk score (PDR) 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[2,9,12,15-17]. The total risk score (TRS) was defined as the sum of all risk scores per behaviour. A higher TRS depicts 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 grams per day and ≥2 pieces per day, respectively). Score 1 and 2 both represent a 'nearly adequate' intake (vegetable intake of 150-<200 grams and a fruit intake of 1.5–<2 pieces per day), taken 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 gram 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. 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 did neither receive 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-square 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 program with those who resigned prematurely.

We used an exponential survival model, equivalent to a Poisson model, to estimate the associations between the total risk score 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 to conceive 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 six weeks 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 six weeks 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 getting pregnant is included as an offset (i.e. a variable for which the coefficient is not estimated but fixed at one[18]. 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 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 women as separate groups; those who participated alone and those who participated with their male partner as a couple. In addition, we performed analyses discriminating between participants completed the program or resigned 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 Centre, Rotterdam, in the Netherlands. 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.

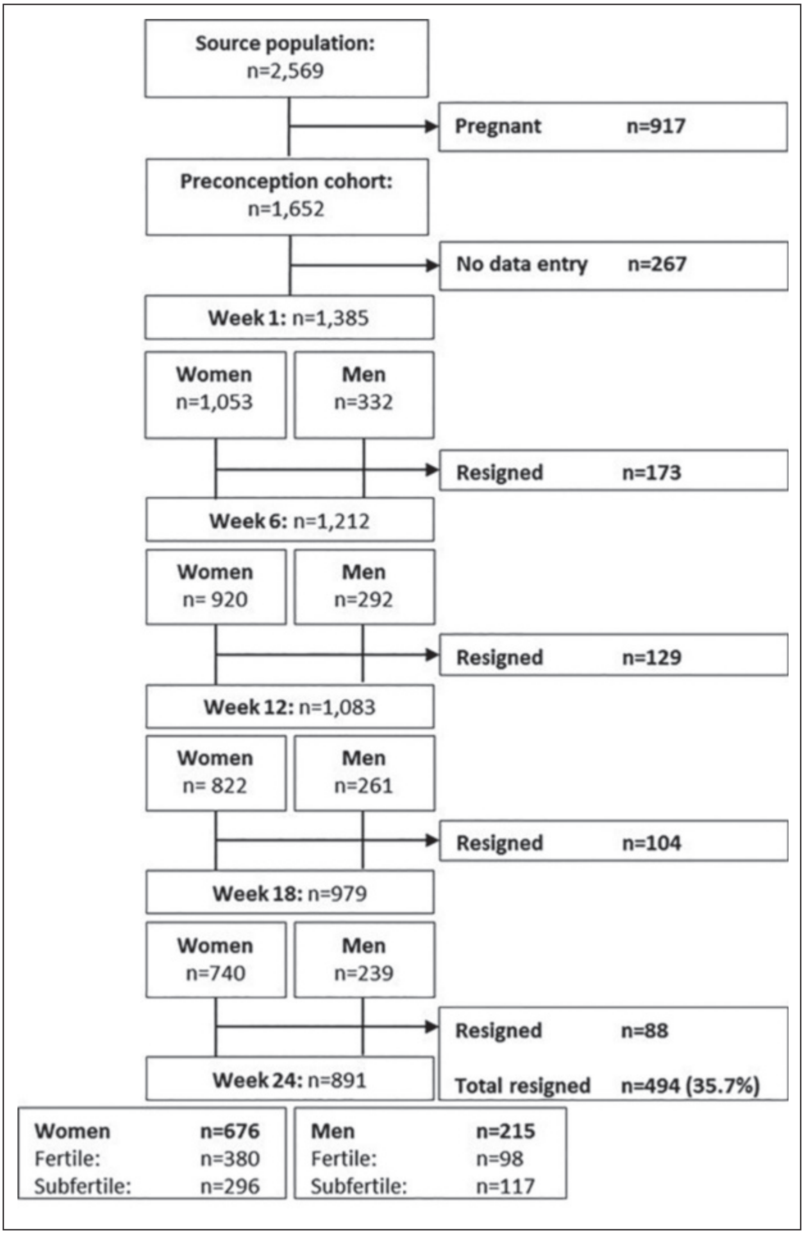

Figure 1 | Flowchart of source population and total cohort of participants in the Smarter Pregnancy program. Percentage based on total participants (n=1,385) in week 1.

Table 1 | Baseline characteristics and baseline risk scores of all women (Total) and subdivided into a fertile and subfertile group. To improve readiness, a legend of the risk scores was added. *SD: Standard deviation, BMI: Body mass index, IQR: Inter quartile range.*

		Women			
	Risk Score	**Total (n=1,053)**	**Fertile (n=620)**	**Subfertile (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)	0.598
Underweight (BMI <20), n (%)		96 (9.1)	55 (8.9)	41 (9.5)	
Normal (BMI ≥20-<25), n (%)		516 (49.0)	304 (49.0)	212 (49.0)	
Overweight (BMI >25–<30), n (%)		285 (27.1)	175 (28.2)	110 (25.4)	
Obese (BMI ≥30), n (%)		155 (14.7)	86 (13.9)	70 (16.2)	0.827
Vegetables, gram per day					
<150, n (%)	3	582 (55.3)	369 (59.5)	213 (49.2)	
150-200, not motivated, n (%)	2	19 (1.8)	10 (1.6)	9 (2.1)	
150-200, 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 (34.0)	
1.5-2, not motivated, n (%)	2	21 (2.0)	15 (2.4)	6 (1.4)	
1.5-2, 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)	0.071
Smoking, cigarettes per day					
>15, n (%)	6	22 (2.1)	15 (2.4)	7 (1.6)	
5-15, 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)	0.168
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)	
0-1, 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

Table 2 | Baseline characteristics and baseline risk scores of all men (Total) and subdivided into 2 groups: fertile and subfertile. To improve readiness, a legend of the risk scores was added. *SD: Standard deviation, BMI: Body mass index, IQR: Inter quartile range.*

	Risk Score	Men			p-value
		Total (n=332)	**Fertile (n=158)**	**Subfertile (n=174)**	
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)	0.547
BMI (kg/m²), median (IQR)		25.1 (4.0)	25.1 (3.9)	25.2 (4.2)	0.429
Underweight (BMI <20), n (%)		8 (2.4)	4 (2.5)	4 (2.3)	
Normal (BMI ≥20-<25), n (%)		146 (44.0)	74 (46.8)	72 (41.4)	
Overweight (BMI >25–<30), n (%)		150 (46.2)	66 (41.8)	84 (48.3)	
Obese (BMI ≥30), n (%)		28 (8.4)	14 (8.9)	14 (8.0)	0.493
Vegetables, gram per day					
<150, n (%)	3	175 (52.7)	89 (56.3)	86 (49.4)	
150-200, not motivated, n (%)	2	7 (2.1)	2 (1.3)	5 (2.9)	
150-200, motivated, n (%)	1	77 (23.2)	34 (21.5)	43 (24.7)	
≥200, n (%)	0	73 (22.0)	33 (20.9)	40 (23.0)	0.307
Fruit, pieces per day					
<1.5, n (%)	3	173 (52.1)	83 (52.5)	90 (51.7)	
1.5-2, not motivated, n (%)	2	5 (1.5)	5 (3.2)	0 (0.0)	
1.5-2, motivated, n (%)	1	33 (9.9)	14 (8.9)	19 (10.9)	
≥2, n (%)	0	121 (36.4)	56 (35.4)	65 (37.4)	0.666
Smoking, cigarettes per day					
>15, n (%)	6	25 (7.5)	7 (4.4)	18 (10.3)	
5-15, 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)	0.05
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)	
0-1, n (%)	1	116 (34.9)	54 (34.2)	62 (35.6)	
No drinking, n (%)	0	169 (50.9)	76 (48.1)	93 (53.4)	0.104
Total risk score, median (IQR)	0-15	5.0 (4.0)	5.0 (4.0)	5.0 (4.25)	0.834

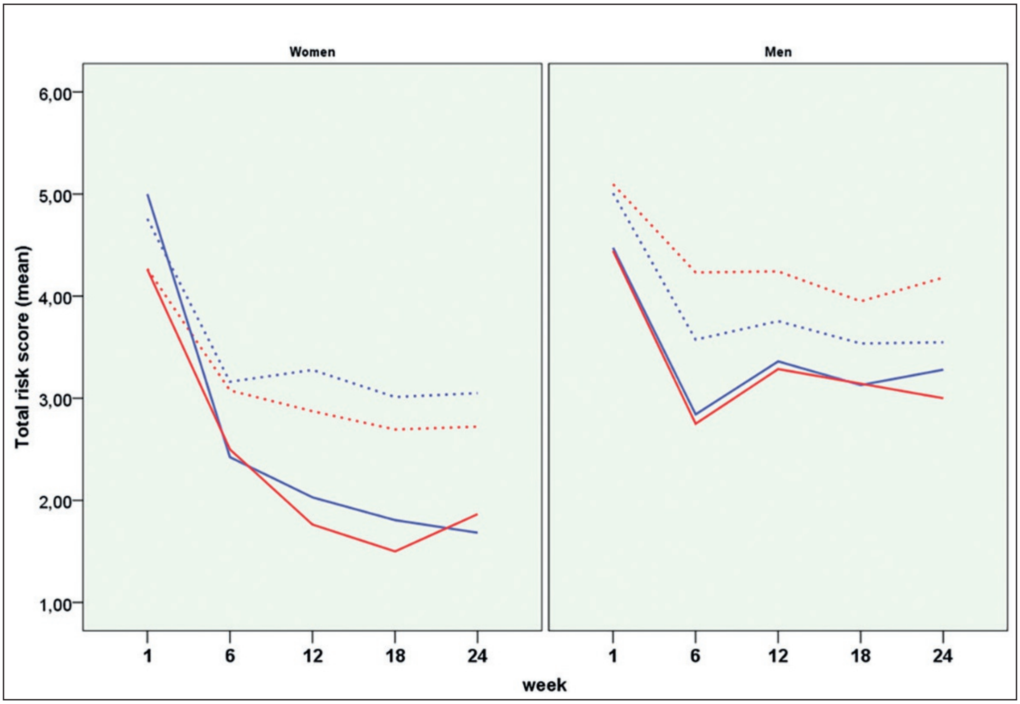

Figure 2 | Mean total risk score over time in women (left) and men (right) using the mHealth programme in the fertile and infertile population. *Blue dotted line: Fertile, not pregnant or partner not pregnant. Red dotted line: Infertile, not pregnant or partner not pregnant. Blue continuous line: Fertile, pregnant or partner pregnant. Red continuous line: Infertile, pregnant or partner pregnant*

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

		Crude model		Adjusted model	
	n	HR	95% CI	HR	95% CI
Women, total	1,053	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	731	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

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.

	Week 1	Week 6	Week 12	Week 18	Week 24	Cumulative
Total women	**1.053**	**920**	**822**	**740**	**676**	**–**
Fertile women						
Total, n	620	543	476	421	380	–
Pregnant, n (%)	–	25 (4.6)	35 (7.3)	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 (2.7)	40 (9.2)

DISCUSSION

This survey shows that empowerment of women and men to change poor nutrition and lifestyle using personalised mHealth coaching over a time span of 26 weeks is associated with an increased chance of pregnancy. Although our program was not tailored to fertility status, these associations were shown in both infertile and fertile couples. These findings also support our previous studies and that of others, which suggest that improvement of poor nutrition and lifestyle enhances fertility in fertile and infertile populations[1,9,19]. 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[3,20,21].

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 subsequently can alter the epigenome with consequences for not only reproduction and pregnancy but also for health and disease in later life[9-11,22]. 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[23-28]. 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 larger than women who participate without a male partner[3]. In this study, the prevalence of participating men was also relatively low (24%), but we observe a positive influence of male participation on the association between healthy behaviour and the chance of pregnancy. 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 health care delivery, including tools to increase awareness by providing information, e.g., regarding nutrition and lifestyle, to a specific target population[29,30]. 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[31]. Online anonymity has been highly valued before because it provides a "comfort zone" and encourages honest feedback[32]. Online resources are also often used by young women who seek information regarding nutrition and lifestyle in relation to fertility and pregnancy[33]. Therefore, we believe that tailored mHealth programs can contribute to not only improving the awareness of the importance of nutrition and lifestyle as a part of preconception care, but also support women and men contemplating pregnancy to improve their nutrition and lifestyle prior to conception.

Strengths of our study are its large sample size, the high compliance of 64% completion of the 26 weeks 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 behavioral 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 behavioral 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 inquiry 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 coaching program 'Smarter Pregnancy' can support these women. Further development of this program including the tailoring on language, cultural-, social- 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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Supplementary Table 1 | Baseline characteristics of participants who completed the programme compared to those who dropped out prematurely. Significant differences regarding age (P=0.04) and fertility status (P=0.02) were observed in women. No significant differences were observed in men.

	Women (n=1053)		Men (n=332)	
	Completed (n=676)	Drop-out (n = 377)	Completed (n=215)	Drop-out (n=117)
Age (years), median (IQR)	30.8 (6.1)	31.6 (6.4)	33.6 (6.0)	34.2 (8.2)
Height (cm) median (IQR)	169.3 (7.5)	169.5 (7.3)	184.1 (7.7)	184.3 (6.6)
BMI (kg/m^2)				
Underweight (BMI <20), *n* (%)	64 (9.5)	32 (8.5)	5 (2.3)	3 (2.6)
Normal (BMI 20–25), *n* (%)	324 (47.9)	193 (51.2)	97 (45.1)	51 (43.6)
Overweight (BMI 25–30), *n* (%)	181 (26.8)	104 (27.6)	96 (44.7)	52 (44.4)
Obese (BMI ≥30), *n* (%)	107 (15.8)	48 (12.7)	17 (7.9)	11 (9.4)
Fertility status				
Fertile, *n* (%)	296 (43.8)	137 (36.3)	98 (45.6)	60 (51.3)
Infertile, *n* (%)	380 (56.2)	240 (63.7)	117 (54.4)	57 (48.7)
Vegetables				
Too low (<150 g/day), *n* (%)	379 (56.1)	203 (53.8)	115 (53.5)	60 (51.3)
Low, not motivated, *n* (%)	10 (1.5)	9 (2.4)	6 (2.8)	1 (0.9)
Low, but motivated, *n* (%)	141 (20.9)	88 (23.3)	43 (20.0)	34 (29.1)
Adequate, *n* (%)	146 (21.6)	77 (20.4)	51 (23.7)	22 (18.8)
Fruit				
Too low (<2 pieces/day), *n* (%)	245 (36.2)	139 (36.9)	111 (51.6)	62 (53.0)
Low, not motivated, *n* (%)	12 (1.8)	9 (2.4)	3 (1.4)	2 (1.7)
Low, but motivated, *n* (%)	77 (11.4)	50 (13.3)	23 (10.7)	10 (8.5)
Adequate, *n* (%)	342 (50.6)	179 (47.5)	78 (36.3)	43 (36.8)
Folic acid supplement use				
Inadequate, *n* (%)	163 (24.1)	78 (20.7)	–	–
Adequate, *n* (%)	513 (75.9)	299 (79.3)	–	–
Smoking				
>15 cig/day, *n* (%)	16 (2.4)	6 (1.6)	14 (6.5)	11 (9.4)
>5 cig/day, *n* (%)	50 (7.4)	24 (6.4)	17 (7.9)	11 (9.4)
1–5 cig/day, *n* (%)	34 (5.0)	11 (2.9)	16 (7.4)	3 (2.6)
Non-smoking, *n* (%)	576 (85.2)	336 (89.1)	168 (78.1)	92 (78.6)
Alcohol				
>2/day, *n* (%)	3 (0.4)	1 (0.3)	6 (2.8)	5 (4.3)
1–2/day, *n* (%)	19 (2.8)	14 (3.7)	20 (9.3)	16 (13.7)
0–1/day, *n* (%)	174 (25.7)	115 (30.5)	81 (37.7)	35 (29.9)
Non-drinking, *n* (%)	480 (71.0)	247 (65.5)	108 (50.2)	61 (52.1)
Total risk score, median (IQR)	4.0 (3.0)	4.0 (3.0)	4.0 (4.0)	5.0 (4.0)

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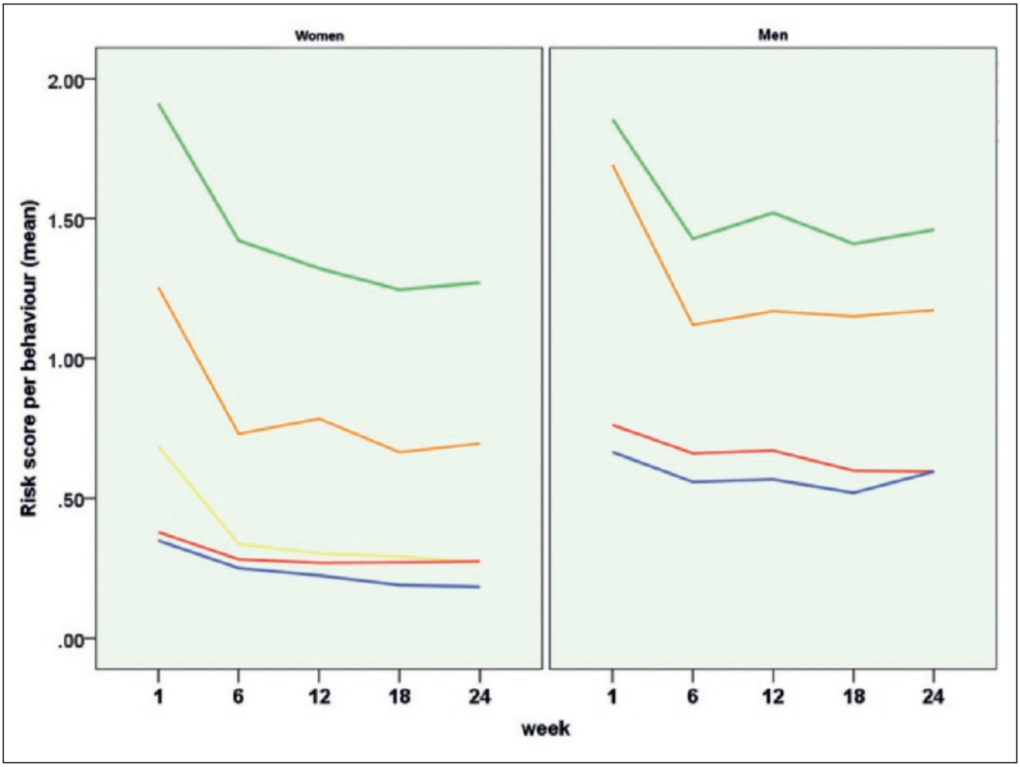

Supplementary Figure 1 | Mean risk score per behaviour over time in women (left) and men (right). *Green: vegetable intake. Orange: Fruit intake. Yellow: Folic acid supplement use. Red: Smoking. Blue: Alcohol consumption.*

SUPPLEMENT 1

Smarter Pregnancy, an extensive description of the intervention

The coaching model developed for the Smarter Pregnancy platform is based on our research and expertise from the last 25 years on the impact of nutrition and lifestyle on reproduction as well as on pregnancy course and outcome. In addition, we incorporated the following into the platform: results from the literature, Prochaska and Diclemente's transtheoretical model with a focus on the readiness for behavioral change, Bandura's social cognitive theory for self-efficacy, and Fogg's behavior model to include triggers to motivate and increase the ability to change. Features of the attitude, social influence, and self-efficacy (ASE) model for coaching are applied; the ASE model has been frequently used for developing health education and prevention. Elements of this model comprise individual attitude, social influence, and self-efficacy aimed at the understanding and motives of people to engage in specific behavior.

The content of the individual coaching consisted of the baseline screening and follow-up screening at 6, 12, 18, and 24 weeks of the program. Coaching also included a maximum of three interventions per week comprised of short message service (SMS) text messaging and email messages containing tips, recommendations, vouchers, seasonal recipes, and additional questions addressing behavior, pregnancy status, body mass index (BMI), and adequacy of the diet. Every 6 weeks, participants were invited to complete a short, online, follow-up screening survey to monitor the change in their inadequate nutrition and lifestyle behaviors. Results from the screening session compared to the previous screening sessions were shown on their personal page (see Figure 1). This page also provided access to additional modules (ie, applications) to support physical activity, an agenda to improve the compliance of hospital appointments and intake of medication, and a module to monitor the safety of prescribed medication. A summary of all individual results were available to be obtained at any point by the participant, and to be handed over or sent by email to the health care professional for further evaluation and support of preconceptional and antenatal care.

This mHealth platform complied with the highest rules of legislation for medical devices in Europe; therefore, it received the Conformité Européenne, classe 1 (CE-1), classification (2013) and can be used to improve the quality of medical care.

Reference: Van Dijk MR, Huijgen NA, Willemsen SP, Laven JS, Steegers EA, Steegers-Theunissen RP. Impact of an mHealth Platform for Pregnancy on Nutrition and Lifestyle of the Reproductive Population: A Survey. JMIR Mhealth Uhealth 2016;4(2):e53. DOI: 10.2196/mhealth.5197

Chapter 4

Neighborhood deprivation and the effectiveness of mHealth coaching to improve periconceptional nutrition and lifestyle in women: a survey in a large, urban municipality in the Netherlands

Submitted

Gootjes DV
Van Dijk MR
Koster MPH
Willemsen SP
Steegers EAP
Steegers-Theunissen RPM

ABSTRACT

Background

Living in a deprived neighborhood is associated with several adverse pregnancy outcomes. This can be explained by the accumulation of risk factors, such as inadequate nutrition and lifestyle behaviors, in residents who live in those deprived neighborhoods. In 2011, we launched the ''Smarter Pregnancy'' mHealth coaching program, which has proven to be effective to improve inadequate nutrition and lifestyle behaviors in (pre-)pregnant women. It is not known whether this mHealth program is equally effective in women who live in deprived neighborhoods.

Objective

To study the association between neighborhood deprivation and (improvement of) inadequate nutrition and lifestyle behaviors of (pre-)pregnant women who subscribed to the ''Smarter Pregnancy'' program.

Methods

We analyzed data from women who are contemplating pregnancy or already pregnant and used the ''Smarter Pregnancy'' program between 2011-2016. The program consisted of 24 weeks of coaching on five nutrition and lifestyle behaviors of which adequate daily intakes were defined as an intake of ≥200 grams of vegetables, two pieces of fruit, daily folic acid supplement use of 400 μg per day, and no smoking or alcohol consumption. Neighborhood deprivation was determined according to the status scores of the Netherlands Institute for Social Research. Logistic regression analyses and generalized estimating equation models were used to assess the association between the neighborhood status score (NSS) and (the improvement of) inadequate nutrition and lifestyle behaviors, adjusted for maternal age, body mass index, geographic origin, pregnancy status and participation as a couple.

Results

A total of 2,554 women were included of whom 521 participated with their male partner. Overall, daily vegetable intake was most frequently inadequate at the start of the program (n=1,985; 77.7%). Women with a higher NSS (i.e. living in a less deprived neighborhood) less often smoked (adjusted OR 0.85, 95% CI 0.77;0.93), more often consumed alcohol (adjusted OR 1.14, 95% CI 1.04;1.24) and were less likely to complete the 24 weeks of coaching (OR 0.91, 95% CI 0.88;0.95) compared to women who live in a neighborhood with a lower NSS. In the total study group, the relative improvement of inadequate nutrition and lifestyle behaviors after 24 weeks of coaching was between 26% and 64%. NSS was negatively associated with this improvement, indicating that women with a higher NSS were less likely to improve inadequate nutrition and lifestyle behaviors, especially vegetable intake (adjusted OR 0.89, 95% CI 0.82;0.97).

Conclusions

The ''Smarter Pregnancy" mHealth coaching program empowers women to improve inadequate nutrition and lifestyle behaviors. Unexpectedly, the program seemed more effective in women who live in more deprived neighborhoods. It is important to unravel differences in needs and behaviors of specific target groups in order to further tailor the mHealth program based on demographic characteristics, such as neighborhood deprivation.

INTRODUCTION

Worldwide, there are substantial differences in perinatal morbidity and mortality rates between and within countries, which may indicate inequalities in perinatal as well as population health[1,2]. Several underlying factors can explain these differences, such as maternal-specific (e.g. age, body mass index (BMI) and parity), environmental (e.g. air pollution and extreme temperature) and community-derived (e.g. housing conditions and poverty) factors[3-6]. As in other countries, perinatal morbidity and mortality rates in the Netherlands also differ between country parts, with particularly high mortality rates in the country's four largest cities. This is mainly due to the large number of deprived neighborhoods in these cities[7-9].

Risk factors for adverse pregnancy outcomes, such as poor nutrition, lifestyle and housing conditions as well as lower health literacy, often accumulate in residents of deprived neighborhoods[6,9,10]. However, living in a deprived neighborhood itself has also been described as an independent risk factor for poor health outcomes[11]. Exposure to abovementioned risk factors during the periconception period (i.e. the 14 weeks prior to conception until 10 weeks after conception[12,13] can have a detrimental effect on subsequent maternal and neonatal outcome. Moreover, on the longer term, the effect of these adverse outcomes is not only limited to perinatal health, but does also extend to the child's health later in life[14,15].

It is thus important to change inadequate nutrition and lifestyle behaviors during the periconception period. According to the transtheoretical model of behavioral change, intentional behavioral change can be achieved after passing six different stages, from pre-contemplation to maintenance and termination[16]. However, behavioral change is more challenging for individuals who have limited health literacy or impaired financial resources, who are less educated, and live in more deprived neighborhoods[3,17,18]. From this background, we hypothesize that women who live in more deprived neighborhoods are less likely to improve inadequate nutrition and lifestyle behaviors before and during pregnancy compared to women who live in less deprived neighborhoods.

Currently, mobile Health (mHealth) applications are widely available and used for health improvement. mHealth applications can be designed to a specific population and target of interest and may be offered anytime and anywhere at low costs[19,20]. Therefore, mHealth is a promising medium to support people to improve nutrition and lifestyle behaviors[19]. In 2011, after more than 30 years of research on the impact of nutrition and lifestyle behaviors on reproduction, we developed and launched the ''Smarter Pregnancy" mHealth coaching program[21] for (pre-) pregnant women and their male partners[22-24]. This mHealth program has proven to effectively improve nutrition and lifestyle behaviors (i.e. vegetable and fruit intake, folic acid supplement use, smoking and alcohol consumption) in (pre-)pregnant couples, which also resulted in an enhanced pregnancy chance in fertile and subfertile couples[22,25].

The aim of the current study was to investigate the association between neighborhood deprivation and the improvement of inadequate nutrition and lifestyle behaviors of (pre-)pregnant women of the ''Smarter Pregnancy" program.

METHODS

Data collection

We analyzed all data of (pre-)pregnant women that registered for a free subscription to the ''Smarter Pregnancy" programbetween December 2011 and September 2016[21]. Registration to this mHealth program was recommended to patients who visited the Department of Reproductive Medicine of the Erasmus MC and to women who attended a midwife in the Rotterdam area, but since the website had an open access policy, all visitors were able to register. Participating women either had a wish to conceive or were already pregnant (<13 weeks). Women could either participate alone or together with their male partner. Due to the sample size, in this study we only analyzed data from women, but participation as a couple was taken into account as a co-variate.

Intervention

The coaching program started with a baseline screening on nutrition (i.e. vegetable and fruit intake and folic acid supplement use) and lifestyle (i.e. smoking and alcohol consumption) behaviors that significantly impact fertility and pregnancy course and outcome[26,27]. The mHealth coaching lasted for a period of 24 weeks and was only targeted on the nutrition and lifestyle behaviors that were inadequate at the start of the program. Coaching consisted of a maximum of three interventions per week comprising of short message service (SMS) text messages and e-mail messages containing recommendations, vouchers and seasonal recipes. Follow-up screening took place at 6, 12, 18 and 24 weeks after registration. Besides nutrition and lifestyle behaviors, there were additional questions addressing pregnancy status and BMI. A detailed description of the content of the ''Smarter Pregnancy" program has previously been published by van Dijk et al.[22].

Outcomes

Compliance to the ''Smarter Pregnancy" program was defined as the percentage of participants who filled in the last questionnaire of the program after 24 weeks of coaching. At baseline and after 24 weeks of coaching, the reported nutrition and lifestyle behaviors were classified as 'adequate' or 'inadequate'. Adequate behavior was defined as a daily intake of at least 200 grams of vegetables and at least two pieces of fruit, daily folic acid supplement use of at least 400 µg starting before conception and lasting until the 12th week of pregnancy, and no smoking or alcohol consumption[28].

Covariates

Demographic characteristics and anthropometric measurements of the participants were retrieved from the ''Smarter Pregnancy" database: sex (male or female), age (continuous), pregnancy status (pregnant or not pregnant) and BMI (calculated from self-reported height and weight). Geographic origin was not reported by participants themselves. Therefore, we used the surnames of the participants to ascribe them a geographic origin, a method which is considered valid when self-identification is not available[29]. Classification was performed by three investigators (D.G., M.R.D. and M.P.H.K.) who separately categorized all participants' surnames into two groups, i.e. Western and non-Western origin. Any disagreement was resolved by discussion between the three investigators.

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To adjust for nutrition and lifestyle behaviors, a total risk score (TRS) was calculated. For vegetable and fruit intake, folic acid supplement and alcohol use, 0 points were assigned in case a participant had an adequate intake or use[25]. For inadequate intake or use, 3 points were assigned. For smoking 6 points were assigned in case of inadequate use, due to its known strong negative impact on pregnancy course and outcome[30,31]. Consequently, the TRS in this study ranges from 0 (most adequate) to 18 (most inadequate).
Zip codes of the participants were used to assign them a neighborhood deprivation state, which was based on the status scores of the Netherlands Institute for Social Research. These scores follow a standard normal distribution by design and are calculated for all 4-digit zip codes in the Netherlands based on four neighborhood characteristics: the average income, the number of non-employed residents, the number of lower educated residents, and the number of households with a low income[32]. A low neighborhood status score (NSS) indicates a more deprived neighborhood status where a high NSS indicates a less deprived neighborhood status[33]. Since 1998, the NSS is calculated every four years. For this study, the NSS of the year 2014 was used to determine the classification of the neighborhood participants lived in while using the ''Smarter Pregnancy" program. In the year 2014, the interquartile range (IQR) of the NSS in the Netherlands was -0.57 to 0.71.

Data analysis

All participants who started the program were included in the analysis at baseline. However, improvement of nutrition and lifestyle behaviors was only examined in those individuals that scored inadequate at any of the these behaviors the start of the program. In order to minimize selection bias, multiple imputation using chained equations was performed to handle missing data of women who prematurely resigned from the program. For those women, it was assumed that the adequacy of their nutrition and lifestyle behaviors at the last reported screening moment would not have changed until the end of the program (24 weeks).

Univariate linear and logistic regression analysis was used to study associations between demographic characteristics of the study population (maternal age, BMI, geographic origin, pregnancy status, whether a woman participated as a couple or alone, and TRS) and the NSS at the start of the program. Logistic regression analysis was used to examine the association between the NSS and (in)adequate nutrition and lifestyle behaviors at the start of the program. To study the improvement of inadequate nutrition and lifestyle behaviors after 24 weeks of coaching, generalized estimating equations (GEE) with an independent working correlation matrix were used to model the fraction of the study population that scored inadequate at baseline. Interaction tests were performed to study interactions of geographic origin, participation as a couple or being pregnant at the start of the program on the association between NSS and nutrition and lifestyle behaviors.
Statistical analyses were performed using SPSS version 21 software package (IBM Corp, Armonk, NY) and R version 3.4 (Foundation for Statistical Computing, Vienna, Austria). P-values <0.05 were considered statistically significant. No alpha-adjustment for multiple comparisons was made.

RESULTS

General characteristics

A total of 3,776 women registered to the "Smarter Pregnancy" program, of whom 1,222 (32.4%) were excluded due to absence of activating the registration, incomplete registration or incomplete data entry at the start of the program (Figure 1). Consequently, a total of 2,554 women were included in the analysis of whom 521 participated with their male partner. The median age of the women at the start of the program was 31 years and most women were of Western geographic origin (n=1,862; 80.0%). Of all nutrition and lifestyle behaviors, daily vegetable intake was most frequently inadequate at the start of the program (n=1,985; 77.7%) (Table 1).

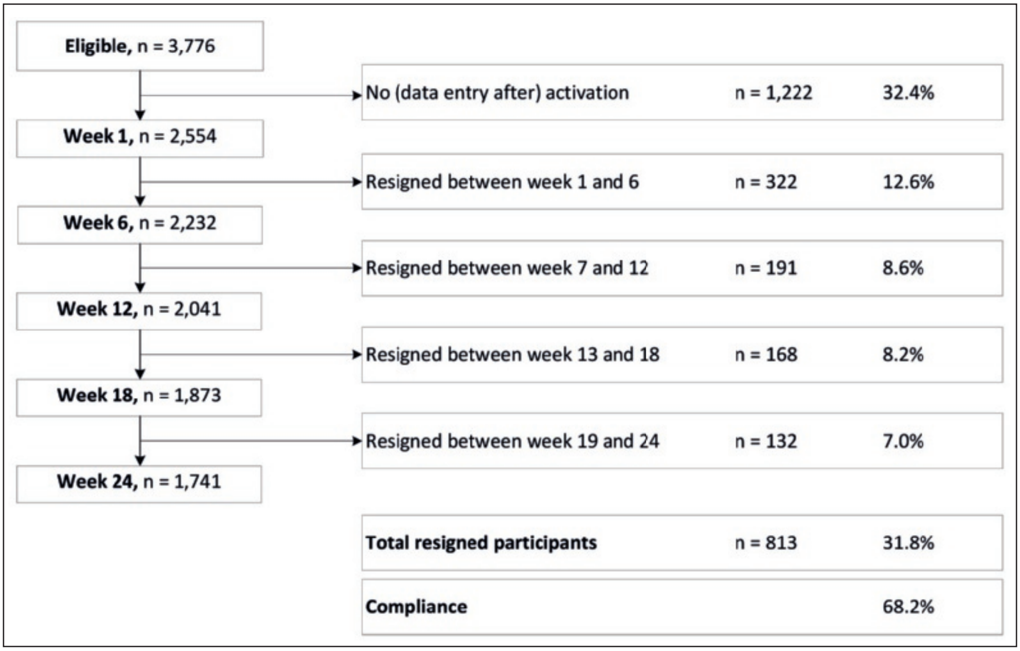

Figure 1 | Flowchart of study participants that completed or resigned from the "Smarter Pregnancy" mHealth coaching program.

Women with a higher NSS (i.e. who lived in a less deprived neighborhood) were older (β=0.04, 95% CI 0.03;0.05) and more often participated as a couple (β=0.18, 95% CI 0.11;0.25). Moreover, these women were more often pregnant at the start of the program (β=-0.30, 95% CI -0.41;-0.19), had a lower BMI (β=-0.03, 95%CI -0.04;-0.02), and were less often of non-Western geographic origin (β=-0.78, 95% CI -0.85;-0.70). (Table 2)

Compliance to the ''Smarter Pregnancy" program was 68.2% (Figure 1). Women with a higher NSS were less likely to finish the 24 weeks of coaching (OR 0.91, 95%CI 0.88;0.95).

Table 1 | Demographics of the study population, and nutrition and lifestyle behaviors at the start and after 24 weeks of coaching with the ''Smarter Pregnancy" mHealth coaching program.

	Women (n=2,554)
Demographics	
Age (years), median (IQR)†	31 (28-34)
Neighborhood status score, median (IQR)	-0.18 (-1.14-0.69)
Pregnant at baseline (yes), n (%)	1,300 (50.9)
Body mass index (BMI; kg/m^2), median (IQR)†	23.9 (21.4-27.5)
Participating as couple (yes), n (%)	521 (20.4)
Geographic origin (Western), n (%)†	1,862 (80.8)
Nutrition and lifestyle behaviors	
Vegetable intake (inadequate), n (%)	
At start of the program	1,985 (77.7)
At 24 weeks	1,462 (57.2)
Fruit intake (inadequate), n (%)	
At start of the program	1,024 (40.1)
At 24 weeks	576 (22.6)
Folic acid supplement use (inadequate), n (%)	
At start of the program	316 (12.4)
At 24 weeks	114 (4.5)
Smoking (yes), n (%)	
At start of the program	252 (9.9)
At 24 weeks	182 (7.1)
Alcohol consumption (yes), n (%)	
At start of the program	605 (27.0)
At 24 weeks	339 (13.3)
Total risk score, median (IQR) *	3 (1-6)

† Age, BMI and geographic origin were missing in 1.2%, 0.4% and 9.6% of the study population, respectively. IQR: interquartile range

Nutrition and lifestyle behaviors

Since coaching was only aimed at nutrition and lifestyle behaviors that were reported as inadequate at the start of the program, improvement of these behaviors was only studied in subsets of women. Overall, women who used the "Smarter Pregnancy" program improved all nutrition and lifestyle behaviors (Table 1). At the start of the program, vegetable intake was most frequently inadequate (n=1,985; 77.7%). After 24 weeks of coaching, this was reduced to 57.2% (n=1,462), which is a relative improvement of 26%. The largest improvement (relative improvement of 64%) was achieved for folic acid supplement use; this was inadequate in 12.4% (n=316) women at the start of the program and reduced to 4.5% after 24 weeks (n=114).

At the start of the program, women with a higher NSS were significantly less likely to smoke (adjusted OR 0.85 95% CI 0.77;0.93), but more likely to consume alcohol (adjusted OR 1.14, 95% CI 1.04;1.24) (Table 3). The NSS was not associated with the amount of improvement in smoking and alcohol consumption after 24 weeks of coaching (Table 4). However, the NSS was significantly negatively associated with improvement of vegetable intake after 24 weeks of coaching: women with a higher NSS improved their vegetable intake less than women with a lower NSS (adjusted OR 0.89 95% CI 0.82;0.97). Improvement of the other nutrition and lifestyle behaviors did not significantly depend on NSS (Table 4).

Interaction tests showed that the association between NSS and nutrition and lifestyle behaviors was not significantly different in women who did or did not participate as a couple and who were pregnant or not pregnant at the start of the program. However, at the start of the program, the association between NSS and alcohol consumption was stronger in non-Western (adjusted OR 1.74, 95% CI 1.33;2.28) compared to Western women (adjusted OR 1.12, 95% CI 1.00;1.25). This difference between non-Western and Western women was not observed for the association between the NSS and improvement of alcohol consumption.

Table 2 | Univariate associations between the neighborhood status score (NSS) and demographic factors.

Total n = 2,554	β (95% CI)	p-value
Age (years)†	0.04 (0.04;0.05)	<0.001
Pregnant at baseline (yes)	-0.30 (-0.41;-0.19)	<0.001
Body mass index (kg/m²)†	-0.03 (-0.04;-0.02)	<0.001
Participating as couple (yes)	0.18 (0.11;0.25)	<0.001
Geographic origin (non-Western)†	-0.78 (-0.85;-0.70)	<0.001
Total risk score	-0.01 (-0.02;0.001)	0.42

† Age, body mass index and geographic origin were missing in 1.2%, 0.4% and 9.6% of the study population, respectively. β: effect size; CI: confidence interval

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Table 3 | The association between the neighborhood status score (NSS) and inadequate nutrition and lifestyle behaviors in all participating women at the start of the program.

Total n=2,554	Crude		Adjusted*	
	Baseline		Baseline	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Vegetable intake (inadequate)	1.04 (0.98;1.11)	0.21	1.04 (0.98;1.12)	0.20
Fruit intake (inadequate)	1.03 (0.97;1.09)	0.29	1.01 (0.95;1.07)	0.74
Folic acid supplement use (inadequate)	1.00 (0.92;1.08)	0.94	1.00 (0.90;1.09)	0.85
Smoking (yes)	0.85 (0.78;0.92)	**<0.001**	0.85 (0.77;0.93)	**<0.001**
Alcohol consumption (yes)	1.23 (1.15;1.32)	**<0.001**	1.14 (1.04;1.24)	**0.004**

**Adjusted for body mass index, age, geographic origin, pregnancy status and participation as a couple. OR: odds ratio; CI: confidence interval*

Table 4 | The association between the neighborhood status score (NSS) and improvement of inadequate nutrition and lifestyle behaviors after 24 weeks of coaching in all women who scored inadequatly at the start of the mHealth program.

		Crude		Adjusted*	
		After 24 weeks		After 24 weeks	
	n	OR (95% CI)	P-value	OR (95% CI)	P-value
Vegetable intake (inadequate)	1,462	0.86 (0.79;0.94)	**.001**	0.89 (0.82;0.97)	.02
Fruit intake (inadequate)	576	0.90 (0.81;1.00)	.051	0.93 (0.84;1.04)	.21
Folic acid supplement use (inadequate)	114	1.00 (0.80;1.24)	.97	1.02 (0.80;1.30)	.87
Smoking (yes)	182	0.87 (0.69; 1.10)	.23	0.90 (0.69;1.16)	.40
Alcohol consumption (yes)	339	1.04 (0.9;1.19)	.57	1.05 (0.91;1.21)	.49

**Adjusted for body mass index, age, geographic origin, pregnancy status and participation as a couple. OR: odds ratio; CI: confidence interval.*

DISCUSSION

Principal results

Following the results of van Dijk *et al.*, this study again demonstrates that women improve their inadequate nutrition and lifestyle behaviors after 24 weeks of mHealth coaching using the ''Smarter Pregnancy" program. However, especially with regard to vegetable intake, this improvement becomes less when a woman's NSS is higher, which indicates living in a less deprived neighborhood. Although women with a higher NSS were less likely to smoke and more likely to consume alcohol at the start of the program compared to women with a lower NSS, we observed no significant differences in the amount of improvement of these lifestyle behaviors. Furthermore, NSS was significantly associated with compliance to the "Smarter Pregnancy" program; women with a higher NSS were less likely to complete the 24 weeks of coaching than women with a lower NSS.

Strengths and limitations

Strengths of our study are the large number of included participants (n=2,554), the high overall compliance of 68.2% of women who completed the 24 weeks of coaching, the fact that several potential confounders were taken into account in the adjusted models, and the imputation of missing data. In our study, the NSS –based on a well-defined index– was used as a proxy for socio-economic health inequality between neighborhoods. This continuous measure of neighborhood deprivation was used instead of a dichotomous measure (i.e. deprived vs. non-deprived), which provides a more precise evaluation of the effect of neighborhood deprivation. The use of area-based indices as a proxy for socio-economic health is well supported in the literature, thus the used neighborhood deprivation index can be considered a valid indicator[34,35]. The NSS is a measure based on factors that are specific for (the residents in) that particular neighborhood. Indeed, we found that the NSS is a representative measure for deprivation characteristics on the individual level; in less deprived neighborhoods, participating women had a lower BMI and were more likely to be of non-Western geographic origin. Furthermore, the distribution of the NSS in this study cohort (IQR -1.14;0.69 [data not shown]) was comparable with the national NSS in the year 2014 (IQR -0.57;0.71).

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Despite the fact that the inclusion period of the study population and the coaching with the ''Smarter Pregnancy" program covers several years, the NSS of 2014 was used as the measure of neighborhood deprivation for the whole study population. Since the NSS and the ratio of score between the neighborhoods does not change much over time, we consider this a valid determinant of the neighborhood deprivation within the study population.

Although geographic origin is known to be a potential confounding variable for associations with deprivation, information regarding geographic origin was not directly available from our database. In order to take geographic origin into account, we retrospectively performed geographic classification. This approach is considered a valid method for ascribing individuals to geographic groups when self-identification is not available[30], but unfortunately does not permit any further subdivision into more specific geographic groups besides Western and non-Western.

Limitations of this study are the absence of validation of nutritional status by biomarkers and the absence of a control group, although this is inherent to our study design. Furthermore, the "Smarter Pregnancy" program was only available in Dutch, which consequently excludes potential women without sufficient knowledge of the Dutch language. This may have led to a form of selection bias, whereas people of non-Western geographic origin, who mainly live in deprived neighborhoods, are underreported. Another form of selection bias may have been induced because the ''Smarter Pregnancy" program was not routinely used or recommended as part of (pre)pregnancy care and participants mostly subscribed upon their own initiative. Therefore, women could have been mainly women who are already intrinsically motivated to change nutrition and lifestyle behaviors before starting the mHealth program[36]. Together, these limitations may contribute to the generalizability of our study results.

Comparison with prior work

In our study population, women who lived in less deprived neighborhoods were less likely to smoke, but more likely to consume alcohol, which is in line with previous studies[9,37,38]. Despite recent studies stating that residents who live in deprived neighborhoods are difficult to motivate to change unhealthy behaviors[3,17,18], in our study, women who live in more deprived neighborhoods were more likely to complete the 24 weeks of mHealth coaching and improve their nutrition and lifestyle behaviors more than women who live in less deprived neighborhoods. An explanation may be that participants who live in more deprived neighborhoods adapt less quickly to new behaviors and need longer guidance from the program to eventually do so[36,39]. In a focus group study among women of the ''Smarter Pregnancy" program, higher educated participants (who are often more represented in less deprived neighborhoods) indeed suggested improvements to the program. For example, they stated that the coaching program could be more comprehensive, with extend features such as positive feedback on behaviors they already scored adequately on. Besides, they mentioned to find the program to simple and therefore quitted before finishing the 24 weeks of coaching[40].

Conclusions and future perspectives

Overall, we can conclude that the ''Smarter Pregnancy" mHealth coaching program is able to motivate women from more and less deprived neighborhoods to improve their nutrition and lifestyle behaviors. Though, women who live in more deprived neighborhoods seem to improve their nutrition and lifestyle behaviors more compared to women from less deprived neighborhoods. Together, these findings underline the need for a more tailored version of the program, adapted to the needs of its participants based on demographic characteristics, such as neighborhood deprivation, so that the program can adequately and optimally empower all women to improve their nutrition and lifestyle behaviors. Besides further tailoring the content to optimize the effect of the ''Smarter Pregnancy" coaching, using translated versions of the program may prevent the selection bias induced by the exclusive Dutch availability of the program.

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Chapter 5

Opportunities of mHealth in preconception care: preferences and experiences of patients and health care providers and other involved professionals

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Van Dijk MR
Koster MPH
Rosman AN
Steegers-Theunissen RPM

ABSTRACT

Background

The importance of the preconception period and preconception care (PCC) are broadly acknowledged and the potential benefits regarding health promotion have been studied extensively. PCC provides the opportunity to identify, prevent, and treat modifiable and nonmodifiable risk factors to optimize the health of couples trying to become pregnant. The prevalence of modifiable and nonmodifiable risk factors in these couples is high, but the uptake of PCC remains low.

Objective

The aim of this study is to identify the preferences and experiences of women and men (patients) trying to become pregnant and of health care providers and other involved professionals regarding mobile health (mHealth), in particular the coaching platform Smarter Pregnancy, and its potential role in PCC.

Methods

Patients who participated in the Smarter Pregnancy randomized controlled trial (RCT) and health care providers and professionals also involved in PCC were invited to participate in a qualitative study. The barriers, benefits, and opportunities of big data collection by mHealth were discussed in focus group sessions, prompted with statements regarding PCC.

Results

We composed five focus groups, consisting of 27 patients in total (23 women and 4 men), who participated in the RCT, and nine health care providers and other professionals. Of the patients, 67% (18/27) were familiar with the concept of PCC, but only 15% (4/27) received any form of PCC. A majority of 56% (combined percentages of statements 1 [n=18], 2 [n=11], and 3 [n=16]) of the patients believed in the benefit of receiving PCC, and all agreed that men should be involved in PCC as well. Patients did not have a problem using anonymized data obtained from mHealth tools for scientific purposes. Patients and health care providers and other professionals both acknowledged the lack of awareness regarding the importance of PCC and stated that mHealth provides several opportunities to support clinical PCC.

Conclusions

Our findings substantiate previous studies addressing the low uptake of PCC due to unawareness or lack of perception of its relevance by couples who are trying to become pregnant. The positive judgment and experiences with mHealth, in particular Smarter Pregnancy, will stimulate future research and further development of effective and cost-effective personalized mHealth apps for patients, health care providers, and other professionals as an add-on to clinical PCC.

INTRODUCTION

Since the recommendation of preconceptional folic acid supplement use for the prevention of neural tube defects in the early 1990s, the importance of the preconceptional period in the physiology and pathophysiology of pregnancy outcome and preconception care (PCC) is broadly acknowledged. The potential benefits of health promotion and interventions during this period of at least 14 weeks before conception has been extensively studied[1-3]. PCC can be used to identify, prevent, and treat modifiable and nonmodifiable risk factors and optimizes health of couples trying to conceive and, ultimately, pregnancy outcome[4]. In the Netherlands, PCC is only delivered to a select group of women, mainly those who have a fertility problem or a high risk for adverse pregnancy outcome due to a known genetic or medical condition or a previous poor pregnancy outcome. However, at their own request, couples can receive PCC from a health care professional, but so far only a very small proportion of the general population takes advantage of this. The low uptake of PCC, combined with the high prevalence of unhealthy nutrition and lifestyle behaviors, illustrates the lack of awareness regarding the importance of PCC in couples who are trying to conceive[5-7].

Currently, rapid developments in the field of telemedicine by means of electronic health (eHealth) and mobile health (mHealth) are opening doors to new opportunities to empower patients and health care providers and professionals and to fill the gaps in patient care[8,9]. In 2010, more than 200 million health-related online apps were downloaded, suggesting that mHealth indeed has the potential to reach, inform, and educate a large population[10]. Inherent to such mHealth apps, programs, or services, an enormous amount of data, referred to as "big data," can be obtained and stored by integrating data of online questionnaires, biofeedback, and diagnostic and monitoring tools. Consequently, big data can be used to study specific populations of interest and is therefore considered to be of great medical and scientific importance in the future[11]. Because nearly all women and men of reproductive age have Internet access and/or own a mobile phone, we believe that mHealth can play a role in providing information that can induce awareness and eventually support the implementation of PCC. Although there are many pregnancy-related mHealth solutions, mHealth solutions focusing on PCC are scarce[12]. Therefore, we consider this study regarding "Smarter Pregnancy" as a pioneer in the field of PCC using mHealth.

The aim of this qualitative study was to explore the preferences and experiences of women and men regarding mHealth, including big data, and its potential role in PCC. Moreover, we discussed these preferences and experiences with health care providers and other involved professionals in the field of PCC.

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METHODS

Participants and recruitment

All participants (hereafter referred to as "patients" to improve readability) of the Smarter Pregnancy randomized controlled trial (RCT) (ie, fertile and subfertile couples trying to conceive) who completed the first six months of the program or resigned prematurely, were invited to participate. The details of the Smarter Pregnancy mHealth platform and the RCT design have previously been published[13,14]. In short, during the Smarter Pregnancy RCT, the intervention group received individual coaching consisting of a baseline screening and a follow-up screening at 6, 12, 18, and 24 weeks regarding nutrition and lifestyle behavior. Coaching also included a maximum of three interventions per week, which consisted of short message service (SMS) text messages and email messages containing tips, recommendations, vouchers, seasonal recipes, and additional questions addressing gender, behavior, first day of last menstrual period, pregnancy status, body mass index, and adequacy of the diet. The control group did not receive the weekly personal coaching after the baseline screening and only received a minimum of feedback on the screening questionnaires at baseline and at 12 and 24 weeks.

For this qualitative study, all potential participants received an email that included an invitation to participate in a focus group session. In this email, we stated that we were interested in their feedback on our mHealth coaching platform and their views on the general concept of mHealth and big data by means of a semistructured interview, prompted with statements about PCC (Table 1).

Table 1 | Statements used during the focus groups with patients.

Statement	Topic
1. I consider the background information and coaching received by the mHealth program Smarter Pregnancy as useful.	Preconception care
2. Personal coaching by email and text messages is a valuable additive.	mHealth
3. Smarter Pregnancy has a pleasant way of communicating.	mHealth
4. Mobile health is a right method to give preconception care.	mHealth
5. Data obtained from Smarter Pregnancy can be (anonymously) used for other (non) commercial purposes.	Big data

Data collection procedure

To compose homogeneous focus groups and consequently lower the barrier to participate and increase the response rate, we chose to stratify the groups according to gender, known fertility status, and RCT study group (ie, intervention or control group). We aimed to recruit 6 to 10 patients per group. One week before the meeting, patients received a list of the statements that were going to be discussed during the focus group. At the start of a focus group, patients were asked to fill out a questionnaire regarding their personal information, medical information, and experiences and knowledge on PCC in general.

Every focus group meeting took place at the Erasmus MC, University Medical Centre, Rotterdam (the Netherlands), and was preceded by an individual introduction of each patient and a short presentation by a researcher (MRvD) to repeat the aim of the meeting and to ensure confidentiality. During the 2 to 2.5 hour focus group session, a professional moderator (ANR) guided the discussion. The involved researcher (MRvD) took minutes and ensured optimal audio recording.

Health care providers and professionals

After the focus group sessions with the patients, we also invited health care providers and professionals involved in the fields of reproductive medicine, obstetrics or PCC, policy makers, and representatives of a health care insurance company. Because all focus group sessions with the patients had already been processed and analyzed, health care providers and other professionals were not only asked to discuss their own views regarding PCC, mHealth, and big data, but also to reflect on the patients' input on these topics.

Theoretical Framework and Data Analysis

This study is based on a framework described by Fleuren et al[15], which identifies four main stages in innovation processes: dissemination, adoption, implementation, and continuation. These processes can be considered as potential failure points in which the transition from one stage to another is determined by both positive and negative factors (determinants). The framework considers characteristics of the organization, the innovation itself, the end user, and the sociopolitical environment. By using statements prompted during the focus groups, determinants regarding patients' preferences and experiences were derived. The same was done within the focus group of the professionals; however, specific information from the patient's focus groups was added and discussed.

All recorded audio was transcribed verbatim, using the minutes as guidance. To perform thematic analysis, a set of preliminary codes was developed from the notes and transcripts and discussed between the researchers involved. Subsequently, the codes were structured to the concepts of determinants as previously described. Two researchers (MRvD and MPHK) coded one transcript independently and then compared the coding to reach consensus. Thereafter, the remaining scripts were coded by MRvD. All coding took place using NVivo version 10 (QSR International, Cambridge, MA, USA).

Ethical considerations

All data were anonymously processed. This qualitative study 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 Centre, Rotterdam, in the Netherlands. Informed consent was obtained from all participants to use anonymized data for analysis.

RESULTS

Study population

A total of 509 patients received an invitation, of which 23 women and 4 men accepted the invitation and were able to participate in four focus groups. Patients who had an indication to receive fertility treatment by means of an in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) were labeled as the IVF-ICSI population, whereas patients who did not receive this treatment were labeled as the general population. Groups were composed as follows:

1. Women, general population (n=5);
2. Women, IVF-ICSI population, intervention group (n=9);
3. Women, IVF-ICSI population, control group (n=9);
4. Men, IVF-ICSI population (n=4).

Overall, baseline characteristics of these women and men, such as age, ethnicity, educational level, and lifestyle were comparable between patients of the four focus group sessions (Table 2).

Table 2 | Baseline characteristics of all patients, based on the additional questionnaire (N=27).

	General population (n=5)	IVF-intervention group (n=9)	IVF-control group (n=9)	Men (n=4)
Focus group, n	1	2	3	
Age (years), mean (SD)	3.0 (5.1)	33.65 (5.1)	35.2 (4.3)	43.3 (17.47)
Marital status, n (%)				
Single	–	–	1 (11)	–
Married or living together, without children	1 (20)	4 (44)	3 (33)	4 (100)
Married or living together, with children	4 (80)	5 (56)	5 (56)	–
Ethnicity, n (%)				
Dutch or Western	5 (100%)	8 (89)	9 (100%)	4 (100)
Non-dutch, non-western	–	1 (11)	–	–
Education				
None	–	–	–	–
Low	–	–	1 (11)	–
Middle	1 (20)	3 (33)	1 (11)	–
High	4 (80)	6 (67)	7 (78)	4 (100)
Smoking (yes), n (%)	–	–	1 (11)	1 (25)
Alcohol consumption (yes), n (%)	1 (20)	1 (11)	4 (44)	4 (100)
Drug use, n (%)	–	–	–	–
Vitamin use, n (%)	1 (20)	7 (78)	7 (78)	1 (25)
Medication use, n (%)	1 (20)	–	1 (11)	1 (25)
Comorbidity, n (%)	3 (60)	2 (22)	3 (33)	2 (50)
Mode of conception				
Spontaneous	3 (60)	1 (11)	1 (11)	–
Hormonal treatment	–	–	–	–
IVF or ICSI	–	5 (56)	4 (44)	2 (50)
Nulliparous	1 (20)	6 (67)	5 (56)	4 (100)
Familiar with preconception care, n (%)	2 (40)	8 (89)	4 (44)	4 (100)
Received preconception care, n (%)	2 (40)	–	2 (22)	–

The focus group session with health care providers and professionals consisted of nine attendants (ie, a gynecologist, a midwife, a general practitioner, a fertility doctor, a preventive health care center physician, a dietician, a medical advisor from a health insurance company, a representative of the municipality of Rotterdam, and a representative of the Dutch association of parent and patient organizations).

Preconception Care: Beliefs and Perception

A summary of the patients' answers on the additional questionnaire at the start of the focus group session is shown in Table 3, illustrating their perceptions and beliefs regarding PCC. Despite the observation that only 67% (18/27) of patients were familiar with the current concept of PCC (ie, a consultation with a health care professional), and only 15% (4/27) received any form of PCC (Table 2), a majority of 56% (combined percentages of statements 1 [n=18], 2 [n=11], and 3 [n=16] in Table 3) indicated the benefits of receiving PCC and adopting a healthy lifestyle when trying to conceive. Whether they believe that if they become pregnant, their child benefits from received PCC remains questionable because only 32% (combined percentages of statements 4 [n=7] and 5 [n=10] of Table 3) agreed with this statement.

Table 3 | Patients perceptions and beliefs regarding PCC, prior to the focus group (N=27).

Header Patients perceptions and beliefs regarding PCC.	Focus group, n				Overall, %
	1	2	3	4	
1. PCC will make me adopt a healthy lifestyle.					
Strongly disagree	0	0	0	0	0
Disagree	0	0	2	1	11
Neither agree nor disagree	1	1	3	1	22
Agree	4	8	4	2	67
Strongly agree	0	0	0	0	0
2. Through PCC, I know whether it's wise to become pregnant.					
Strongly disagree	0	0	0	0	0
Disagree	0	2	2	1	19
Neither agree nor disagree	1	4	4	2	41
Agree	4	3	3	0	37
Strongly agree	0	0	0	1	4
3. Through PCC, I'm better prepared to become pregnant.					
Strongly disagree	0	0	0	0	0
Disagree	0	0	1	1	7
Neither agree nor disagree	1	4	3	1	33
Agree	4	5	4	2	56
Strongly agree	0	0	1	0	4

Table 3 | (*Continued*)

Header Patients perceptions and beliefs regarding PCC.	Focus group, n				Overall, %
	1	2	3	4	
4. PCC reduces the risk of complications during pregnancy or labor.					
Strongly disagree	0	0	0	0	0
Disagree	0	1	0	0	4
Neither agree nor disagree	3	6	5	4	67
Agree	2	2	3	0	26
Strongly agree	0	0	0	0	0
5. PCC makes my baby more healthy.					
Strongly disagree	0	0	0	0	0
Disagree	0	1	2	0	11
Neither agree nor disagree	3	6	2	3	52
Agree	2	2	4	1	33
Strongly agree	0	0	1	0	4
Preconception care: logistics					
6. PCC should be obligated					
Yes	1	1	1	1	15
No	4	8	8	3	85
7. PCC should be given to:					
Women only	0	0	0	0	0
Men only	0	0	0	0	0
Women and men	5	9	9	4	100
8. When should PCC be reimbursed by an insurance company					
Only if a woman has a high-risk (medical) condition	0	5	3	2	37
Always	5	4	6	2	63
9. For whom should PCC be reimbursed					
Women only	2	7	4	2	56
Couples only	0	1	1	1	11
No opinion	3	1	4	1	33
Preconception care: conditions and content					
10. Would you prefer anonymous PCC over personal					
Yes	0	0	1	0	4
No	5	9	8	4	96
11. PCC should consist of one consultation					
Yes	3	2	1	1	26
No	2	7	7	3	74
12. PCC by mobile health can be useful					
Yes	4	7	9	4	93
No	1	1	0	0	7
13. PCC can be used unconditionally regarding treatment					
Yes	4	5	8	3	74
No	1	4	1	1	26

Preconception Care: Logistics

All patients acknowledged that men should be involved in PCC. On the contrary, more than half (15/27, 56%) stated that only the costs of PCC received by women should be reimbursed by the insurance company. Despite the agreement on the importance of PCC, 85% (23/27) stated that it should not be mandatory for couples trying to conceive.

Preconception Care: Conditions and Content

Most patients (26/27) would not prefer anonymous PCC. Despite previous findings showing a majority stating PCC should not be obligatory, 74% (20/27) stated that PCC should be mandatory as a part of fertility treatment (Table 3).

mHealth

In general, patients feel comfortable using mobile apps. They believe that using mobile devices in health care is a good development and a modern approach to provide patients with information and background. Most male patients acknowledged that mobile health can be used to substitute for certain parts of regular consultations, especially during fertility treatment, but women emphasized the importance of face-to-face contact and nonverbal communication and stated that mHealth should only be used as an additive to routine clinical care:

> *It is not necessary to have a face-to-face consultation, if I need to discuss something, I'll find my way to contact a health care professional.* (man, group 4)
>
> *If they ask me over the phone through an app, how am I doing, I'll just say "I'm doing good," but if they ask me during a consultation, they can see me and notice I'm not doing okay.* (woman, group 1)

Awareness

The most frequently discussed topic during most focus group sessions was "awareness." Some female patients specifically mentioned the visual feedback, as provided by the Smarter Pregnancy platform, as a trigger and motivator to improve behavior. Knowing they would perform better on the next monitoring questionnaire gave them perceived control, but a high frequency of coaching and incorporated positive feedback is needed to secure adherence to the program and to truly improve awareness:

> *It makes you more aware of what you're eating, so when you're tired you won't eat an unhealthy snack because you want to reach the best score on the questionnaire.* (woman, group 2)
>
> *If you truly want to change someone's behavior, one reminder per week is nice, but not enough to provide sufficient information.* (woman, group 3)
>
> *Besides all the coaching on what to improve, it's also nice to hear you're doing a good job.* (woman, group 2)

Education

Patients agreed that background information on the importance of healthy nutrition and lifestyle as a part of PCC improves awareness, but only if they believe it is trustworthy and preferably evidence-based. The Smarter Pregnancy coaching platform is supported by multiple health care organizations of which the logos are displayed at the website. This was highly appreciated by the patients:

> *Information found at an online community can be from anyone, and I don't like to be told what to do by an amateur.* (man, group 4)

Using received information as an online reference book, which was always accessible on demand, was suggested to be of great value. Also adding visual content by means of images and videos was considered valuable.

Personalized mobile health

In addition to awareness, participants agreed on the fact that mHealth needs to be highly personalized to be really effective. Impersonal messages or general messages were considered not effective or even countereffective. Men and women both suggested that the psychological aspect of trying to conceive should be integrated in mHealth as well as the functionality of asking online questions to a health care professional:

> *I guess it would really work if patients can use an accessible "chat function" or "email service" to ask questions to a health care professional.* (woman, group 3)

Big data

Scientific and commercial use

All patients were asked their opinion on data obtained through a mHealth platform being used either anonymously or nonanonymously, for scientific purposes. Patients were very willing to support prepregnancy- and pregnancy-related research in general in this way, provided it was anonymous, because they considered it to be helpful for other patients and future parents. Some patients approved of nonanonymous scientific use of their data. Also "medical-related" companies and organizations, such as hospitals and pharmaceutical companies, were considered to be relevant purposes. On the contrary, most patients did not allow usage of nonanonymous or anonymous data for commercial purposes. There was a general perception that companies or organizations, and health care insurance companies in particular, should not benefit from this data, although one participant mentioned this could be an opportunity to develop profitable PCC:

> *I am willing to help science, but not willing to help a company sell more of its products.* (woman, group 1)
>
> *I really value that I decide what to share with the outside world, and with whom.* (woman, group 1)

Safety and Monitoring

In general, patients were not worried about data leakage due to limited safety of storage by mHealth devices. It was believed that every medical institute itself, or together with governmental support, could guarantee data safety and monitoring.

Health Care Providers and Professionals

Preconception Care

Participating health care providers and professionals also agreed on the general lack of awareness for PCC. To create awareness, the importance of evidence-based information and education was emphasized. For example, consistent online and offline information can educate patients and health care providers and professionals and consequently increase the intrinsic motivation to change certain unhealthy behavior that are not often addressed in health care and PCC. It was suggested that awareness in general can be increased by offering PCC through employers or, even better, through secondary schools integrated within biology or sex education lessons. The health care providers and professionals recognize the fact that patients are familiar with the broad and inconsistent spectrum of online information regarding PCC and notice that especially higher-educated patients use the Internet to obtain information regarding fertility and pregnancy, whereas more lower-educated patients with limited health literacy and the highest health risks prefer to visit a professional first:

> *It feels like selling something to someone who doesn't want to buy it. You are trying to convince them of something they don't believe it's important.* (gynecologist)
>
> *With the existence of online communities, patients are "educated" by peers instead of professionals. That is their preconception care.* (fertility doctor)

mHealth

Health care providers and professionals were familiar with mHealth, especially apps to monitor menstrual cycles, fetal development during pregnancy, and for online questionnaires to identify risk factors for certain conditions (eg, depression and anxiety). In addition to monitoring, they were concerned whether mHealth can reach and educate those who need it the most, for example due to a language barrier. Therefore, it is suggested that developing apps in multiple languages will overcome this. If so, it is believed that mHealth can be used to substitute for certain elements of routine consultations (eg, nutrition and lifestyle recommendations). Replacing consultations by alternative techniques, such as video chat, is believed to be an upcoming development, but is currently not appreciated due to the lack of technical support and security.

All health care providers and professionals were very enthusiastic about the concept of using an online questionnaire, such as the one incorporated in the Smarter Pregnancy platform, including a link between the given answers and the patient's medical record. The prospect of having all the results before a face-to-face PCC consultation was considered very useful and time-saving. Moreover, providing questionnaires to patients was in itself already thought to increase awareness:

> *Monitoring over time is very useful, because knowing whether a patient is improving gives the opportunity to give them a compliment, which can be very helpful.* (gynecologist)

Big Data

The health care providers and professionals unanimously agreed that big data can be of great medical and scientific importance. By obtaining detailed information on target groups and populations, interventions can be designed and clinical care can be tailored at specific behaviors, needs, or risk factors of specific patient groups. Although the health care providers and professionals were aware of the perception of patients toward the use of big data, they believed that commercial use could also be beneficial in creating large-scale awareness.

DISCUSSION

Principal Findings

This qualitative study addressed the preferences and experiences of patients and health care providers and other professionals regarding PCC in general and mHealth in particular. Based on the four focus group sessions with patients the following can be summarized:

1. Patients are familiar with PCC in general and confirm that there is a lack of awareness regarding the importance.
2. Patients believe that mHealth can play a role in PCC, especially regarding awareness and providing evidence-based information, but mainly as an additive to standard care with face-to-face contact with a health care professional.
3. Patients also believe that mHealth should be personalized, customized, and tailored to their needs, risks, and behaviors to reach its full potential and become truly effective.
4. Patients approve that data obtained from mHealth, referred to as big data, can be used anonymously for scientific purposes.

The health care providers and other professionals agree on the potential role of mHealth in PCC, especially as an effective tool to inform and educate couples to improve awareness of the importance of PCC care in general. They are optimistic about the concept of mHealth integrated into the patients' medical records, but emphasize that the current situation is not suitable for this innovation due to the lack of technical support.

Comparison With Literature

Our findings correspond with existing literature, in which low uptake of PCC due to unawareness or a lack perception of relevancy by couples trying to conceive have been described[16-18]. Concerning mHealth and its role in PCC, previous studies have suggested that tailored interventions may improve the uptake of PCC, especially when added to standard care[19,20]. Currently, the development and uptake of commercial and non-evidence-based apps continues, whereas there is an ongoing debate on the efficacy of mHealth in general, because the scientific merit is questionable due to the absence of robust evidence[13,20-23]. Therefore, many studies are conducted to provide scientific evidence on the effectiveness of mHealth interventions in general[14,24-28.] To our knowledge, the perception of patients regarding the use of big data for scientific purposes has not been described before.

Regarding the preferences and experiences of patients using mHealth interventions in general, our findings are in line with previous studies. The personalized character and credibility of mHealth interventions have recently been described to be important to enhance adherence to therapy and nutrition and lifestyle recommendations[29-31].

Strengths and Limitations

Patient involvement during the designing phase of an intervention is essential, followed by end user participation and evaluation of an intervention to further improve customization[32,33]. Consequently, the main strength of this study is the involvement of several end users of our mHealth platform (ie, participants of the Smarter Pregnancy RCT), including the participation of men. Also, we included multiple health care providers and other professionals, representing various organizations and professions in the field of PCC, which is an important strength. These professionals were able to state their own opinion, substantiated by the policy of the organization or profession they represent. Due to the careful stratification and composition of the focus groups, we created a safe environment for the patients in which the structured discussion took place. Furthermore, with the presence of a professional moderator, we were able to give all participants the opportunity to express and interactively discuss their opinions, experiences, and feelings equally and without any consequences. The most important limitation to address is the low acceptance rate resulting in a very small number of patients in total and per focus group, although this can be considered as confirmation of the main underlying problem: the lack of knowledge and awareness regarding PCC. This, together with the involvement of end users, may also introduce selection bias; the patients involved in this study are generally highly educated and probably more engaged with the topic because they already participated in a previous study regarding mHealth and PCC. Although this bias is hard to overcome when conducting qualitative studies in general, and especially in this field of research with a population of interest that is very hard to reach, it needs to be addressed because it could influence the external validity of the results.

Conclusions

Overall, we conclude that patients and health care providers and professionals believe that mHealth has several unique opportunities for PCC. Our findings imply that future research should focus on the development of mHealth apps as an add-on to standard care, preferably integrated or connected to patients' medical records, allowing health care providers and other professionals to become involved and support their patients. The first step to increase awareness would be to provide evidence-based information, followed by providing apps or programs containing this information, but also tailored to individual conditions. Therefore, patient involvement and end user participation will be indispensable in designing effective interventions.

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Part II

Chapter 6

The use of the mHealth program Smarter Pregnancy in preconception care: rationale, study design and data collection of a randomized controlled trial

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Van Dijk MR
Oostingh ECO
Koster MPH
Willemsen SP
Laven JSE
Steegers-Theunissen RPM

ABSTRACT

Background

Unhealthy nutrition and lifestyle contribute to the worldwide rising prevalence of non-communicable diseases. This also accounts for the reproductive population, in which unhealthy behavior affects fertility and pregnancy outcome. Maternal smoking, alcohol consumption and inadequate folic acid supplement use are strongly associated with fetal complications as small for gestational age, premature birth and congenital malformations. In the Netherlands 83% of the perinatal mortality rate is due to these complications and is relatively high compared to other European countries. In order to reduce this prevalence rate, preconception care should be focused on the promotion of health of prospective parents by identification and intervention on modifiable nutrition and lifestyle risk factors. We developed the personal mHealth program 'Smarter Pregnancy' (Dutch version available on: www.slimmerzwanger.nl) to provide individual coaching and information to improve nutrition and lifestyle during the preconception period in order to improve health of the reproductive population and subsequent generations.

Methods

Women between 18 and 45 years of age, and trying to conceive are eligible for inclusion in a randomized controlled trial. Participants are allocated either to a general population cohort or a subfertile (IVF/ICSI) population cohort. The intervention group receives personal online coaching based on the identified nutrition and lifestyle risk factors at baseline. Coaching comprises recipes, incentives, additional questions including feedback and text and e-mail messages, with a maximum of three per week. The control group only receives one recipe per week to maintain adherence to the program and prevent drop out. Screening questionnaires are send in both groups at 6, 12, 18, and 24 weeks of the program to monitor the change in the identified risk factors.

Discussion

We expect to demonstrate that the mHealth program 'Smarter Pregnancy' can effectively improve nutrition and lifestyle in couples contemplating pregnancy. By the identification and improvement of modifiable nutrition and lifestyle risk factors on a large scale, both reproductive and pregnancy outcomes can be improved and subsequent perinatal morbidity and mortality rates are expected to be reduced. The current use and rapid development of mHealth applications offers new opportunities to reach and educate large populations, which can facilitate the implementation of preconception care.

Trial registration: Dutch trial register: NTR4150.

BACKGROUND

Unhealthy nutrition and lifestyle, characterized by a high caloric intake and vitamin deficiencies, derange metabolic and endocrine pathways and are causing obesity which contributes to the development of non-communicable diseases (NCDs), such as cardiovascular and metabolic diseases[1,2]. Although awareness of the impact of unhealthy nutrition and lifestyle is increasing, its prevalence remains very high, not only in general, but also in the reproductive population in which health consequences range from subfertility to congenital malformations or even perinatal death[3-7]. Most evidence is available on the detrimental impact of maternal smoking, alcohol consumption and inadequate folic acid supplement use, which are strongly associated with embryonic growth and small for gestational age (SGA) and congenital malformations[8-12]. Currently, several studies that focused on the adherence of maternal dietary patterns have shown the benefits of healthy foods such as fruits and vegetables on perinatal outcome[13,14].

In the Netherlands, particularly in large cities such as Rotterdam, perinatal mortality rates and the prevalence of perinatal complications, such as SGA, premature birth and congenital malformations (also referred to as Big3 complications), is relatively high compared to other European countries[15-17]. In order to reduce these prevalence rates, preconception care (PCC) should be implemented, focused on the promotion of health and the identification of (modifiable) risk factors of prospective parents as well as the next generation[18-20]. In order to create awareness and to implement PCC on a large scale, new approaches need to be explored and (mobile) technologies can be used. Previously, we developed and implemented a preconception outpatient clinic tailored to improve nutrition and lifestyle of which the results were promising, i.e. 30% reduction of inadequate nutrition and lifestyle and a 65% increased chance of ongoing pregnancy after IVF treatment[4,21]. However, this outpatient clinic could only provide PCC on a small scale due to the required expertise, time and costs. To overcome these barriers we have developed the personal mHealth coaching program 'Smarter Pregnancy' (Dutch version available on: www.slimmerzwanger.nl, English equivalent available on: www.smarterpregnancy.co.uk/research), providing individual, tailored and continuous information on a large scale during 26 weeks. Previous studies have shown that women seek online information with regard to healthy nutrition and lifestyle which suggests that online interventions using mobile technology can be effective[22,23]. Also, women embrace online anonymity to control and self-manage online information[24,25]. Smarter Pregnancy identifies the most important risk factors regarding nutrition and lifestyle and subsequently provides tailored information and motivational coaching by text and e-mail messages[6].

We hypothesize that our mHealth program will effectively improve nutrition and lifestyle in couples contemplating pregnancy. Based on our previous studies and that of others we designed a randomized controlled trial (RCT) to study the effectiveness of "Smarter Pregnancy", defined as a significant improvement of vegetable and fruit intake and folic acid supplement use, when started preconceptional[4,6,7,21,26]. This intervention can be considered as a primary prevention tool resulting in a reduction of Big-3 complications, perinatal morbidity and mortality in the short-term and NCDs in the long-term[2,27,28].

OBJECTIVES

A randomized controlled trial is conducted in two independent populations, i.e. couples from the general population and couples undergoing IVF/ICSI treatment, to study whether unhealthy nutrition and lifestyle can be improved by the Smarter pregnancy coaching program as an intervention tool. Furthermore, we will determine whether couples will have a higher pregnancy rate and if their risk for Big3 complications can be reduced by improving nutrition and lifestyle.

Primary outcome

Improvement (percentage reduction) of unhealthy nutrition and lifestyle in women and men contemplating pregnancy or already pregnant, determined by using a dietary risk score (DRS), 24 weeks after starting the "Smarter Pregnancy" intervention.

Secondary outcomes

(1) A reduction in smoking by women and men contemplating pregnancy; (2) pregnancy rates in couples; (3) birth prevalence rate of Big-3 complications in the entire study population; (4) cost-effectiveness of the Smarter Pregnancy intervention.

Tertiary outcomes

The influence of participation of men, pregnancy, age, low socioeconomic status on the primary outcome and (1) Improvement (defined as the percentage of reduction) of unhealthy nutrition and lifestyle 36 weeks after starting the "Smarter Pregnancy" intervention; (2) the compliance and reliability of "Smarter Pregnancy" among both women and men. To study the latter, we aim to determine the: (1) The percentage of the target group that meets all the inclusion criteria for the study, but does not participate; (2) The percentage of participants that is still participating after three months (compliance); (3) The prevalence and nature of technical problems.

STUDY DESIGN

Eligibility

Women residing in the Netherlands who are between 18 and 45 years of age and contemplating pregnancy are considered eligible to be included in this study. To participate, women need to be in possession of a smartphone with Internet access. Women with insufficient knowledge or understanding of the Dutch language, women who are treated by a dietician to lose weight in the context of a fertility treatment, and women who have a specific diet (e.g. vegans) cannot participate in the study. Male partners are also invited to participate, but only if they meet the same criteria, except that there is no upper age limit for male participants.

Recruitment, cohort composition and randomization

Women are invited to participate by a (health care) professional from their midwifery practice, children's daycare, childhealth center, or hospital. Self-registration through the website is also possible. Potentially eligible participants are contacted after registration by one of the researchers to verify their eligibility, to provide more details and answer questions about "Smarter Pregnancy" and to confirm their registration.

Participants are allocated either in a general population cohort or the IVF/ICSI- (ART) population cohort, depending on whether they will receive fertility treatment (Figure 1). Randomization of the participants is stratified by cohort and per center of inclusion. For each stratum a permuted block design is used and programd beforehand. Hereby, allocation concealment is ensured.

Smarter Pregnancy

The mHealth program Smarter Pregnancy was launched in 2012 and provides personal coaching, tailored on personal conditions, gender, nutrition and lifestyle in both women and men contemplating pregnancy. The program is based on nearly 30 years of research and expertise by our group on the influence of nutrition and lifestyle on reproduction and pregnancy course and outcome. We used elements of Prochaska and Diclemente's transtheoretical model with a focus on the readiness for behavioral change, Bandura's social cognitive theory for self-efficacy and Fogg's behavior model to include triggers to motivate and increase the ability to change[29-31]. Features of the attitude, social influence, and self-efficacy (ASE) model for coaching are applied; aimed at the understanding and motives of people to engage in specific behavior[32].

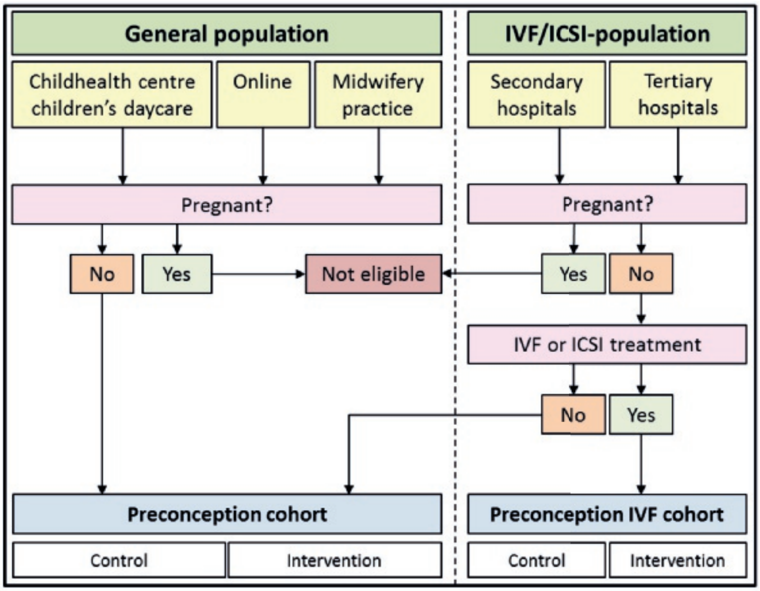

Figure 1 | Overview of the recruitment and composition of the multi-center study and both cohorts.

Intervention group

The content of the individual coaching is based on the baseline screening on personal conditions, nutrition and lifestyle and monitoring questionnaires at 6, 12, 18, and 24 weeks of the Smarter Pregnancy program. At these time points, participants are invited to complete a short, online questionnaire to monitor the change in their nutrition and lifestyle. Results from the questionnaires are compared with the previous results and shown on a personal online page to show a participant's progress.

The tailored coaching includes a maximum of three interventions per week comprising short message service (SMS) text and email messages containing tips, recommendations, vouchers, seasonal recipes, and additional questions addressing behavior, pregnancy status, body mass index (BMI) or adequacy of the diet (Figure 2, colored arrows above black arrows).

The personal page also provides access to additional modules (i.e. applications) to support physical activity, an agenda to improve the compliance with hospital appointments and medicine adherence, and a module to monitor the safety of prescribed medication. A summary of all individual results can be obtained at any moment by the participant, and can be handed over or sent by email to the health care professional for further evaluation and support of preconception and antenatal care.

Control group

Participants who are randomized in the control group will not receive personal coaching after the baseline screening. They do receive access to their personal page and will receive one seasonal recipe per week to maintain adherence and prevent drop out (Figure 2, lower red arrows). At baseline as well as at 12 and 24 weeks, participants in the control group receive the monitoring questionnaire about nutrition and lifestyle, but without feedback on the results. Also, every 6 weeks the controls receive a request to adjust their pregnancy status if needed.

Biomarker validation

To validate the self-administered questionnaires, we will analyze several blood biomarkers in a random sample of both study populations and both groups (intervention and control group). A team of qualified medical students will take blood samples at the participants home address or at the hospital. These blood samples will be taken on three time points (t=0, 12 and 24 weeks) during the study; each time 20 ml will be collected. Samples are kept at -20 degrees Celsius for a maximum time period of 4 hours. Aliquots of residual blood will be stored at -80 degrees Celsius for future research on DNA and epigenetics.

Additional study questionnaires and follow-up

At baseline, for both the intervention and the control group additional information on social and demographic characteristics is obtained using an additional online study questionnaire implemented in the coaching program. The first follow-up study questionnaire will be send at 36 weeks, i.e. 12 weeks after the last screening moment (Figure 2). One year after enrollment, participants receive their last study questionnaire, which consists of questions regarding medical and obstetric history, medication use, whether they became pregnant during enrollment and, if applicable, the pregnancy outcome.

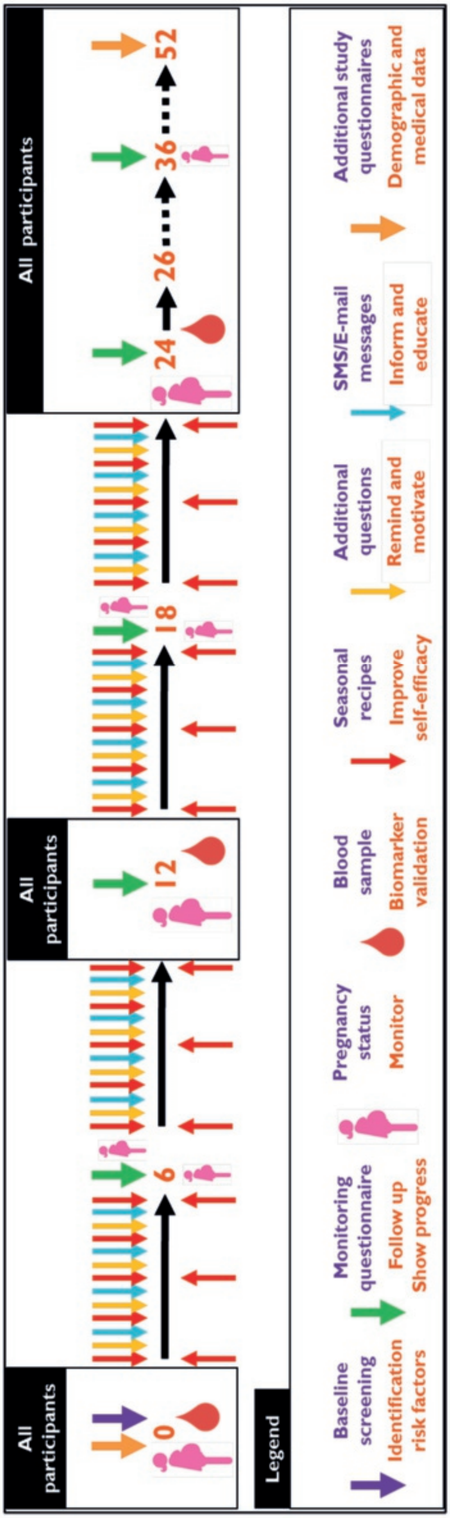

Figure 2 | Overview of both the intervention and control group during their enrollment. The upper arrows pointing downwards depict the intervention group. The lower arrows pointing upwards depict the control group. All boxed icons depict aspects of the trial that account for all participants in both groups, i.e. baseline screening, screening questionnaires (at t=12 and t=24 weeks), additional questionnaires at baseline and 52 weeks, pregnancy status per 6 weeks and blood samples.

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Statistical considerations

Sample size calculations are based on our primary outcome measure (DRS). Based on our previous studies and the survey using Smarter Pregnancy, we expect a reduction of approximately 0.5 DRS points (based on a standard deviation of 2.7) in the intervention group compared to the control group. Considering alpha=0.05 and power=0.80 we will need to include a total of 916 women in our study (2 arms of 458 each). Due to expected drop outs of approximately 10%, we aim to include 1,000 fertile (2 arms of 500 each) and 1,000 subfertile women (2 arms of 500 each) in our study. For 50% of these women, we expect their male partner (n=250 in each arm) to participate as well. Due to the lower SD (2.0) in men, with this sample size we are also able to demonstrate a reduction of at least a 0.5 DRS points in the male partners.

Statistical analysis

A flowchart will be used to depict the total participants of each cohort and divided per group, subdivided per gender. Also, the amount of resigning participants will be shown per time point (6 weeks). General and baseline characteristics will be compared between groups and shown in a baseline table. The primary analysis will be based on intention to treat (ITT). For men and women in both the intervention and the control group the DRS will be calculated at baseline and after 24 weeks and used for further analyses. This continuous outcome measure will be analyzed by the 'difference in difference principle' and used in a linear regression model, including the initial/ baseline value of the DRS. Repeated measurements will be used to investigate the effects of the intervention over time and the interaction of the intervention with socio economic status, ethnicity and age. Chi-square analysis and ANCOVA will be used to study the effects of the intervention on the pregnancy outcome and Big-3 complications. To measure the compliance and reliability of 'Smarter pregnancy' we will analyze the percentage of randomized women who fill in the questionnaire after 12 weeks of participation and the percentage of participants who experienced technical problems. Corresponding confidence intervals will be given. The influence on the primary outcome of participation of men, if pregnancy occurred during participation, age and low socio economic status will be analyzed by including these variables and their interaction with both groups, one by one in the model which will be used for the primary outcome. If there is heterogeneity of the treatment effect, the effect will be determined per subgroup separately.

DISCUSSION

This study will contribute to the implementation of easily accessible PCC in order to increase awareness regarding the importance of healthy nutrition and lifestyle in couples contemplating pregnancy and health care professionals. Subsequently, this can reduce the relatively high rates of perinatal morbidity and mortality (Big3 complications) in the Netherlands.
Initiating behavioral change(s) by the identification of risk factors during the preconception period can be a useful first step to not only create awareness, but also to lower the threshold to approach a healthcare professional during this period. Discussing or revealing involuntary childlessness

remains a burden for many women as well as for men, due to the perception that they have failed by not being able to conceive. This results in a situation in which risk factors for poor reproductive and pregnancy outcome persist, while adopting a healthy lifestyle during this preconception period can be beneficial on both the short and long term. Most reproductive failures originate due to deranged metabolic pathways. The lack of co-factors and substrates as a result of vitamin deficiencies (e.g. vitamin B12 and folate) can influence oocyte en semen quality and early embryonic development resulting in failed implantation and miscarriages. Also, it can cause epigenetic modifications to DNA methylation of the offspring[19,33,34]. Therefore, we consider the preconception period as the window of opportunity to initiate a healthy lifestyle.

Currently, research in the field of mobile technology is mainly aimed on the use of mHealth in low- and middle-income countries, because this new form of health care delivery can reach the poorest regions in which the prevalence of NCDs and poor maternal and child health are the highest[35-38]. By our opinion, also high income countries comprise specific target groups, such as the reproductive population, in which risks for poor reproductive and pregnancy outcome accumulate, because of the lack of knowledge and self-efficacy with regard to PCC[39]. Therefore, we consider mHealth a promising method to approach the large group of reproductive women and men which is currently wrongly assumed to be at low risk for poor reproductive and pregnancy outcome, although it is known that the prevalence of risk factors in this population is high[4,6,11]. Given that 98.7% of all Dutch women and men between 18 and 45 years old have access to the internet and 95.4% can access the internet by their mobile phone makes this mHealth approach justifiable[40].

Strengths of this RCT are the longitudinal observations and the longitudinal biomarker validation in blood. Also, additional study questionnaires for short-term and long-term follow-up (respectively 12 and 26 weeks after the last questionnaire at 24 weeks), including sociodemographic data and medical record validation, are considered important strengths of this study. A limitation of this RCT is the potential selection bias, which is unfortunately inherent to participation in a study, especially on behavioral change, as well as the exclusion of participants without sufficient knowledge of the Dutch language.

With this RCT we expect to demonstrate the effectiveness of our Smarter Pregnancy program and its positive effect on reproductive and pregnancy outcome in both fertile and subfertile couples. Healthcare professionals are often also not aware of the importance of PCC nor have tools containing information and guidelines to provide nutrition and lifestyle care for medical practice[41]. Therefore, we consider this study a unique intervention regarding the implementation of accessible preconception care.

SPIRIT-Table

	Study period							
	Enrollment	Allocation	Post-allocation					Close-out
Timepoint (weeks)		t_0	t_6	t_{12}	t_{18}	t_{24}	t_{36}	t_{52}
Eligibility screen	X							
Informed consent	X							
Allocation		X						
Intervention group								
Screening questionnaire		X	X	X	X	X	X	
Additional questionnaire		X						X
Coaching			●	—	—	●		
Pregnancy status		X	X	X	X	X	X	
Blood collection*		X		X		X		
Control group								
Screening questionnaire		X		X		X	X	
Additional questionnaire		X						X
Coaching								
Pregnancy status		X	X	X	X	X	X	
Blood collection*		X		X		X		
Assessments								
Baseline		X						
– Age								
– Length								
– Weight								
– BMI								
– Vegetable intake								
– Fruit intake								
– Folic acid supplementation								
– Smoking								
– Alcohol consumption								
– Pregnancy status								
– Physical activity								
– Demographics								

SPIRIT-Table *(Continued)*

	Study period							
	Enrollment	**Allocation**	**Post-allocation**					**Close-out**
Outcome variables		X	X	X	X	X	X	
– Weight								
– BMI								
– Vegetable intake								
– Fruit intake								
– Folic acid supplementation								
– Smoking								
– Alcohol consumption								
– Pregnancy status								
– Physical activity								
Blood collection		X		X		X		
– Nutrients								
Follow-up								X
– Medical history								
– Pregnancy outcome								

** Determined in a random sample. BMI: body mass index; RBC: red blood cell count; Hb: hematoglobin; Ht: hematocrite.*

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Chapter 7

A coaching program on the mobile phone improves nutrition in women before and during early pregnancy: a single centre randomized controlled trial

Submitted

Van Dijk MR
Koster MPH
Oostingh EC
Willemsen SP
Steegers EAP
Steegers-Theunissen RPM

ABSTRACT

Background

Unhealthy nutrition contributes to the worldwide rising prevalence of non-communicable diseases. In the reproductive population, unhealthy nutrition affects fertility, pregnancy course and pregnancy outcome. As most adverse reproductiveoutcomes originate during the periconception period, effective interventions are needed to improve nutrition during this period. Therefore, we developed the online coaching program Smarter Pregnancy, to encourage healthy nutritioninwomen and men before and during pregnancy. The objective of this randomized controlled trial was to determine the compliance of this mHealth program and whether or not it improves nutrition in women prior to conception and during early pregnancy.

Methods

Women between 18 and 45 years of age who were contemplating pregnancy or already pregnant (<13 weeks of gestational age) were included. After baseline screening, the intervention group received personal online coaching if one or more of the following three risk factors was identified: inadequate intake of vegetables, fruit or folic acid supplements. The sum of all risk factors was used as a dietary risk score (DRS), ranging from 0 (healthy) to 9 (unhealthy).The program was tailored to sex, pregnancy state (pregnant or non-pregnant) and DRS at baseline. The control group received no personal online coaching. We applied an intention-to-treat principle and used a multivariable linear regression model, adjusted for the DRS baseline value, to evaluate the change in DRS after 24 weeks as our primary outcome. Compliance was defined as the percentage of women and men in each group who completed the screening questionnaire at 24 weeks.

Results

218 women were recruited, 177 of whom completed the program. This resulted in a compliance in women of 81.2% (intervention: n=91 (83%), control: n=86 (79%), p=.948). After 24 weeks of coaching, the reduction in DRS in women in the intervention group was significantly larger than in the control group (β=0.75, 95% CI: 0.18;1.34). This reduction was mainly due to increased vegetable intake (β=0.55, 95% CI: 0.25;0.86).

Conclusions

The high compliance and the larger improvements observed in nutritional behaviours, especially vegetable intake, in women before and during pregnancy emphasizes the potential of the Smarter Pregnancy program for this target population.

Trial registration: Netherlands trial register: NTR4150.

BACKGROUND

Poor nutrition contributes to the development of non-communicable diseases (NCDs), such as obesity, diabetes, and cardiovascular and metabolic disease[1-4]. In recent decades, the prevalence of NCDs and corresponding mortality rates have increased rapidly[5]. Vitamin deficiencies and high caloric intake combined with inadequate physical exercise are key risk factors for metabolic and endocrine derangements that contribute to obesity and a wide spectrum of NCDs. These risk factors are also highly prevalent in the reproductive population, where health consequences range from subfertility and even perinatal death[6-16]. Moreover, poor parental nutrition and lifestyle also confer a transgenerational risk of their children developing NCDs[2,17-19].

There is increasing evidence for a need for effective interventions to improve modifiable risk factors in women who are trying to get pregnant[20], particularly in the periconception period: the period 14 weeks prior to conception up to 10 weeks after conception[18]. As most adverse reproductive and pregnancy outcomes originate during this period, it is considered the earliest "window of opportunity" for interventions. However, since the periconception period is often neglected in regular health care, with specific periconception care rarely implemented, the prevalence of these modifiable risk factors remains high in the reproductive population[7,8,21].

In order to translate the scientific evidence currently available into accessible periconception care, various barriers need to be overcome. These barriers include the lack of intrinsic motivation in the target population, the low levels of awareness and a lack of clarity regarding responsibility and financing[22,23]. One way of overcoming some of these barriers is to make use of recent developments in electronic health or eHealth. These include using the broad range of functions available on mobile and handheld devices, with or without Internet access, also known as mobile health (mHealth)[24]. Indeed, the global use of smartphones has opened new doors for health care delivery. New and innovative approaches in the fields of preventive and personalized medicine can provide patients with both general information and individualized content[24,25]. In 2011, we launched an mHealth program called "Smarter Pregnancy" that aims to encourage healthy nutrition and a healthy lifestyle in couples who are contemplating pregnancy or already expecting a child. The program was based on existing evidence of the impact of nutrition and lifestyle on fertility, maternal pregnancy and neonatal outcome, and provided coaching on five major risk factors: inadequate vegetable, fruit, and folic acid supplement intake, and smoking and alcohol consumption[7,9,10,26-30]. Since an inadequate daily intake of fruits and vegetables is the most prevalent risk factor, we expect that improving these intakes also improves individual nutrition, resulting in a more healthy lifestyle in general.

The aim of this randomized controlled trial was to determine the compliance with the Smarter Pregnancy intervention and the effectiveness regarding the improvement of fruit, vegetable and folic acid supplement intake in women prior to conception and during early pregnancy.

METHODS

Trial design, participants and recruitment

A detailed study protocol has been published previously[30]. In short, women between 18 and 45 years of age were considered eligible for inclusion in this study if they owned a smartphone with Internet access, were resident in the Netherlands, and were contemplating pregnancy or already pregnant (<13 weeks of pregnancy). We excluded women if they had insufficient knowledge or understanding of the Dutch language, if they were being treated by a dietician to lose weight in the context of fertility treatment, or if they adhered a vegan diet. Dutch-speaking male partners with smartphones were also invited to participate unless they were receiving dietary advice, or adhered to a vegan diet.

We performed a single-centre, open, randomized controlled trial. Women eligible for inclusion were invited to participate by a health care professional working in one of the following locations in the Rotterdam region of the Netherlands: an academic hospital, four teaching hospitals, four midwifery practices and several children's day care and child health centres. After online registration, each woman was contacted by one of the study researchers to verify her eligibility, to provide her with more details about the study, to answer any questions about the "Smarter Pregnancy" program and to confirm her inclusion in the study. After the study researcher had verified the eligibility of women willing to participate in the study, inclusion occurred by signing an online (i.e. digital) patient informed consent form, which was automatically sent by e-mail to the participant through a secure study e-mail account. Men were always assigned the same group as their female partner.

Randomization

Randomization was stratified according to the location from which they had been recruited. A pre-programd permuted blocking design (two intervention and two control allocations per block) ensured that the number of women from the different locations was balanced between the two treatment groups, and that the allocation into groups was concealed from the researchers. Also, the participants were asked to print, sign the informed consent form to ensure compliance with the guidelines laid down in the Declaration of Helsinki. Participants were able to resign from the study at any time, without having to give a reason. All procedures involving patients were approved by the medical ethical and institutional review board of the Erasmus MC, University Medical Centre, Rotterdam, the Netherlands.

Intervention

The design and development of the coaching program led to the availability of two versions that we could use in our research: a full version that included all functionality and personalised interaction (the intervention), and a modified version, that had limited functionality and no personalised interaction, which was used in the control group. Detailed information on the coaching program can be found in the study protocol[30]. Because the focus of the current study was on evaluating nutrition, details on the cessation of smoking and alcohol consumption are not addressed here.

Men and women in the intervention group received tailored coaching based on their answers in the baseline questionnaire to questions regarding vegetable intake, fruit intake and folic acid supplement use. Vegetable intake and fruit intake were both subdivided into a risk score of 0, 1.5 or 3, where 0 represents an adequate daily intake (vegetable intake of ≥200 grams per day or a fruit intake of ≥2 pieces per day). A score of 1.5 represents a "nearly adequate" intake (vegetable intake of 150-200 grams per day or a fruit intake of 1.5-2 pieces per day). A score of 3 represents an inadequate daily intake (vegetable intake <150 grams per day or a fruit intake of <1.5 pieces per day). Folic acid supplement use was considered adequate (score 0) or inadequate (score 3) based on the international recommended dose of 400 µg per day. The dietary risk score (DRS) was calculated as the sum of the scores for vegetable intake, fruit intake, and folic acid supplement use, thus ranging from 0 to 9 in women, in which 9 was the most unhealthy risk score. In men, the DRS ranged from 0 to 6, as they did not receive any coaching regarding folic acid supplement use.

The tailored coaching was comprised of a maximum of three e-mails or text messages per week. These e-mails and messages contained seasonal recipes, incentives, feedback, recommendations and additional questions regarding their diet. Progress regarding the adoption of healthy behaviour was monitored using online questionnaires at 6, 12, 18 and 24 weeks in the intervention group, while the control group only received these questionnaires at 12 and 24 weeks.

The first follow-up study questionnaire was sent at 36 weeks, i.e. 12 weeks after the final screening questionnaire, and contained the same questions on nutrition, lifestyle and pregnancy status as the other online questionnaires at baseline, 12 and 24 weeks.

All participants were given access to a personal online webpage that provided access to additional modules (i.e. applications) that promoted physical activity, a calendar to improve compliance with hospital appointments and taking their folic acid supplements, and a module to monitor the safety of any prescribed medication.

Outcome measures

The main outcome measures of this study were:

1. Compliance of all participants, defined as the percentage of all participants who completed the online screening at 24 weeks.
2. The degree of improvement in nutrition in women 24 weeks after starting the Smarter Pregnancy program, as reflected by a reduction in the dietary risk score (DRS).

Statistical analysis

We analysed data from all participants, both those who completed the Smarter Pregnancy program and those who resigned prematurely, whereby missing data were handled using the Last-Observation-Carried-Forward method.

For all participants, the DRS was calculated at baseline (t=0), 12 weeks (t=12) and 24 (t=24) weeks. In further analyses, we included all women with a DRS >0 at baseline since these women were able to improve unhealthy behaviours and thereby reduce their risk scores. The primary analysis was based on intention to treat. The "difference in differences" principle was used to analyse the continuous outcome measures which were used in a multivariable linear regression model, adjusted for the

baseline value of the DRS. Bootstrapping was performed on all analyses because residuals of the linear regression analyses were not normally distributed[31].
All analyses were performed using Statistical Package for the Social Sciences software (IBM SPSS, Statistics for Windows, version 21.0). The study was registered in the Netherlands Trial Register, under code number NTR4150 on 19 August 2013. The final analyzed dataset of this trial will be available from the corresponding author on reasonable request.

Patient involvement

The design of this trial was based partly on patient evaluations obtained during a survey of the Smarter Pregnancy program[9]. During the current study, we also received questions and feedback from participants, which we used to optimize trial procedures and improve participant satisfaction.

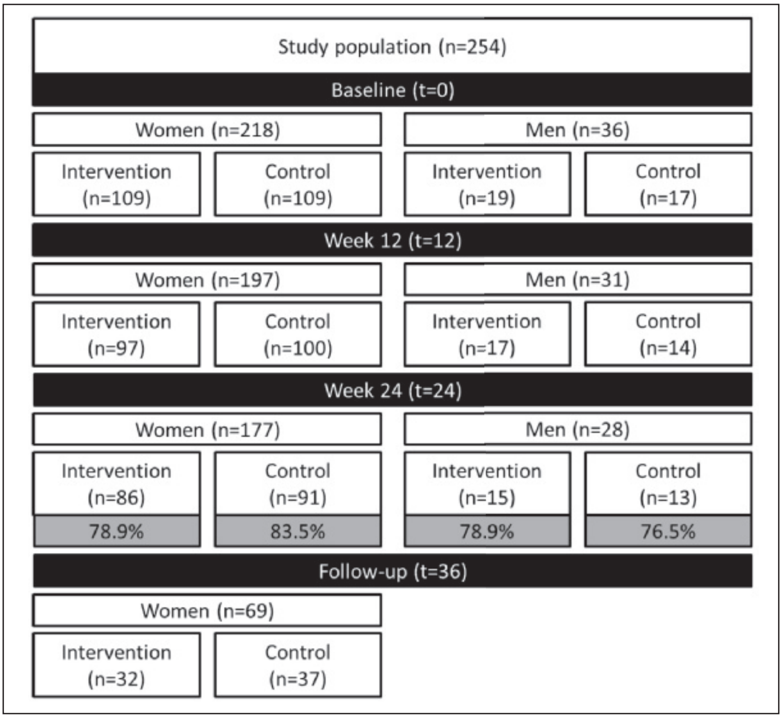

Figure 1 | Flow chart of the total study population, stratified by sex.

RESULTS

Participant characteristics

From May 2014 until January 2017, 218 women and 36 men were included in the study. After randomization, the intervention group consisted of 109 women and 19 men, and the control group of 109 women and 17 men (Figure 1). Baseline characteristics of all women in the study population are depicted in Table 1. Median age, median body mass index (BMI), pregnancy status and partner participation were similar for women in the intervention and control groups. In both groups most women were highly educated and of Dutch origin.

Table 1 | Baseline characteristics of all women in the intervention and control groups.

Women (n=218)		Intervention (n=109)	Missing	Control (n=109)	Missing
Age (years), median (IQR)		30.6 (5.3)		30.7 (5.7)	
Height (cm), median (IQR)		170 (9)		170 (9)	
BMI (kg/m²), median (IQR)		24.2 (6.0)		23.7 (5.4)	
Pregnant at enrolment, n (%)		36 (33.0)		37 (33.9)	
Partner participation, n (%)		19 (17.4)		18 (16.5)	
Geographic origin			6		6
Dutch, n (%)		83 (76.1)		86 (78.9)	
Western, n (%)		5 (4.6)		2 (1.8)	
Non-western, n (%)		15 (13.8)		15 (13.8)	
Education			**9**		**7**
High, n (%)		62 (56.9)		76 (69.7)	
Intermediate, n (%)		37 (33.9)		23 (21.1)	
Low, n (%)		1 (0.9)		3 (2.8)	
Vegetables, grams per day	**DRS**		0		0
<150, n (%)	3	65 (59.6)		65 (59.6)	
150-200, n (%)	1.5	19 (17.4)		24 (22.0)	
≥200, n (%)	0	25 (22.9)		20 (18.3)	
Fruit, pieces per day			**0**		**0**
<1.5, n (%)	3	39 (35.8)		37 (33.9)	
1.5-2.0, n (%)	1.5	8 (7.3)		14 (12.8)	
≥2.0, n (%)	0	62 (56.9)		58 (53.2)	
Folic acid supplement use			0		0
Inadequate, n (%)	3	10 (9.2)		10 (9.2)	
Adequate, n (%)	0	99 (90.8)		99 (90.8)	
DRS, median (IQR)	0-9	3 (4.5)		3 (3)	
Alcohol consumption, n (%)		85 (78.0)	0	82 (75.2)	0
Smoking, n (%)		5 (4.6)	0	12 (11.0)	0

DRS: dietary risk score, BMI: body mass index, IQR: interquartile range

Regarding nutrition and lifestyle, in both groups almost two-thirds of women reported having an inadequate vegetable intake. Fruit intake was inadequate in about a third of women in both groups. In both groups, almost one in ten women reported inadequate folic acid supplement use. These figures resulted in a median DRS at baseline of 3 in both groups.

The baseline characteristics of the participating men are depicted in Supplementary Table 1, which shows that the men in both groups had a higher DRS and a higher prevalence of smoking compared with the women.

Table 2 | Baseline characteristics of all women, stratified by adherence, defined as whether they completed the questionnaire at 24 weeks or resigned before this time point.

Women (n=218)		**Completed (n=177)**	**Missing**	**Resigned (n=41)**	**Missing**	**p-value**
Age (years), median (IQR)		30.8 (6.0)		30.1 (6.0)		.326
Height (cm), median (IQR)		170 (10)		169 (8)		.861
BMI (kg/m²), median (IQR)		23.4 (5.8)		25.6 (4.5)		.126
Pregnant at enrolment, n (%)		63 (33.9)		10 (31.3)		.772
Partner participation, n (%)		31 (16.7)		6 (18.8)		.772
Geographic origin			7		5	
Dutch, n (%)		145 (78.0)		24 (75.0)		.209
Western, n (%)		7 (3.8)		0		
Non-western, n (%)		27 (14.5)		3 (9.4)		
Education			11		5	
High, n (%)		119 (64.0)		19 (59.4)		.014
Intermediate, n (%)		53 (28.5)		7 (21.9)		
Low, n (%)		3 (1.6)		1 (3.1)		
Vegetables, grams per day	**DRS**		0		0	
<150, n (%)	3	106 (57.0)		24 (75.0)		.128
150-200, n (%)	1.5	38 (20.4)		5 (15.6)		
≥200, n (%)	0	42 (22.6)		3 (9.4)		
Fruit, pieces per day			0		0	
<1.5, n (%)	3	59 (31.7)		17 (53.1)		.058
1.5-2.0, n (%)	1.5	19 (10.2)		3 (9.4)		
≥2.0, n (%)	0	108 (58.0)		12 (37.5)		
Folic acid supplement use			0		0	
Inadequate, n (%)	3	16 (8.6)		4 (12.5)		0.480
Adequate, n (%)	0	170 (91.4)		28 (87.5)		
DRS, median (IQR)	0-9	3 (4.5)		4.5 (3)		<.01
Alcohol consumption, n (%)	–	40 (21.5)		11 (34.4)		.136
Smoking, n (%)	–	13 (7.0)		4 (12.5)		.283

DRS: dietary risk score, BMI: body mass index, IQR: interquartile range

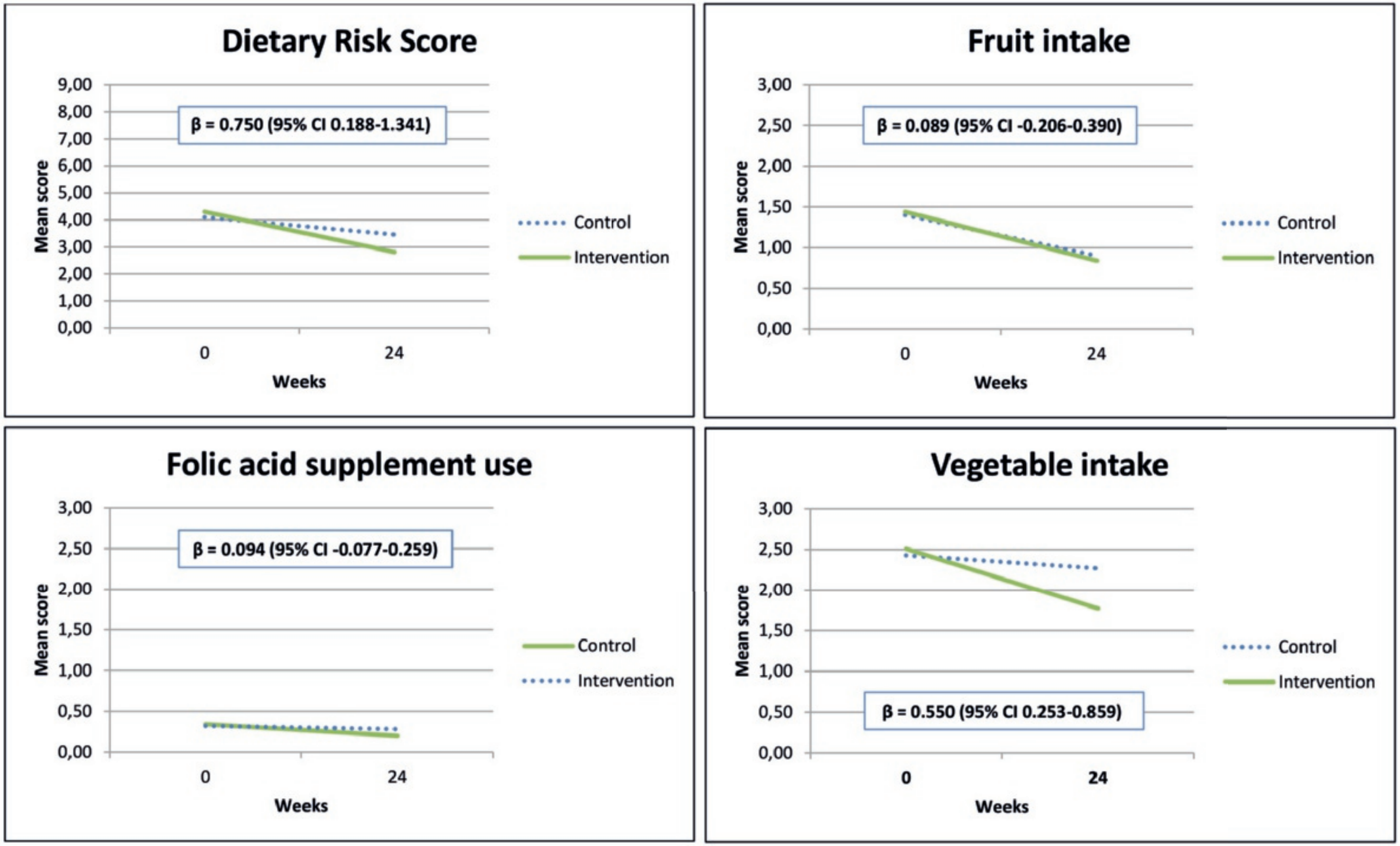

Figure 2 | Dietary risk score and separate risk factors over time in all women (with a baseline DRS >0) in the intervention and control groups. The linear regression model includes adjustment for baseline DRS and randomization.

Compliance and dropout

Of all women entering the study (n=218), compliance was 81.2% (n=177). In the intervention group, compliance was 78.9% (n=86) and in the control group it was 83.5% (n=91) (p=.948). In men, compliance was 77.8% (n=28), with 78.9% (n=15) in the intervention group and 76.5% (n=13) in the control group (p=.586).

When we compared the baseline characteristics of all women who completed the program (n=177) with those of women who resigned prematurely (n=41), we observed that women who resigned prematurely had a significantly higher median DRS (p=<.01) and a significantly lower level of education (p=.014) (Table 2).

Dietary risk score

The outcomes of the multivariable linear regression model regarding the DRS and, subsequently, the separate risk factors, are depicted in Figure 2. Compared with participants in the control group, participants in the intervention group had a significantly larger reduction in the DRS (β=0.750; 95% CI, 0.188-1.341) and in vegetable intake (β=0.550; 95% CI, 0.253-0.859). There were no significant differences between groups regarding fruit intake and folic acid supplement use

Follow-up

A total of 69 women (27.1%) filled in the follow-up questionnaire 36 weeks after randomization. Although women did not receive any coaching during the period between 24 and 36 weeks, the mean DRS appeared to continue to decrease in both the intervention group (n=32) and control group (n=37) (Figure 3).

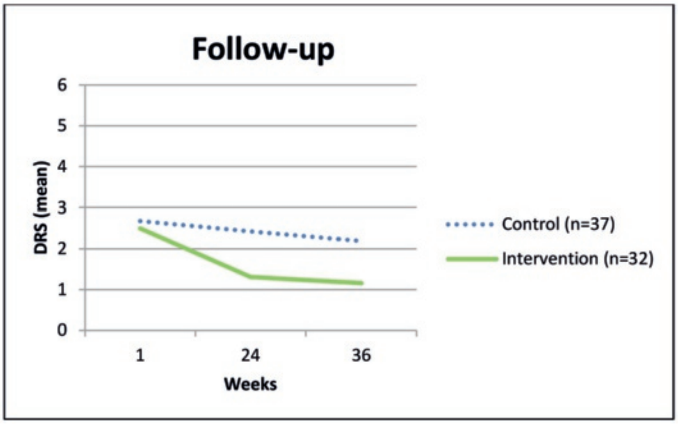

Figure 3 | Mean DRS over time in all women (n=69) who completed the follow-up questionnaire at 36 weeks.

DISCUSSION

The results of this randomized controlled trial indicate that compliance with the Smarter Pregnancy program is high. Our findings also indicate that the program improves nutrition in women prior to conception and during early pregnancy. The follow-up results also suggest that the intervention has an ongoing positive effect on participants' nutrition 12 weeks after stopping the intervention.

Strengths and limitations of this study

Major strengths of this study are the randomized controlled trial design, the fact that we used a standard and light version of the Smarter Pregnancy intervention, as well as the uniform collection of data in both the intervention and control group at baseline, 12, 24 and 36 weeks. By providing the control group with limited information and interaction, we encouraged participants in this group to adhere to the program, thereby ensuring high compliance and preventing dropout. The high compliance rates observed in both groups support this strategy. A further strength is that a wide range of professionals – also non-health professionals – recruited women for the study, as women were approached not only during a scheduled hospital or midwifery visit, but also at children's day care centres for example. Women who had not been personally invited could also enrol via the designed website that we set up, thereby limiting selection bias. Additional strengths of this study are the longitudinal observations, the fact that partners also participated, and that we collected additional information regarding lifestyle factors, educational level, geographic origin, and pregnancy status at enrolment.

In terms of weaknesses, we experienced difficulties enrolling sufficient women who were in the preconception period, which was why we expanded our inclusion criteria to include women up to 13 weeks of pregnancy. The consequence was a limited sample size through which we were not able to carry out subgroup analyses which would have provided additional quantitative data regarding lifestyle, fertility, pregnancy course and outcome, and cost-effectiveness.

A further limitation was that the Smarter Pregnancy program was only available online and in Dutch, thereby excluding women who have insufficient knowledge of the Dutch language or who have no Internet access from participation in this trial. This might have excluded a high-risk population of women who might have benefitted the most from the program.

An English version is now also available for research purposes (https://www.smarterpregnancy.co.uk/research).

Comparison with other studies

To date, there is little scientific evidence for the success of nutrition and lifestyle interventions during the preconception or periconception period. Most preconception interventions studies have focused on micronutrient supplementation or weight gain for example[32] or on specific subgroups and disease-related conditions, such as fertility treatment,[33] polycystic ovary syndrome (PCOS)[34] or pre-existing/gestational diabetes[35,36]. Even fewer studies have looked at mHealth interventions specifically focused on the preconception and periconception periods[35,37]. There is however a clear need for high-quality evidence that intervening in these periods in general is indeed effective[38-40].

A key problem underlying this lack of evidence is the lack of awareness of periconception care among both patients and health care professionals, resulting in low adherence and uptake of such care. This was already described in 2002 by De Weerd et al.[41]. While this barrier is widely acknowledged, and various studies have already focused on how to overcome it, unfortunately the barrier still remains[23,27,42,43]. It is has been suggested that modern marketing campaigns, such as those increasingly found online, might help to overcome, or at least lower, this barrier[40]. Taking into account, together with the wide uptake of mobile devices and online information[44], we believe that our approach – using an mHealth intervention specifically targeted at identifying and improving periconceptional risk factors – can contribute to lowering the unawareness barrier.

Conclusions and future perspectives

To our knowledge, the Smarter Pregnancy program is the first mHealth intervention shown to be effective in improving nutrition before and during early pregnancy. We therefore consider this study a good example of a successful mHealth intervention study, the findings of which support the considerable potential of using mHealth applications. Current awareness among health care professionals of their responsibility to inform their patients about healthy nutrition is very low[45]. However, we assume that the increasing amount of evidence for the importance of nutrition in the periconception period will make health care professionals in particular more aware, and make them more likely to recommend evidence-based mHealth interventions to their patients. This too will contribute to an increase in the general awareness of the importance of the periconception period. As a result, we hope that periconception care will become more easily and more widely accessible, thereby improving reproductive and pregnancy outcomes in both fertile and subfertile couples.

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Supplementary Table 1 | Baseline characteristics of all men in the intervention and control groups.

Men (n=36)		Intervention (n=19)	Missing	Control (n=17)	Missing
Age (years), median (IQR)		31.7 (5.0)		32.0 (4.6)	
Height (cm), median (IQR)		182 (11)		183 (10)	
BMI (kg/m²), median (IQR)		24.3 (6.4)		25.8 (3.5)	
Partner pregnant at enrolment, n (%)		2 (10.5)		1 (5.9)	
Geographic origin			1		5
Dutch, n (%)		13 (68.4)		11 (64.7)	
Wwestern, n (%)		1 (5.3)		0	
Non-western, n (%)		4 (21.1)		1 (5.9)	
Education			**1**		**5**
High, n (%)		12 (63.2)		10 (58.8)	
Intermediate, n (%)		5 (26.3)		2 (11.8)	
Low, n (%)		1 (5.3)		0	
Vegetables, grams per day	**DRS**		0		0
<150, n (%)	3	8 (42.1)		9 (52.9)	
150-200, n (%)	1.5	6 (31.2)		3 (17.6)	
≥200, n (%)	0	5 (26.3)		5 (29.4)	
Fruit, pieces per day			0		0
<1.5, n (%)	3	8 (42.1)		6 (35.3)	
1.5-2.0, n (%)	1.5	2 (10.5)		3 (17.6)	
≥2.0, n (%)	0	9 (47.4)		8 (47.1)	
DRS, median (IQR)	0-6	3 (3)		3 (4.5)	
Alcohol consumption, n (%)	–	15 (78.9)		11 (64.7)	
Smoking, n (%)	–	5 (26.3)		3 (17.6)	

DRS: dietary risk score, BMI: body mass index, IQR: interquartile range

Chapter 8

Maternal lifestyle impairs embryonic growth: The Rotterdam Periconception Cohort

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Van Dijk MR
Borggreven NV
Willemsen SP
Koning AHJ
Steegers-Theunissen RPM
Koster MPH

ABSTRACT

Previously, embryonic growth has been assumed to be uniform, but in recent years, it has become more clear that genetic and environmental factors may influence the intrauterine environment and therefore embryonic growth trajectories as well as pregnancy course and outcome. The objective of this study was to investigate associations between modifiable maternal nutrition and lifestyle factors during the periconception period and embryonic growth. We established a prospective cohort including 342 women less than 13 weeks pregnant. At enrollment, women filled out a questionnaire regarding demographic and medical data and a validated food frequency questionnaire. Participants received multiple 3-dimensional ultrasound examinations up until the 12th week of pregnancy, and crown–rump length (CRL) and embryonic volume (EV) were measured offline using V-Scope Virtual Reality software (version 1.0.0) in a Barco I-Space. Associations between maternal periconception vegetable and fruit intake, folic acid supplement use, smoking, and alcohol consumption and embryonic growth measurements were assessed by linear mixed models adjusted for potential confounders. No or postconception initiation of folic acid supplement use was significantly associated with a 0.76 mm (-7.8%) and 1.63 mm (-3.7%) smaller CRL and a 0.01 cm^3 (-19.5%) and 0.86 cm^3 (-12.2%) smaller EV at 7+0 and 11+0 weeks of gestation, respectively. Smoking, alcohol consumption, and inadequate fruit and vegetable intake showed weaker associations with embryonic growth parameters. These results emphasize the influence of periconceptional maternal folic acid supplement use on embryonic growth. Results regarding maternal nutrition and lifestyle factors also suggest an association with embryonic growth, but this has to be confirmed in a larger study.

INTRODUCTION

Early embryonic growth has traditionally been assumed to be uniform among humans, but in the past decade subtle differences in embryonic growth trajectories have been shown[1-3]. These differences not only concern embryonic development, but are also suggested to predict a poor pregnancy course and outcome[4]. Embryonic development and growth is under the constant influence of the intrauterine environment, which is determined not only by genetic factors, but also by parental environmental and lifestyle factors, of which most are modifiable[5,6]. In high-income countries, unhealthy lifestyle (including unhealthy nutrition) is an increasing problem[7]. A shift towards behavioral changes, resulting in high caloric intake, vitamin deficiencies, smoking, alcohol consumption and physical inactivity, are causing an increasing prevalence of obesity and other non-communicable diseases (NCDs)[8,9].

Unfortunately, the high frequency of unhealthy lifestyle is also present among women of reproductive age, even in those undergoing fertility treatment, and despite the known negative effects on fetal growth and pregnancy outcome, and the health of mother and child later in life [10]. For example, maternal smoking, alcohol consumption and nutritional deficiencies are associated with fetal growth restriction and increased risks of miscarriage and fetal death[11-14]. On the long term, unhealthy maternal lifestyle increases the risk of cardiovascular and metabolic disease in offspring[15-18].

We hypothesize that increased fruit and vegetable intake and folic acid supplement use during the vulnerable periconception period (i.e. the 14 weeks before and 10 weeks after conception), are positively associated with embryonic growth, whereas smoking and alcohol consumption are negatively associated. These five nutrition and lifestyle factors are not only known to affect fertility, they are also easy to address for a clinician and easy to (self-)report for a patient. Therefore, the aim of this study was to investigate associations between these five modifiable maternal periconception lifestyle risk factors and first trimester embryonic growth, making use of the novel state-of-the-art techniques of three-dimensional ultrasound (3D-US) combined with the virtual reality technology of the Barco I-Space[19-21].

PARTICIPANTS AND METHODS

Study population

This study was part of the Rotterdam Periconception Cohort (Predict study), an ongoing prospective tertiary hospital-based study embedded in the outpatient clinic of the department of Obstetrics and Gynaecology of the Erasmus MC, University Medical Centre Rotterdam, the Netherlands. A detailed cohort description has previously been published[22]. From November 2010 to December 2014, women of at least 18 years of age who were less than thirteen weeks pregnant with a singleton pregnancy were eligible for participation.

Data collection

All pregnancies that were conceived spontaneously or through intra-uterine insemination (IUI), semen donation and hormone therapy were considered to be spontaneous in comparison with pregnancies conceived through in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). Pregnancies were dated as described previously[22]. In short, gestational age (GA) was either based on the last menstrual period (LMP) in spontaneous pregnancies or on the conception date in IVF and ICSI pregnancies. To obtain information on demographic characteristics and five periconception lifestyle factors (i.e. vegetable intake, fruit intake, folic acid supplement use, smoking and alcohol consumption), participants completed a self-administered questionnaire at enrollment, together with a validated semi-quantitative food frequency questionnaire (FFQ), which were verified for completeness and consistency by the researcher or research nurse at study entry[22,23].

Adequate daily fruit and vegetable intake was defined according to Dutch guidelines as two pieces of fruit (equivalent to 200 gram) and 200 grams of vegetables, respectively. Folic acid supplement use of 400 µg per day is recommended during the periconception period (i.e. from four weeks prior to conception up to eight weeks after conception)[24,25]. Therefore, preconception initiation of folic acid supplement use was defined as adequate, whereas no or post-conception initiation of folic acid supplement use was defined as inadequate. Total abstinence of smoking and alcohol consumption during the periconception period was considered adequate. Anthropometrics (i.e. maternal blood pressure, weight and height) were measured at study entry by a research nurse.

From November 2010 to December 2012 participants received weekly transvaginal three-dimensional ultrasound scans (3D-US) from enrollment up to week 12 of gestation (range: 6^{+0} to 12^{+6} weeks) by experienced sonographers. From the end of 2012 onwards the number of scans was reduced to three, performed in the 7^{th}, 9^{th} and 11^{th} week of gestation, as the pilot study showed that three scans are sufficient to accurately model embryonic growth curves[2,26]. Obtained 3D-US datasets were transferred to the Barco I-Space (a Cave Automatic Virtual Environment (CAVE)-like virtual reality system) to create an interactive virtual reality hologram. Trained researchers performed offline measurements using the I-Space and V-Scope software. CRL was measured three times and the mean of these measurements was used for analysis. EV measurements were performed once using a semi-automatic method based on grey levels[27].

Statistical analysis

General characteristics of the study sample and source population were compared using Mann-Whitney U-tests (for continuous variables) or Chi-square tests (for categorical variables). To take into account the correlation between measurements of the same pregnancy, linear mixed models were used to assess associations between adequate periconception maternal lifestyle and embryonic growth. A square root transformation of CRL and third root transformation of EV data led to linearity with GA and a constant variance independent of GA and were therefore used in the analysis. In the first model we adjusted for GA only to increase the precision of the measurements. In the second model, we additionally adjusted for maternal age, BMI, ethnicity, educational level, parity and mode of conception. In the final model we also adjusted for folic acid supplement use, fruit intake, vegetable intake, alcohol consumption and smoking (all dichotomous; adequate or inadequate) to investigate the independent effects of the lifestyle factors. In all models, embryonic growth rates for both CRL and EV were calculated by including an interaction term between the gestational age and the five risk factors of interest. P-values below 0.05 were considered statistically significant. All analyses were performed using IBM SPSS Statistics version 21.0 for Windows.

Ethical approval

All data were anonymously processed. This study 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 Centre, Rotterdam, the Netherlands. Written informed consent was obtained from all participants at enrollment.

RESULTS

From a total of 723 first trimester pregnancies enrolled in the Predict study between 2010 and 2014, CRL and EV measurements were available for 563 pregnancies. Of these pregnancies 221 were excluded because of the following reasons: miscarriage, ectopic pregnancies, congenital anomalies, perinatal death, twin pregnancies, oocyte donation, pregnancy termination, irregular menstrual cycle, observed CRL discrepancy >6 days from expected CRL, missing questionnaires and withdrawal (Figure 1). Thus, a total of 342 pregnancies were included in the analyses.

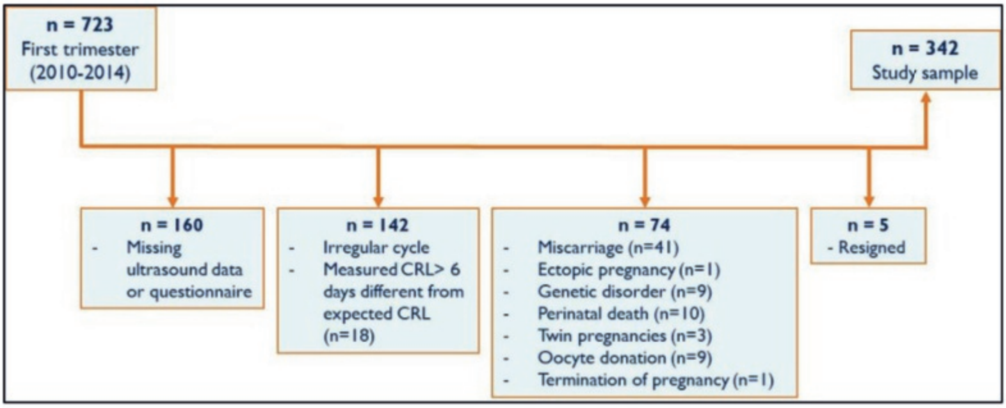

Figure 1 | Flowchart of the study population**.** CRL: Crown-rump length.

In these pregnancies, the median number of 3D-US examinations per pregnancy was 4 (range 1-7) with a median GA at the first 3D-US examination of 7^{+3} weeks (range: 6^{+0} - 12^{+2}). This yielded a total of 1,443 ultrasounds, of which 1,255 (87.0%) were of sufficient quality to perform CRL measurements and 1,116 (77.3%) to perform EV measurements.

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Women in our study sample more often conceived through IVF or ICSI compared with the source population of the Predict study (40.9% versus 26.5%; p<0.001) (Table 1). In the study sample, nearly all women used a folic acid supplement (n=329, 98.2%) and 278 (83.0%) women started folic acid supplement use preconceptional. A total of 48 (14.2%) women smoked and 112 (33.2%) consumed alcohol during the periconception period. Fruits and vegetable intake was inadequate in 162 (52.9%) and 110 (35.9%) women, respectively.

Inadequate folic acid supplement use was significantly negatively associated with CRL (-0.124, 95% CI -0.222;-0.026) as well as EV (-0.059, 95%CI -0.105;-0.014) (Table 2). Retransformation to the original scale showed that the CRL of an embryo of a woman with inadequate folic acid supplement use was on average 0.75 mm (reduction of 7.8%) and 1.63 mm (reduction of 3.7%) smaller at 7+0 and 11+0 weeks of gestation respectively, compared to a woman with adequate folic acid supplement use (Figure 2a). In women with inadequate folic acid supplement use, the EV was on average 0.01 cm3 (reduction of 19.5%) and 0.86 cm3 (reduction of 12.2%) smaller at 7+0 and 11+0 weeks of gestation, respectively (Figure 2b). The interaction between gestational age and folic acid supplement use was statistically significant (p=0.03) for EV, indicating that embryonic growth rates differed between both groups (i.e. higher in women who adequately used folic acid supplements) (Figure 2b). Smoking as well as inadequate fruit intake showed comparable negative associations with CRL and EV, though not statistically significant (Table 2).

Table 1 | Baseline characteristics of the study sample and source population. iqr: interquartile range, bmi: body mass index, ivf: in vitro fertilization, icsi: intracytoplasmic sperm injection.

	Study sample (n=342)	Missing	Source population (n=723)	Missing	p-value
Maternal characteristics					
Age (y), median (IQR)	32.0 (29.0-35.0)	5	32.0 (28.0-35.0)	6	0.278
Ethnicity		3		1	0.518
Western, n (%)	291 (85.8)		616 (85.3)		
Non-western, n (%)	48 (14.2)		106 (14.7)		
Education		3		9	0.953
Low, n (%)	29 (8.6)		68 (10.9)		
Intermediate, n (%)	120 (35.4)		256 (35.9)		
High, n (%)	190 (56.0)		390 (54.6)		
BMI, kg/m^2, median (IQR)	24.3 (22.0-27.8)	30	24.6 (22.1-28.5)	52	0.371
Nulliparous, n (%)	107 (31.5)	2	224 (31.2)	5	0.621
Mode of conception		0		3	**<0.001**
Spontaneous, n (%)	202 (59.1)		529 (73.5)		
IVF/ICSI, n (%)	140 (40.9)		191 (26.5)		
Periconception nutrition and lifestyle					
Fruits, gr/day, median (IQR)	211.5 (84.5-232.6)	36	205.0 (85.3-230.5)	77	0.532
Inadequate (<200g), n (%)	162 (52.9)		326 (50.5)		0.488
Adequate (≥200g), n (%)	144 (47.1)		320 (49.5)		
Vegetables, gr/day, median (IQR)	167.1 (101.5-240.6)	36	162.2 (100.0-233.3)	77	0.627
Inadequate (<200g), n (%)	110 (35.9)		223 (34.5)		0.663
Adequate (≥200g), n (%)	196 (64.1)		423 (65.5)		
Folic acid supplement use		7		4	0.291
Yes preconception, n (%)	278 (83.0)		564 (78.6)		
Yes postconception, n (%)	51 (15.2)		134 (18.7)		
No, n (%)	6 (1.8)		17 (2.4)		
Smoking, n (%)	48 (14.2)	4	112 (15.7)	11	0.519
Alcohol consumption, n (%)	112 (33.2)	5	223 (31.3)	10	0.525

Table 2 | Effect estimates from the linear mixed model analysis for maternal nutrition and lifestyle factors and the embryonic growth parameters crown-rump length (CRL) and embryonic volume (EV).

		Crown-rump length (CRL)						Embryonic volume (EV)					
		Model 1[a]		Model 2[b]		Model 3[c]		Model 1[a]		Model 2[b]		Model 3[c]	
	n	Effect estimate (95% CI), √mm	p	Effect estimate (95% CI), √mm	p	Effect estimate (95% CI), √mm	p	Effect estimate (95% CI), $^3\sqrt{cm^3}$	p	Effect estimate (95% CI), $^3\sqrt{cm^3}$	p	Effect estimate (95% CI), $^3\sqrt{cm^3}$	p
Smoking													
Adequate	290	0 [reference]		0 [reference]		0 [reference]		0 [reference]		0 [reference]		0 [reference]	
Inadequate	48	-0.046 -0.137;0.044)	0.31	-0.047 -0.145;0.051)	0.34	-0.055 -0.159;0.050)	0.30	-0.040 -0.084;0.004)	0.08	-0.047 -0.094;0.0003)	0.05	-0.042 -0.089;0.006)	0.08
Alcohol													
Adequate	225	0 [reference]		0 [reference]		0 [reference]		0 [reference]		0 [reference]		0 [reference]	
Inadequate	112	-0.041 -0.108;0.027)	0.23	-0.031 -0.103;0.041)	0.40	-0.036 -0.112;0.040)	0.35	-0.011 -0.044;0.022)	0.52	-0.0035 -0.039;0.032)	0.85	-0.0051 -0.040;0.030)	0.77
Folic acid													
Adequate	278	0 [reference]		0 [reference]		0 [reference]		0 [reference]		0 [reference]		0 [reference]	
Inadequate	57	-0.081 -0.165;0.003)	0.06	-0.107 -0.202;-0.012)	0.03	-0.124 -0.222;-0.026)	0.01	-0.036 -0.078;0.006)	0.10	-0.053 -0.100;-0.007)	0.02	-0.059 -0.105;-0.014)	0.01
Fruits													
Adequate	170	0 [reference]		0 [reference]		0 [reference]		0 [reference]		0 [reference]		0 [reference]	
Inadequate	149	-0.045 -0.110;0.020)	0.17	-0.051 -0.121;0.018)	0.15	-0.049 -0.120;0.022)	0.18	-0.023 -0.055;0.008)	0.14	-0.031 -0.063;0.002)	0.06	-0.028 -0.061;0.005)	0.09
Vegetables													
Adequate	117	0 [reference]		0 [reference]		0 [reference]		0 [reference]		0 [reference]		0 [reference]	
Inadequate	202	0.0050 -0.062;0.072)	0.88	0.0002 -0.074;0.074)	1.00	0.016 -0.058;0.090)	0.67	-0.0036 -0.036;0.029)	0.83	-0.0053 -0.040;0.029)	0.76	0.0041 -0.030;0.038)	0.82

Adequate daily intake of fruits and vegetables was defined as at least 200 grams of each food group. inadequate folic acid supplement use was defined as no or postconception initiation of folic acid supplement use. a adjusted for ga, b adjusted for ga and maternal characteristics, c adjusted for ga, maternal characteristics and risk factors.

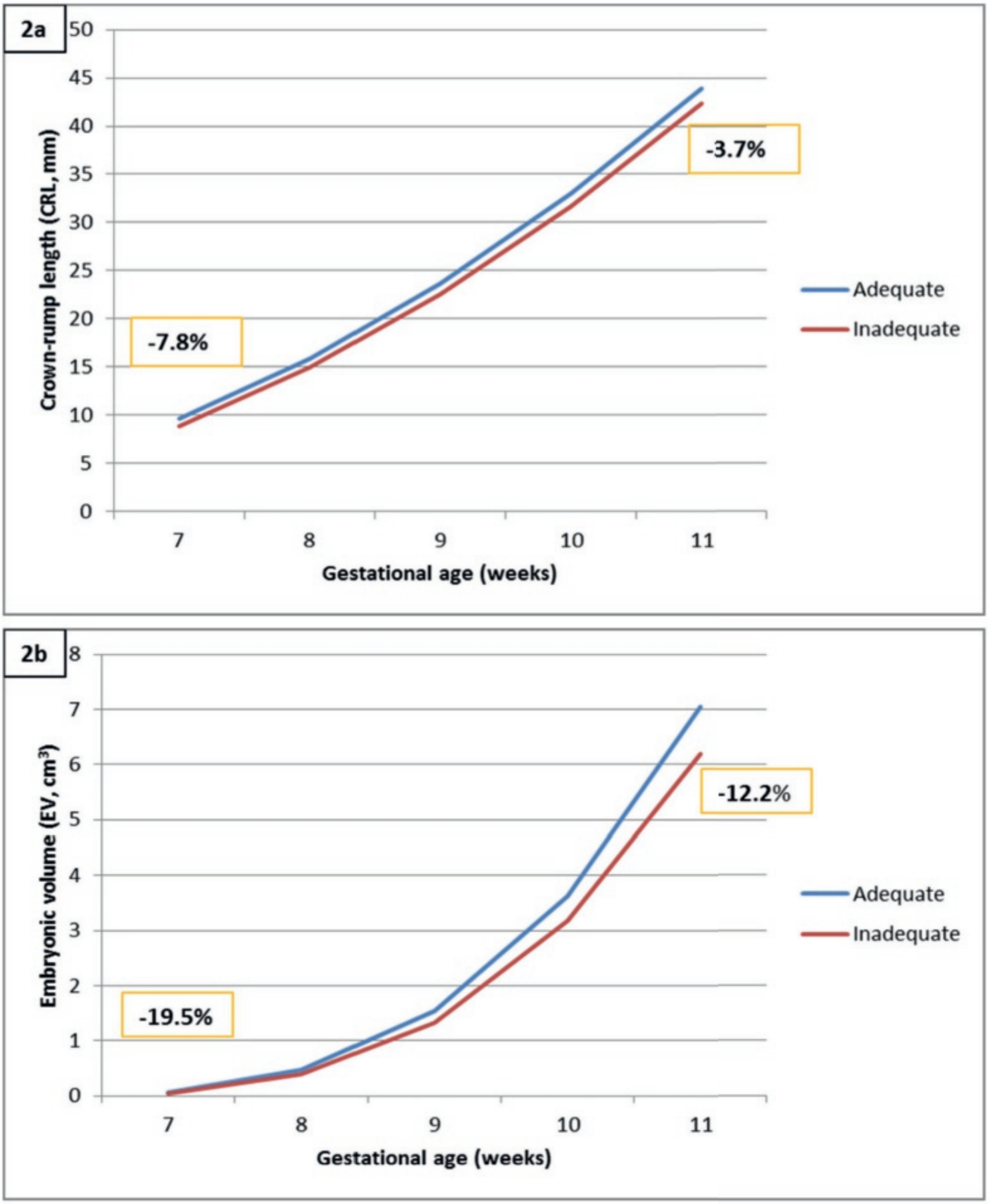

Figure 2 | Embryonic growth trajectories for a) crown-rump length (CRL) and b) embryonic volume (EV). Adequate folic acid supplement use (preconception initiation, blue line) and inadequate folic acid supplement use (postconception initiation or no, red line), including the relative differences at 7 and 11 weeks of gestational age.

DISCUSSION

In this study we found a significant negative association between inadequate maternal folic acid supplement use and embryonic growth, measured as CRL and EV as well as growth rate during the first trimester. Maternal smoking and inadequate fruit intake showed comparable results, with nearly significant negative associations, but alcohol consumption and vegetable intake revealed no significant associations with embryonic growth in our study. Folate is an important substrate used by the one-carbon metabolism, in which one-carbon groups are provided to critical processes, such as synthesis of DNA and proteins and epigenetic programming. This B vitamin is particularly known for its role in the prevention of neural tube defects (NTDs)[17,28]. As early pregnancy is a critical period with rapid cell division, growth and proliferation as well as high responsiveness to external influences, optimal maternal folate concentrations are crucial. Optimal concentrations are frequently not achieved through regular dietary folate intake and deficiencies can lead to impaired epigenetic programming associated with long-term health consequences[29]. This may explain the reduced embryonic size and growth in women with inadequate folic acid supplement use in our study. However, our previous studies also showed that very high levels of maternal folate are associated with reduced embryonic and cerebellar growth, suggesting there is an optimum maternal folate status for embryonic growth[30,31]. Nutritional factors as fruit and vegetable intake may also contribute to stable and reversible methylation abnormalities and impaired embryonic development, by means of insufficient supply or reduced uptake of cofactors of the one-carbon metabolism. However, it is clear that this is only one of several metabolic pathways that are affected by maternal nutrition and as such influencing embryonic growth.

Longitudinal studies that focus on first trimester embryonic growth are scarce, but negative associations between maternal smoking and alcohol consumption and embryonic growth have been demonstrated[4,26]. This can be partly explained by their known deranging effects on the one-carbon metabolism, but also by the direct toxic effects of smoking on embryogenesis, placental development and function and by the vasoconstrictive effects of alcohol consumption[32-34]. One of the main strengths of this study is the longitudinal collected ultrasound data (with a median of four 3D-US scans per pregnancy) combined with detailed and validated information regarding lifestyle. Also, offline virtual reality measurements of these 3D-US images show high reliability by their excellent inter- and intra-observer agreement[20,27]. Another strength of this study is the exclusion of pregnancies with an unreliable gestational age, whereas pregnancy dating is often a strong confounder in studies on embryonic growth, due to the variation in timing of ovulation and implantation in spontaneously conceived pregnancies. A limitation of this exclusion on the other hand is the smaller study sample and a relatively high percentage of pregnancies conceived through IVF/ICSI, although we did not observe any differences in association between nutrition and lifestyle and embryonic growth between both groups (data not shown). In this study we have included both high and low quality 3D-US images. Explanations for low quality 3D-US images could be uterine position, movement of the embryo, and maternal BMI. Although 3D-US and virtual reality provide a more authentic and detailed view of the developing embryo, performing measurements on low quality data can be difficult. In the future, results of separate analyses of high and low quality images could be compared to determine whether the quality actually influences the results.

Since diet is very complex and consists of a variety of foods and nutrients, focusing on a single food group, such as fruits or vegetables, may be less suitable to demonstrate associations between maternal nutrition and embryonic growth. Thus, it might be worth considering to study associations between dietary patterns and embryonic growth. However, it will be very time consuming in routine clinical practice to determine a patient's dietary pattern, while simple food groups, and consequently nutrient deficiencies, are much easier to query and to report. Our results emphasize the need to inform women who are contemplating pregnancy of the importance of preconception initiation of folic acid supplement use. Taking into account the high prevalence of inadequate nutrition and lifestyle in the reproductive population and the previously described associations between maternal lifestyle and fetal growth and pregnancy outcomes, preconception care should also focus on these inadequacies.

In conclusion, inadequate folic acid supplement use is negatively associated with embryonic growth and embryonic growth rate. We also show that there might be associations between periconception maternal smoking, alcohol consumption, inadequate fruit and vegetable intake and impaired embryonic growth. Further research with larger study samples of different (general) populations should elucidate the association between periconception maternal lifestyle and embryonic growth, as the next step towards the early identification of pregnant women at risk for poor pregnancy course and outcome.

Key messages:

- Inadequate maternal folic acid supplement use and to a lesser extend smoking and inadequate fruit intake showed a significant negative association with embryonic growth.
- Knowledge about associations between periconception maternal lifestyle and embryonic growth can be used for the early identification of pregnant women at risk for poor pregnancy course and outcome.
- Nutrition and lifestyle are modifiable factors and therefore targets for both primary and secondary preventive medicine interventions.

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Chapter 9

General discussion and future perspectives

In this chapter the main findings, methodology and clinical implications of the studies described in this thesis are discussed and the recommendations for future research are provided.

MAIN FINDINGS

The survey conducted between 2012 and 2013 aimed to investigate the compliance, usability and effectiveness of the mHealth program Smarter Pregnancy showed a high compliance of 65% to complete the 26 weeks coaching program for women and men who started the program preconceptionally or during pregnancy. Especially women with a participating male partner demonstrated the most significant improvements in adopting healthy nutrition and lifestyle behaviors. In addition, a positive association was observed between the adoption of healthy nutrition and lifestyle during the use of the mHealth program and the chance to conceive in both fertile and subfertile couples. These associations were demonstrated in women, but again also increased when the partner was also a participant of the program. Moreover, we showed that the mHealth program seemed more effective in women who live in more deprived neighborhoods.

These findings were substantiated by the randomized controlled trial, in which it was shown that nutritional behaviors in general and daily vegetable intake in particular can be improved in women by using the mHealth program. Unfortunately, this trial also demonstrated that the awareness of the importance of preconceptional health, in particular of the determinants in nutrition and lifestyle, is still very low in the reproductive population, resulting in a low preconceptional inclusion rate of the participants.

To further explore the perceptions and experiences of the end-users (women, men, (health care) professionals) regarding the role of mHealth in preconception care, we conducted a qualitative focus group study. The most important findings were the unanimous agreement of the end-users about the lack of awareness of preconceptional care and the potential role of mHealth.

The prospective cohort study on the impact of periconception nutrition and lifestyle on embryonic development, revealed negative associations between inadequate folic acid supplement use, and to a lesser extent smoking and inadequate fruit intake, and embryonic growth and growth rate, expressed as crown-rump length (CRL) and embryonic volume.

Overall, we conclude that poor nutrition and lifestyle are modifiable risk factors that can be improved through the mHealth program Smarter Pregnancy with potential implications on reproductive outcomes, i.e., increased pregnancy chance, larger embryonic growth rates.

Methodological considerations

This thesis comprises multiple study designs. Three studies showed results that were derived from a large survey. By definition a survey provides characteristics of a given population and outcomes without a control group[1]. In our survey, we investigated a reproductive population during the periconception period using online self-administered screening and monitoring questionnaires of the mHealth program Smarter Pregnancy, in order to obtain data on nutrition, lifestyle and other characteristics. Although our survey has several limitations, such as the absence of a control group, limited external validity and lack of biomarker validation of nutrition and lifestyle behaviors, we consider this data very informative, because of its large sample size of more than 2,500 participating women and 300 men.

These limitations were controlled for in the Smarter Pregnancy randomized controlled trial (RCT) by means of a control group, biomarker validation of nutrition and lifestyle behaviors, and 1:1 randomization of the intervention. Although RCTs are considered the golden standard in human research, possible disadvantages are selection bias and not reflecting the 'real life setting'.

The qualitative study described in this thesis involved end-users of the Smarter pregnancy mHealth program, including men and a variety of health care professionals involved in preconception care. Strengths of this study are the obtained individual opinions and insights of many involved end-users, which can improve future versions of the Smarter Pregnancy program.

As a part of the Rotterdam periconception cohort (Predict study), we also prospectively studied the associations between maternal periconception nutrition and lifestyle[2]. Exposures were measured using a validated self-administered food frequency questionnaire, anthropometrics were measured standardized and performed in one tertiary hospital using the same instruments. Three-dimensional ultrasound (3D-US) scans and offline virtual reality measurements of CRL and embryonic volume were performed by trained sonographers/researchers according to standardized protocols. All questionnaires were validated for completeness and consistency by a researcher or research nurse in order to minimize reporting errors.

As emphasized in this thesis, the periconception period is a crucial but largely neglected period in research[3]. Unfortunately, the unawareness of the importance of this timespan also affected the recruitment of the study populations described in this thesis. This unawareness may have led to selection bias, which is common in these type of studies. The intrinsic motivation, based on the individual perception of importance, plays a significant role and should therefore always be taken into account. This kind of selection bias was particularly experienced when we conducted the Smarter Pregnancy RCT. In this study, it was hard to include participants, probably due to the unawareness of the periconception period and perceived need by patients and (health care) professionals. On the contrary, participants known to be subfertile and known to receive an IVF-treatment were much more motivated to participate (unpublished data).

Interpretation of the findings

The studies that were based on data from the Smarter Pregnancy survey or the RCT, substantiated the existing evidence regarding the high prevalence of poor nutrition and lifestyle in the reproductive population[4-7]. Even patients who receive assisted reproductive treatment have a high prevalence of these unhealthy behavior[8]. In order to reduce the high prevalence of unhealthy behaviors, the first step would be to increase awareness of their reproductive health impact by educating couples on the risks and benefits while contemplating pregnancy[9,10]. Such awareness can only be achieved by delivering information to those who need PCC the most, but, unfortunately, the reproductive population without fertility or specific medical conditions still appears hard to reach. Due to the current burden of obesity, nutrition and lifestyle behaviors are extensively investigated as targets for (preventive) interventions and also during the periconception period[5,9,11-14].Various

approaches with different interventions and health care systems aimed to improve accessibility and implementation of general PCC. Multidisciplinary collaborations, scheduled preventive health programs and personal delivery by a health care professional have been tried, but the uptake of PCC remains low[15-19]. Subsequently, various barriers and facilitators regarding PCC have been identified, such as the accessibility of health care, a lack of social support and, most importantly, the mutual lack of awareness and perceived need of patients and health care professionals[19-23]. Based on existing literature as well as the results of our qualitative focus group study, we consider the poor dissemination of the importance of periconception health and its nutrition and lifestyle determinants one of the major underlying problem of the failure of PCC uptake and implementation[24-26].
In 2006, PCC was described as a product and a social marketing approach was used, stating that it should meet the needs and desires of patients, health care professionals and health care insurers in order to be successfully adopted[27]. This marketing approach, comprising the concept of "selling" PCC as a product, was also mentioned by professionals during our qualitative focus group study. Because the reproductive population is unaware of the importance and even the existence of this type of preventive medicine, a situation may arise in which the need of the health care professional to provide PCC is larger than the patient's need to receive it. Other barriers mentioned by professionals are: time constraint, costs, lack of training and resources, and poor coordination and organization of PCC[22,28-30]. The needs of health care insurers and health care providers are often based on market research and cost-effectiveness analyses. The literature on these analyses are scarce, but there is some evidence that PCC leads to a favorable cost-benefit balance, based on uptake rates of 50-75%, which are currently not met[31].
In general, the potential of mobile health (mHealth) is well-accepted and is already being used for many different purposes. Regarding health care delivery, this includes tools to increase awareness by providing information, e.g., nutrition and lifestyle, to a specific target population[32,33]. Over the last years, the Internet became the first source to which many people turn to for health information. Although health literacy skills are low in general, people use a doctor for a second opinion[34]. This development, combined with the rapid adaptation of mobile devices, is probably the reason why mHealth is ascribed its large potential by patients and professionals. During our focus group sessions, patients and health care professionals agreed upon this potential, which we consider an important finding regarding previously mentioned barriers that need to be overcome. But how do people decide which applications or interventions to use in this wealth of online information? And how do end-users perceive the individual relevance and determines the quality of such information? These aspects are important to address when assessing the role of mHealth in periconception care.
In specific target groups, possible benefits of mHealth are described as 'improving health' and 'enhancing patients' self-reliance'[33]. It has also been described that people who seek information online find it hard to determine the quality of such information[33]. Of all health-related applications, only a small proportion can be classified as a medical device according to EU regulations[35,36]. Our mHealth program Smarter Pregnancy belongs to this small proportion. This was acknowledged in our focus groups; participants agreed on the difficulty of determining the quality of online information, but they stated that the support of recognized (medical) institutions has a positive effect on the trustworthiness of the information.

Despite the above mentioned limitations of qualitative research, we believe that our results can support the development and improvement of mHealth in general and the Smarter Pregnancy program in particular. Therefore, we consider the results obtained from this qualitative study highly valuable.

CLINICAL IMPLICATIONS

This thesis shows that healthy behavior is associated with a higher pregnancy chance and that poor nutrition and lifestyle behaviors are associated with smaller embryos and impaired embryonic growth. We also showed that the mHealth program Smarter Pregnancy supports women and couples who are contemplating pregnancy to improve their nutrition and lifestyle behaviors. This strongly suggests that men should also be involved in periconception care. Health care professionals should inform their patients about the known associations between nutrition and lifestyle behaviors and maternal pregnancy and neonatal outcomes. Because patients are currently more engaged to the Internet than to their health care professional, health care professionals should try to use mHealth as an additive to standard care[34]. This can improve the patient-physician relationship, it can be time-saving and it can induce perceived needs of the reproductive population, which has been described as the key element for PCC to become effective[37-39].
Many mHealth applications focus on high-need, high-cost populations, e.g. patients with diabetes, but they do not focus on the needs of an individual of that population[40]. This was also acknowledged by the patients who participated in our focus groups. Some needs regarding mHealth in general have been described, such as 'on the go' information, behavior tracking or monitoring, acquiring advice and receiving feedback[41,42]. For the reproductive population, there is an enormous amount of commercial pregnancy and baby related applications, but the specific needs of this population have so far not been explored. Mostly, specific target groups are defined in advance, for example obese women or women with gestational diabetes, and certain need related to these conditions are assumed[43-45]. In order to increase the adherence and even the effectiveness of mHealth interventions, future research should reverse this order. As a first step, target groups need to be determined. This can be based on a variety of hypotheses, research (related) questions or other interests. The next step should be to investigate the needs of this population of interest before designing an intervention, for example by means of qualitative research using focus groups or specific interview techniques. Then, by tailoring a mHealth program to the needs of a target population, it is suggested that this will induce a stronger adherence to the program. Customization by the user, for example by incorporating subgroup-related content, might even induce further adherence. This could be established by means of adding variables and conditions, such as gender, cause of subfertility and received treatment, education and socio-economic status for which the program tailors the intervention. Regarding the reproductive population in general, mHealth applications should supply evidence-based information supported by recognized organizations or (medical) institutes to educate their end-users on the one hand, but should also provide information or functionality tailored to the individual needs of the user on the other hand.

FUTURE RESEARCH

Taken into account Hill's criteria for causation, future research on the relations between nutrition and lifestyle behaviors and pregnancy chance, embryonic growth, maternal pregnancy and neonatal outcome should be studied in the general population. By studying a larger sample-size, the likelihood of causality is strengthened. Also, it provides the opportunity to design interventions to investigate biological gradients and dose-response relationships.

Collaborations between scientists, ICT-specialists and marketers should be established to combine expertise in order to develop an evidence-based application using the reproductive population as "general population". The application should fulfill the individual needs of women and men contemplating pregnancy. Preferably including the additional functionality of real-time consultation of a health care professional using text or video messaging. Although this is expensive, it will support patients and professionals to discuss and manage risk factors and monitor behavior prior to conception.

Although outside the scope of this thesis, it is important to mention the consequences arising from an increased awareness of the importance of the periconception period. By educating patients, questions regarding the importance of modifiable risk factors will arise and health care professionals will be confronted with such questions. Therefore, an important aspect for all health care professionals confronted with patients of reproductive age is to be aware of the periconception period and to be educated on the applicable recommendations and how to discuss them with their patients. Recently, this also has been recommended by the ACOG Committee[46].

Ultimately, when general awareness regarding the periconception period and its importance has been established and interventions are proven to successfully reduce the prevalence of poor nutrition and lifestyle behaviors, perinatal outcomes will improve and the global prevalence of NCDs will decline. We consider this approach as the best investment in the health for current and future generations.

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Chapter 10

Summary / Samenvatting

Summary

The periconception period is crucial regarding fertilization and the determination of maternal pregnancy and neonatal outcome. The evidence is overwhelming that interventions during this period, as a part of general preconception care, can be considered as primary and secondary preventive measures. The main aim of this thesis was to investigate the benefits, barriers and (clinical) effectiveness of a personalized mHealth program for both women and men of reproductive age, and tailored on periconception nutrition and lifestyle behaviors. Furthermore, the impact of periconception nutrition and lifestyle behaviors on embryonic development was investigated. In the introduction we provided the background for this thesis (**Chapter 1**).

In the first part of this thesis we evaluated the Smarter Pregnancy mHealth program. **Chapters 2, 3 and 4** describe the studies that contain data obtained from all the participants of the Smarter Pregnancy program between 2012 and 2016. The most important findings of the Smarter Pregnancy survey were the positive effect of the mHealth program on unhealthy behaviors (**Chapter 2**) and, consequently, the beneficial effect on the chance to conceive (**Chapter 3)**. In a total of 1,878 participants (1,525 women and 353 men), we showed a compliance of 64.9% and nutrition and lifestyle behaviors improved by 26.3% (vegetable intake) up to 56.3% (folic acid supplement use). In addition, we observed the pregnancy chance in women with healthy nutrition and lifestyle behaviors was 1.33 times higher compared to women with a higher behavioral risk score. Both studies also emphasized the importance of participating men, since women who participated with their partner showed more improvement of d their inadequate nutrition and lifestyle behaviors.

Chapter 4 shows that the mHealth program ''Smarter Pregnancy" is more effective in improving nutrition and lifestyle behaviors in women who live in more deprived neighborhoods. At baseline, smoking was more prevalent in women from deprived neighbourhoods, while alcohol consumption was more prevalent in women from less deprived neighbourhoods. These differences suggest that tailoring the program to the needs of specific subgroups may be a way to induce further improvement.

Chapter 5 describes a qualitative study comprising four focus groups of end-users, including female and male participants of Smarter Pregnancy. One focus group consisted of only professionals who are involved in periconception care. Patients and health care professionals both acknowledged the potential role of mHealth in preconception care.

The second part of this thesis comprises the study design of the RCT and a prospective study in which we investigated the impact of periconception nutrition and lifestyle on embryonic growth rates.

In **Chapter 6**, we describe the Smarter Pregnancy RCT, which we conducted from May 2014 onwards until January 2017, for which we recruited participants in the area of Rotterdam and online. Findings of this RCT are described in **Chapter 7,** in which we demonstrated a significantly larger improvement, by means of a larger reduction of the dietary risk score (DRS), in the intervention group compared to women in the control group (β=0.75 95% CI: 0.18;1.34). This reduction was mainly due to an increased daily vegetable intake (β=0.55 95% CI: 0.25;0.86), but not due to folic acid supplement use (β=0.09 95% CI: -0.08;0.26) and fruit intake (β=0.09 95% CI: -0.21;0.39).

The most important result of **Chapter 8** was the significant negative association between inadequate folic acid supplement use and embryonic growth; 0.76mm (-7.8%) and 1.63mm (-3.7%) smaller CRL, and a 0.01cm^3 (-19.5%) and 0.86cm^3 (-12.2%) smaller EV at 7+0 and 11+0 weeks of gestation, respectively. To a lesser extent, these associations were also observed between inadequate fruit intake and smoking and embryonic growth. This further substantiates the evidence of the importance of the periconception period and the influence of nutrition and lifestyle on embryonic growth.

Summarizing, in this thesis the evidence of the importance of healthy nutrition and lifestyle during the periconception period is substantiated. We showed that mHealth could play a role in periconception care, which might result in increasing awareness of the importance of periconception care in women and men when contemplating pregnancy.

In order to improve this awareness, future research should focus on the needs of the reproductive population and on developing evidence-based tailored interventions. mHealth in general, and our mHealth program Smarter Pregnancy in particular, can contribute to this.

To improve nutrition and lifestyle behaviors during the periconception period, health care providers and professionals should be educated to become aware of the known associations between such behaviors and pregnancy course and outcome. Consequently, they should inform and support their patients in order to improve their nutrition and lifestyle. Mobile health can support patients and health care professionals by using it as an additive to standard care.

We consider improving periconceptional nutrition and lifestyle as the best investment in the health of current and future generations.

Samenvatting

De periconceptieperiode is cruciaal met betrekking tot de bevruchting én bepalend voor het beloop van de zwangerschap en de uitkomst van de neonaat. Er is overweldigend bewijs dat interventies tijdens deze periode, als onderdeel van algemene preconceptiezorg, kunnen worden beschouwd als primaire én secundaire preventie. Het belangrijkste doel van dit proefschrift was het onderzoeken van de voordelen en bezwaren van het gepersonaliseerde mHealth-coachingsprogramma Slimmer Zwanger, toegesneden op periconceptionele voeding en leefstijl voor zowel vrouwen als mannen in hun reproductieve levensfase. Ook werd de invloed van periconceptionele voeding en leefstijl op de embryonale ontwikkeling onderzocht. In de inleiding wordt kort de achtergrond van dit proefschrift beschreven (**hoofdstuk 1**).

In het eerste deel van dit proefschrift is het mHealth-programma Slimmer Zwanger geëvalueerd. In **hoofdstukken 2, 3 en 4** worden de resultaten van de survey beschreven die data bevatten van alle deelnemers aan Slimmer Zwanger tussen 2012 en 2016. De belangrijkste bevindingen hiervan waren het positieve effect van het programma op ongezonde voeding en leefstijl (**hoofdstuk 2**) en het gunstige effect hiervan op de kans om zwanger te worden (**hoofdstuk 3**). Bij in totaal 1.878 deelnemers (1.525 vrouwen en 353 mannen) toonden we een compliantie aan van 64,9%.Voeding en leefstijl verbeterde met 26,3% (groente-inname) tot 56,3% (foliumzuurinname). De kans op zwangerschap was bij vrouwen met een gezonde voeding en leefstijl 1,33 keer hoger in vergelijking met vrouwen die een hogere, ongezondere, risicoscore hadden. Beide studies benadrukten ook het belang van deelname van partners, omdat vrouwen die met hun partner deelnamen een sterkere verbetering lieten zien van hun ongezonde voeding en leefstijl gewoonten dan vrouwen die zonder partner deelnamen.

In **hoofdstuk 4** wordt beschreven dat het mHealth-programma Slimmer Zwanger effectiever is in het verbeteren van voeding en leefstijl bij vrouwen die in achterstandswijken wonen. Bij aanvang van het programma roken vrouwen uit achterstandswijken vaker, terwijl alcoholgebruik vaker voorkwam bij vrouwen uit minder achtergestelde wijken. Deze verschillen suggereren dat het programma afstemmen op de behoeften van specifieke subgroepen een manier kan zijn om verdere verbetering te bewerkstelligen.

Hoofdstuk 5 beschrijft een kwalitatief onderzoek met vier focusgroepen van gebruikers, waaronder vrouwen én mannen die hadden deelgenomen aan Slimmer Zwanger. Eén focusgroep bestond uit professionals die betrokken zijn bij periconceptiezorg. Patiënten en professionals erkenden beide de potentiële rol die mHealth kan innemen ter ondersteuning van de periconceptiezorg.

Het tweede deel van dit proefschrift beschrijft de resultaten van een gerandomiseerd onderzoek (RCT) en een prospectieve studie waarin we de invloed van periconceptionele voeding en leefstijl op embryonale groei hebben onderzocht. In **hoofdstuk 6** beschrijven we de Slimmer Zwanger RCT, waarvoor we vanaf mei 2014 tot januari 2017 in de regio Rotterdam én online deelnemers hebben geworven. Bevindingen van deze RCT zijn beschreven in **hoofdstuk 7**, waarin we een significant grotere afname van de Dieet-risicoscore (DRS) aantoonden bij vrouwen in de interventiegroep vergeleken met de controlegroep ($\beta = 0{,}75$ 95% CI: 0,18; 1,34). Deze daling was voornamelijk toe te schrijven aan een verhoogde dagelijkse inname van groente ($\beta = 0{,}55$ 95% CI: 0,25; 0,86), maar niet door inname van foliumzuursupplementen (β = 0,09 95% CI: -0,08; 0,26) en fruit (β = 0,09 95% CI: -0,21; 0,39).

Het belangrijkste resultaat van **hoofdstuk 8** was de significante negatieve associatie tussen onvoldoende inname van foliumzuursupplementen en embryonale groei; 0,66 mm (-7,8%) en 1,63 mm (-3,7%) kleinere kruin-romplengte en een 0,01 cm^3 (-19,5%) en 0.86cm^3 (-12.2%) kleiner embryonaal volume (EV) op respectievelijk 7+0 en 11+0 weken zwangerschap. In mindere mate werden deze associaties ook waargenomen tussen een onvoldoende fruitinname en roken en embryonale groei. Dit bevestigt wederom het belang van de periconceptieperiode en de invloed van voeding en leefstijl op de embryonale groei.

Samenvattend is in dit proefschrift het belang van gezonde voeding en leefstijl tijdens de periconceptieperiode weer verder onderbouwd. We hebben aangetoond dat mHealth, en het gebruik van Slimmer Zwanger, een rol kan spelen in de periconceptiezorg. Dit kan leiden tot een groter bewustzijn van het belang van periconceptiezorg en uiteindelijk tot verbetering van de gezondheidsuitkomsten bij vrouwen, én hun partners, die overwegen zwanger te worden.

Om het bewustzijn omtrent periconceptionele voeding en leefstijl verder te vergroten, moet toekomstig onderzoek zich richten op de behoeften van de reproductieve populatie en op het ontwikkelen van evidence-based interventies op maat. mHealth in het algemeen, en ons mHealth-programma Slimmer Zwanger in het bijzonder, kunnen hieraan bijdragen.

Om voeding en leefstijl tijdens de periconceptieperiode te verbeteren, moeten vooral ook zorgverleners worden voorgelicht over het belang hiervan om zich zodoende bewust te worden van de bekende associaties tussen dergelijk gedrag en het verloop én de afloop van een zwangerschap. Vervolgens moeten zij hun patiënten hierover informeren en waar mogelijk begeleiden bij het verbeteren van hun voeding en leefstijl. Mobile health kan zowel de patiënten als de zorgverleners ondersteunen door het als een toevoeging aan de standaard zorg te gebruiken.

Wij beschouwen het verbeteren van periconceptionele voeding en leefstijl als de beste investering in de gezondheid van de huidige en toekomstige generaties.

Addendum

Authors and affiliations

N.V. Borggreven, MSc
LUMC, University Medical Centre,
Leiden, the Netherlands

D.V. Gootjes, MD
Erasmus MC, University Medical Centre,
Rotterdam, the Netherlands
Department of Obstetrics and Gynaecology

N.A. Huijgen, MD, PhD
Erasmus MC, University Medical Centre,
Rotterdam, the Netherlands
Department of Obstetrics and Gynaecology

M.P.H. Koster, MD, PhD
Erasmus MC, University Medical Centre,
Rotterdam, the Netherlands
Department of Obstetrics and Gynaecology

A.H.J. Koning, PhD
Erasmus MC, University Medical Centre,
Rotterdam, the Netherlands
Department of Pathology, unit of Bioinformatics

J.S.E. Laven, MD, PhD
Erasmus MC, University Medical Centre,
Rotterdam, the Netherlands
Department of Obstetrics and Gynaecology

E.C. Oostingh, MD
Erasmus MC, University Medical Centre,
Rotterdam, the Netherlands
Department of Obstetrics and Gynaecology

A.N. Schonewille-Rosman, PhD
Erasmus Medical Centre,
Rotterdam, the Netherlands
Department of Obstetrics and Gynaecology

E.A.P. Steegers, MD, PhD
Erasmus MC, University Medical Centre,
Rotterdam, the Netherlands
Department of Obstetrics and Gynaecology

R.P.M. Steegers-Theunissen, MD, PhD
Erasmus MC, University Medical Centre,
Rotterdam, the Netherlands
Department of Obstetrics and Gynaecology

S.P. Willemsen, PhD
Erasmus MC, University Medical Centre,
Rotterdam, the Netherlands
Department of Biostatistics &
Department of Obstetrics and Gynaecology

Abbreviations

3D-US	Three dimensional ultrasound
AUC	area under the curve
ART	assisted reproductive technology
ASE-model	attitude, social influence, and self-efficacy model
BMI	body mass index
CE-1	conformité européenne, classe 1
CI	confidence interval
CRL	crown-rump length
DNA	deoxyribonucleic acid
DOHaD	developmental origins of health and disease
DRS	dietary risk score
eHealth	electronic health
EV	embryonic volume
FFQ	food frequency questionnaire
GA	gestational age
GEE	generalized estimating equation
GP	general practitioner
(a)HR	(adjusted) hazard ratio
ICSI	intracytoplasmic sperm injection
IQR	inter quartile range
ITT	Intention to treat
IUI	intrauterine insemination
IVF	in vitro fertilization
LMP	last menstrual period
MAR	medical assisted reproduction
mHealth	mobile health
NCD	non-communicable disease
NSS	neighborhood status score
NTD	neural tube defect
(a)OR	(adjusted) odds ratio
PCC	preconception care
PCOS	polycystic ovary syndrome
PTB	preterm birth
RCT	randomized controlled trial
SD	standard deviation
SGA	small for gestational age
SMS	short message service
TRS	total risk score
WHO	world health organization

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PhD Portfolio

Name PhD candidate: M.R. van Dijk
Erasmus MC Department: Obstetrics & Gynaecology
PhD period: 2013-2017
Promotor: Prof. dr. R.P.M. Steegers-Theunissen
Co-promotor: Dr. M.P.H. Koster

	Year	Workload (ECTS)
1 | PhD training		
General courses		
Erasmus MC 'Research integrity'	2014	0.3
NIHES 'Biostatistical Methods I. Basic principles (CC02)'	2014	5.7
EMWO 'Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers	2015	1.0
Erasmus MC 'BKO: Omgaan met groepen'	2015	1.0
R: Basic statistics	2015	1.0
Poster presentations at (inter)national conferences		
David Barker Commemorative, Southampton, England	2014	1.0
10th International DOHaD World Congres, Rotterdam, the Netherlands	2017	1.0
Oral presentations and award(s) at (inter)national conferences		
CJG Rijnmond, Rotterdam, hoofdkantoor	2014	0.5
CJG Rijnmond, Rotterdam, locale vestigingen (13)	2014-2015	6.5
Erasmus MC, dept. of Obstetrics and Gynaecology, research meeting (4)	2014-2017	2.0
45th NVOG Gynaecongres, Leeuwarden, the Netherlands	2014	1.0
Erasmus MC – CJG Rijnmond, refereeravond	2014	1.0
SCEM Congres, Utrecht, the Netherlands	2015	1.0
Erasmus MC, Sophia research day	2015	1.0
Maasstad ziekenhuis, Rotterdam, the Netherlands	2015	0.5
9th International DOHaD World Congres, Cape Town, South-Africa	2015	1.0
St. Franciscus Gasthuis, Rotterdam, the Netherlands	2016	0.5
Ijsselland ziekenhuis, Capelle a/d Ijssel, the Netherlands	2016	0.5
Ikazia ziekenhuis, Rotterdam, the Netherlands	2016	0.5
Erasmus MC, annual Wladimiroff meeting	2016, 2017	2.0
Erasmus MC, Sophia research day	2016	1.0
64th SRI Annual Scientific meeting, Orlando, USA	2017	1.0
SRI President's Presenter's Award		

	Year	Workload (ECTS)
Other attended (inter)national conferences		
Healthy Pregnancy 4 All 2 symposium, Den Haag, the Netherlands	2014	1.0
Erasmus MC, annual Wladimirov meeting	2015	0.5
Attended seminars, workshops, and research meetings		
Erasmus MC 'Implementatie symposium'	2013	0.5
Erasmus MC, dept. of Obstetrics and Gynaecology, weekly research meetings	2013-2017	3.0
Erasmus MC, monthly PREDICT meetings.	2013-2017	1.0
Erasmus MC, attending two-weekly 'Journal Club'	2016-2017	1.0
Other		
Science congress, Rotterdam, the Netherlands	2015	1.0

2 | Teaching activities

Lecturing		
Erasmus MC Hoorcollege minor 'Mystery of creation'	2016	0.5
LUMC, Leiden, the Netherlands Deltadagen (nascholing kinderartsen)	2016	1.0
Tutoring		
Tutor, studiegroep 1.20	2015-2016	1.0
Tutor, studiegroep 1.05	2016-2017	1.0
Begeleider 'Kennismaken met de beroepspraktijk'	2016	1.0
Supervising (medical)students		
Erasmus MC, Meghan Jordaan: Correlation between maternal BMI and embryonic growth.	2014	2.0
LUMC, Nicole Borggreven: Correlation between maternal periconception nutrition and lifestyle and embryonic growth.	2016	2.0
Slimmer Zwanger studententeam	2014-2016	2.0
Slimmer Zwanger promotieteam Science Congres	2015	0.1

	Year	Workload (ECTS)
3 | Others		
Organizing		
Erasmus MC & CJG Rijnmond, refereeravond	2014	1.0
Erasmus MC, Slimmer Zwanger focusgroepen	2016	1.0
Interview(s)		
Smarthealth	2015	0.1
RTV Rijnmond	2015	0.1

Curriculum vitae

Op 13 maart 1986 werd Matthijs Reinoud van Dijk geboren in het Bronovo-ziekenhuis te Den Haag. Een kleine aangeboren aandoening zorgde voor menig ziekenhuisbezoek, waardoor het enthousiasme voor het artsenvak al vroeg ontstond. Wanneer Matthijs niet mocht meekijken tijdens ingrepen was het (zieken) huis vaak te klein. Eén ding was toen al duidelijk, Matthijs zou dokter worden.[1-3] Dat dit daadwerkelijk ging lukken leek op Sorghvliet, de middelbare school, een stuk minder aannemelijk. Echter, na vijf keer met de hakken over de sloten te zijn overgegaan naar de volgende klas en met een succesvol afgerond herexamen Biologie stond de deur naar het Erasmus MC nog wel open.

In 2005, na een jaar wachten en twee keer uitgeloot te zijn voor Geneeskunde, "begon" Matthijs aan zijn vervolgopleiding 'Lichamelijke opvoeding en bewegingswetenschappen' aan de universiteit van Leuven.[1,3] Na het verkrijgen van een verblijfsvergunning en maar liefst 3 dagen een studentenkamer gehad te hebben, werd hij alsnog nageplaatst in zijn favoriete stad Rotterdam. Tijdens zijn studie aldaar leert hij Joyce, zijn latere vrouw, kennen.[6] De universiteit van Leuven heeft hij nooit van binnen gezien.[1-3,8] Uiteindelijk zijn het gynaecologen dr. Hayo Wildschut, dr. Hans Landman en prof dr. Joop Laven die Matthijs door respectievelijk onderzoek, een stage op Curacao en hoorcolleges enthousiast krijgen voor de gynaecologie.[8] Na afgestudeerd te zijn in 2012 gaat Matthijs als ANIOS werken in het Maasstad Ziekenhuis "op Zuid". Na een jaar start hij met zijn promotietraject onder supervisie van zijn promotor prof dr. Régine Steegers-Theunissen, waarbij in 2016 ook co-promotor dr. Wendy Koster aansluit. Tijdens zijn promotietraject is Matthijs betrokken bij het ontwerp en de coördinatie van twee RCTs. Later sluit drs. Eline Oostingh aan, waarna zij samen zorgdragen voor de Slimmer Zwanger-RCTs. Tussen 2013 en 2017 heeft Matthijs zijn resultaten gepresenteerd in Rotterdam, Utrecht, Southampton, Kaapstad en Orlando.

Ten tijde van zijn promotietraject werkt Matthijs in het weekend nog in zijn geliefde Maasstad en zijn vrije tijd besteedt hij het liefst buiten; sportend, naar sport kijkend of in de buitenkeuken. Hij liep tientallen halve marathons, tweemaal een hele marathon en was tot 2016 een fanatiek hockeyer.[3,4,6] In de jeugd was hij 9 jaar lang keeper en hierna nog 11 jaar spits.[5] Echter, na twee gebroken handen te hebben opgelopen, werd de hockeystick aan de wilgen gehangen en werd de zondag op en rond het hockeyveld verruild voor de Kuip.[4,8]

Het was ook 2016 dat Matthijs en Joyce tussen neus en lippen door trouwden én dat hun dochter Ise-Lori werd geboren. Inmiddels is Ise-Lori ruim 2 jaar oud en kan zij zich geen beter vader wensen. Wanneer Matthijs thuiskomt springt ze een gat in de lucht.[6,7]

In 2017 wordt Matthijs aangenomen voor de opleiding tot gynaecoloog en sindsdien is hij werkzaam in het Amphia Ziekenhuis te Breda.[6-7]

Bovenstaande levensloop is geschreven door:

Bram van Dijk[1], Lykke Dijst-Van Driel[2], Robert-Jan van Dijk[3], Wouter van Dijk[4], Marleen van Dijk[5], Joyce van Dijk-Bontje[6], Ise-Lori van Dijk[7], Matthijs van Dijk[8].

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Mijn **co-promotor**, dr. Koster, beste Wendy, wat was het goed dat jij in 2016 aansloot bij mijn promotietraject. Na een behoorlijke mismatch met jouw voorganger was ik oprecht blij een begeleider te krijgen die zowel inhoudelijk als organisatorisch van wanten wist. Zonder jou weet ik niet wat eerder was gebeurd, mijn pensionering of mijn promotie. Ik hoop dat je succesvol wordt met je eigen projecten, dat er nieuwe projecten uit voortvloeien en vooral dat je met plezier je werk doet. Ik denk dat mijn opvolgers erg blij mogen zijn als zij jou als hun co-promotor krijgen. En tja, ik ken niemand die zoveel op z'n telefoon kijkt als jij, dus ook wat dat betreft sluit je perfect aan bij dit proefschrift.
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Mijn **paranimfen**, Eline en Tom. **Eline**, ik heb het bij jouw afscheid ook al geschreven, maar ik had mij geen betere 'partner in crime' kunnen wensen. Het was een mooie tijd op onze kamer op de 22^{e}, met uitzicht over de stad en met een thermostaat die naadloos aansloot bij onze persoonlijkheden. Wees 'ie naar jou, dan werd het warm en gezellig, wees ie mijn kant op, dan werd het koud en kil. Wat dat betreft was het ook goed dat jij voornamelijk de telefoon opnam en alle deelnemers te woord stond. We hebben lief en leed gedeeld, veel gelachen, veel gemopperd en ook heel veel koffie gedronken op mijn parttimedagen, toen ik al weg was op de 22^{e}. Jij en jouw 3 mannen en ik met mijn 2 vrouwen (voor nu) gaan elkaar gegarandeerd nog veel zien, gelukkig.
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De **Haagsche heren**, Ernst en Maurits, onze vriendschap is er al 20-25 jaar en blijft ook bestaan, ondanks dat we elkaar regelmatig langere periodes niet zien. Laten we binnenkort mijn promotie op gepaste wijze vieren.
De maatschap, arts-assistenten, verloskundigen en verpleging van **het Amphia**, jullie maken dat ik vrijwel dagelijks met plezier richting het zuiden rijd. Het is zonde dat "de club" zo groot is, waardoor we weinig met elkaar ondernemen, want dat zou het werk nog leuker maken, zeker in de drukke periodes.
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Zoals in de wetenschap gebruikelijk zijn de laatstgenoemde personen het allerbelangrijkst. Logischerwijs zijn dat mijn lieve vrouw en dochter. **Joyce**, lieverd, ik ben nog altijd blij dat wij elkaar ontmoet hebben en al zo lang samen zijn. Eerlijk is eerlijk, door jou heb ik eigenlijk alles wat ik wil, namelijk een lieve vrouw, een (groeiend) gezin en een carrière. Ondanks dat jij ons gezin draaiend houdt, blijf je energie overhouden voor andere (leuke) dingen. Ik hoop dat die energie er altijd blijft, want dat maakt je niet alleen zo leuk, het maakt je ook de leukste moeder voor Ise-Lori en 2.0.
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