Change in lifestyle behaviors after preconception care: the Healthy Pregnancy 4 All study

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ABSTRACT

Objective: To evaluate the effects of preconception care consultations in terms of change in lifestyle behaviors.

Methods: In this community-based prospective cohort study (Healthy Pregnancy 4 All), we assessed initiation of folic acid supplementation, and cessation of smoking, alcohol consumption, and illicit drug use. Self-reported data and biomarker data on these outcomes were obtained at baseline and approximately three months later. For all individual outcomes, the change between baseline and follow-up was assessed. The study included women aged 18-41 years who visited a participating midwife or general practitioner for a preconception care consultation in 14 Dutch municipalities with a relatively high rate of adverse perinatal outcomes.

Results: Of the 259 included participants, paired analyses were available in 177 participants for self-reported outcomes and in 82 for biomarker outcomes. Baseline self-reported prevalence of no folic acid use was 36%, smoking 12%, weekly alcohol use 22%, and binge drinking 17%. Significant changes in prevalence towards better lifestyle during follow-up were seen for folic acid use (both self-reported ($p<0.001$) and biomarker-confirmed ($p=0.008$)) and for self-reported binge drinking ($p=0.007$).

Conclusion: Our study suggests that preconception care contributes to initiation of folic acid supplementation and cessation of binge drinking in women who intend to become pregnant. This highlights the benefits of preconception care in improving periconception health.

INTRODUCTION

Preconception care (PCC) aims to prevent biomedical, behavioral, and social risks from negatively affecting pregnancy by reducing these risks before conception.[1 2] Regular antenatal care starts too late to avoid risk factors affecting early pregnancy.[3] For instance, lifestyle behaviors such as smoking, alcohol consumption, and inadequate folic acid intake are negatively associated with embryonic development.[4-6] Unfortunately, such behavior is widely prevalent among women in the preconception and early pregnancy periods.[7-10] Furthermore, most risk factors are not easily changed and therefore require a timely approach. Altogether, this emphasizes the need for timely PCC to optimize the potential benefits of risk reduction.

The actual effectiveness of PCC remains debated, since reaching women for PCC is difficult and proven effective PCC interventions for many behavioral risk factors are limited.[11-14] Preconception behavior interventions have focused on folic acid, smoking, and alcohol before with varying effectiveness, but little is known about these behavior changes after a comprehensive PCC intervention in a general population of women planning pregnancy.[12 14-16]

In 2011, the Healthy Pregnancy 4 All (HP4All) program was launched to improve perinatal health and reduce related inequalities in the Netherlands.[17] This program focused on enhancing and evaluating PCC and prenatal risk reduction in daily practice. Women were encouraged to visit a general practitioner or midwife for PCC.[18] The main objective of this study was to evaluate the effect of the program's PCC consultations on lifestyle behaviors. We analyzed baseline and follow-up data, which consisted of self-reported, biomarker, and anthropometric measurements. In addition, a sub-study on patient experience with PCC was performed to identify factors that could be improved.

MATERIALS AND METHODS

A prospective cohort was designed to study the effect of the PCC consultations in the program.[18] The PCC consultations were planned as two individual visits with an interval of three months. During the first visit (T1), risk assessment was performed using a web-based questionnaire and information and advice was provided according to the national guideline.[19] The questionnaire could be uploaded into a web-based file for the health care provider, in order to secure standardization in risk assessment and to formulate management plans.[8] In that file, present risk factors were listed along with protocols to address them. The objective of the second visit (T2), 3 months later, was to evaluate adherence to the formulated plan and to evaluate whether risks had diminished.

The primary outcome of the study was lifestyle behavior change, which was assessed as four independent outcomes: initiation of folic acid supplementation, smoking cessation, reduction or cessation of alcohol consumption and cessation of illicit drug use. A secondary outcome was change in BMI. To further evaluate and understand lifestyle behavior change, we explored subgroup differences, and in a sub-study, women's experience with PCC.

The study was conducted in high-risk neighborhoods of 14 municipalities that were selected because the perinatal morbidity and mortality rates were higher than the national average.[17] In these neighborhoods, a recruitment strategy for PCC was rolled out to promote uptake. The recruitment strategy consisted of PCC invitation letters sent by municipal health services and general practitioners, as well as referral by youth health care professionals and health educators.[18] PCC was offered at local participating general practitioners and midwifery practices. The GPs and midwives received a personal training as well as self-study material and protocols, to deliver PCC in accordance with the study protocol and the national guideline.[18 19]

Women aged 18 up to and including 41 years who made an appointment for a PCC consultation were eligible to participate in the study. The following exclusion criteria applied to the study: no permission to be contacted for participation in the study or not responding when contacted for study counseling, or not attending the PCC appointment, not planning to become pregnant, not understanding written Dutch, English, Turkish, Polish or Arabic language. Women who were willing to participate were requested to sign an informed consent form and partake in data collection. Participants were enrolled between February 2013 and December 2014. Participant recruitment is described in detail in chapter 2. In total, 587 PCC applications were registered and 259 (44%) participants were included in the study. Data collection was continued until May 2015.

We collected baseline measurements (T1) and follow-up measurements (T2) from questionnaires, anthropometric measurements, and blood and urine samples. The questionnaires were filled in on paper or via an Internet link and contained questions on socio-demographic characteristics, pregnancy intention, and the lifestyle behavior outcomes. Anthropometric measurements taken during the PCC consultations included height and weight. From the blood samples, biochemical information on PCC lifestyle behavior was obtained. The following biomarker information was assessed: erythrocyte and serum folate, serum cotinine levels, carbohydrate deficient transferrin (CDT) and phosphatidylethanol (PEth). PEth is less well-known than CDT for the detection of alcohol use, but this direct alcohol biomarker has a relative long half-life and can be detected at low levels. Therefore, it is suitable for retrospective monitoring (2-4 weeks) of moderate alcohol consumption.[20] All blood samples were taken at local laboratory centers after the first visit and the second visit. They were initially processed and stored at -70 or -80°C locally, afterwards, the samples were transferred to a central laboratory for biomarker

analysis.[18] Folate concentrations in erythrocytes and serum were measured using the "Elecsys Folate III" assay (Roche, Mannheim, Germany). Cotinine concentrations were determined using the "Immulite Nicotine Metabolite" assay (Siemens, Erlangen, Germany). CDT was measured using the "N-Latex CDT kit" (Siemens, Erlangen, Germany). PEth was assessed by chromatographic separation using a gradient elution with supercritical chromatography-tandem mass spectrometry (UPC2-MS/MS, Waters Corp., Milford, MA, USA). Urine samples were collected to gain biochemical information on illicit substance use, but we refrained from analyzing these samples. This was due to a combination of factors: higher costs than anticipated and an expected low yield (i.e. relatively small number of samples and a low prevalence).

We dichotomized all self-reported, biomarker, and anthropometric measurement outcomes and used the following definitions of preconception risk factors:

- No folic acid supplementation: self-reported "no" to folic acid use, <20 nmol/L serum folate and <590 nmol/L erythrocyte folate.[21 22]
- Smoking: self-reported "current smoking" and cotinine levels of >25 µg/L, which was the reference value used by the laboratory.
- Alcohol consumption: self-reported drinking of "one unit or more per week" and self-reported binge drinking of "> 6 units per week in past three months", CDT of ≥ 2.2% and one of the homologues of PEth above the lower limit of quatification (LLOQ) of the laboratory, which was > 6 µg/L for POPEth and PLPEth, and > 3 µg/L for DOPEth.
- Illicit substance use: self-reported "current use" or "use within the previous week".
- Obesity: BMI of >30 kg/m^2.

The amount of missing samples varied across the different methods of data collection, as illustrated in figure 1. Overall, a follow up measurement was available for 76% of the participants. The relatively low follow-up rates of the laboratory samples and anthropometric measurements could be explained by the fact that to collect these follow-up data, attendance at the follow-up PCC consultation was required. This follow-up consultation was attended by 152 (59%) of the participants. Since women received the follow-up questionnaire also if they had not attended the second PCC consultation, a higher follow-up rate was achieved (75%) compared to the laboratory samples and anthropometric measurements.

Within the collected data, the number of missing data on socio-demographic characteristics and outcomes did not exceed 5% except for erythrocyte folate (6% at baseline and 12% at follow up).

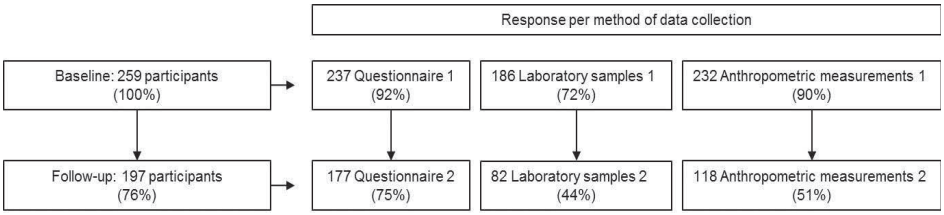

Figure 1. Flowchart of data collection within the PCC cohort study
The participants (259) have responded to at least one method of data collection at baseline. At follow-up, 197 (76%) participants responded to at least one method of data collection. The percentages given at follow-up illustrate the response relative to the baseline response.

We described baseline characteristics of the participants who responded to the questionnaires as numbers and percentages (or as the median, minimum and maximum value in case of continuous variables). These characteristics included age, self-defined ethnicity (Dutch or other), educational attainment, pregnancy intention (when intending to become pregnant), and history of pregnancy and fertility treatment. For the primary outcome lifestyle behavior change, we first tested whether there was ≥20% increase in self-reported folic acid intake and ≥5% decrease in self-reported smoking using the exact binomial test with a one-sided significance level of 0.025, as specified in the published protocol.[18] Then, all preconception lifestyle and health outcomes were analyzed paired for change between their prevalence at T1 and T2 with the McNemar's test. As supplementary analyses, we included cross tables to illustrated change from T1 to T2 for each outcome as well as for 'pregnancy intention'. To provide more information about the preconception lifestyle outcomes, data is shown on self-reported prevalence of not taking folic acid supplementation, smoking and alcohol consumption at baseline and follow-up based on the sub-groups of the baseline patient characteristics. Another subgroup was added on self-reported pregnancy since PCC. Lastly, subgroups were defined as women who filled in the baseline questionnaire before the PCC consultation and who filled in the questionnaire on the day of the consultation or even later, since this could have affected the primary outcome. For all analyses, we used SPSS software for Windows, version 21. Statistical significance was accepted at 0.05 unless stated otherwise.

In May 2015, an additional sub-study on PCC experience was conducted. The subgroup of participants (n=117) that had a PCC consultation in 2014 was sent an additional questionnaire regarding their experience with the PCC consultation. This questionnaire was based on the ReproQ questionnaire, which was developed using the WHO Responsiveness model to measure performance of maternity care from a client's perspective.[23] The experience questionnaire had eight responsiveness domains consisting of a total 22 experience statements with four answer categories (totally disagree - disagree - agree - totally agree). We determined the median domain specific score and overall score. Scores could range from 1 to 4 being most positive. No domain score was obtained if more than half of the items were missing. In addition, we evaluated the responses to three separate questions about appreciation of the PCC service.

The study (including the additional sub-study) has been approved by the Medical Ethical Committee of the Erasmus Medical Center of Rotterdam (MEC 2012-425).

RESULTS

The baseline characteristics of the 237 participants who filled in the first questionnaire (92% of the total participants as shown in figure 1) are presented in table 1. Characteristics were stratified by the group of participants who responded to both questionnaires and the group of participants who were lost to follow-up for the second questionnaire. With the exception of ethnicity, we only found small differences between the groups.

Table 1. Questionnaire baseline characteristics of the participants stratified by complete cases and cases lost to follow-up

Characteristics at baseline (Q1) *		**Q1+Q2 N=177**		**Missing Q2 N=60**	
Age	Median age in years (min- max)	30.0	(19 – 41)	30.5	(20 – 41)
	< 25 years	19	(10.9)	5	(8.3)
	≥ 25 years and < 35 years	116	(66.3)	43	(71.7)
	≥ 35 years	40	(22.9)	12	(20.0)
Ethnicity † ‡	Dutch	119	(68.8)	26	(46.4)
Educational attainment §	Low	13	(7.5)	5	(8.9)
	Intermediate	59	(33.9)	25	(44.6)
	High	97	(55.7)	24	(42.9)
	Other – foreign education	5	(2.9)	2	(3.6)
Pregnancy intention	Currently pregnant	3	(1.8)	1	(1.8)
	Within next 3 months	82	(48.5)	32	(56.1)
	Within next 3 - 6 months	48	(28.4)	11	(19.3)
	After > 6 months	36	(21.3)	13	(22.8)
Subfertility	Current or previous fertility treatment	13	(7.4)	8	(13.8)
Previous pregnancy	Yes	49	(27.7)	20	(33.3)

* Data are expressed as numbers (percentages) unless otherwise specified. Not > 5% missing on an item.

† Self-defined ethnicity.

‡ Significant difference between groups, p <0.05.

§ Educational attainment level was defined as the highest completed educational level classified according to the International Standard Classification of Education (ISCED) i.e. low (level 0-2: early childhood; primary education; lower secondary education); intermediate (level 3-5: upper secondary; post-secondary; short cycle tertiary); and high (level 6-8: bachelor; master; doctoral). Unesco institute for statistics 2014.

A significant increase was observed in the percentage of women with folic acid supplementation between baseline and follow-up from about two thirds to about 80% of the women (table 2). This was seen in both the self-reported data and the serum folate data, but not in the erythrocyte folate data. Within the available paired self-reported data of the women who were not taking folic acid at baseline, 42.1% (24/57) had started taking folic acid by the time of the follow-up measurement (Binomial test ≤20%, p<0.001) (appendix 1, table 1).

The percentages of self-reported smoking (11.7%) and biomarker-confirmed smoking (11.2%) showed no change between baseline and follow-up (table 2). Within the available paired self-reported data of the women who reported to be a current smoker at baseline, 5% (1/20) had quit smoking at the follow-up measurement (Binomial test ≤ 5%, p=0.736) (appendix 1, table 4).

Table 2. Prevalence of preconception risk factors at baseline (T1) and follow-up (T2)

Risk factors	All cases *	Complete cases †		*p value*
	T1 %	T1 %	T2 %	
No folic acid supplementation				
Self-reported	35.6	33.5	20.6	0.000‡
Biomarker: Erythrocyte folate <590 nmol/L	11.5§	7.6	4.5||	0.727
Biomarker: Serum folate <20 nmol/L	30.2	34.2	19.0	0.008‡
Smoking				
Self-reported	12.9	11.7	14.6	0.125
Biomarker: Cotinine ≥25 µg/L	12.1	11.2	11.2	1.000
Alcohol				
Self-reported ≥1 unit/week	22.2	25.6	22.6	0.359
Self-reported binge drinking >6 units/day	17.4	17.6	9.4	0.007‡
Biomarker: CDT >2.2%	0	0	0	N.A.
Biomarker: Homologue of PEth > LLOQ¶	20.2	21.6	14.9§	0.180
Illicit substance use				
Self- reported	2.6	2.4	0.6	0.250
BMI				
>30 kg/m^2	20.0	18.3	17.4	1.000

N.A., not applicable.

* Baseline cases (T1) self-reported outcomes N=237, biomarker outcomes N=186, BMI N=232.

† Complete cases self-reported outcomes N=177, biomarker outcomes N=82, BMI N=118.
Median days between T1 and T2 self-reported outcomes 79, biomarker outcomes 104, BMI 95.

‡ Significant difference between paired groups, *p* <0.05.

§ Missing data between 5 and 10%.

|| Missing data 19.5%.

¶ LLOQ of POPEth and PLPEth > 6 µg/L, and of DOPEth > 3 µg/L

Both regular alcohol consumption and binge drinking was reported by about one fifth of the women at baseline (table 2). Also in one fifth of the women, PEth was above the LLOQ. There were no CDT values >2.2%. Only the decrease in prevalence of binge drinking was statically significant (p=0.007).

Only a few participants reported illicit substance use at baseline (2.4%) and this showed no significant decrease at follow-up (0.6%; p=0.25). The prevalence of being obese (18.3%) did not change during follow-up (17.4;p=1.00).

Exploratory analyses indicated that the prevalence of not using folic acid supplementation, smoking, and alcohol consumption varied across subgroups (table 3). Possible associations with

subgroups were inconsistent for the three risk factors analyzed. For instance, alcohol consumption was more prevalent in older women, women of Dutch ethnicity, women with a higher educational attainment and women who had not been pregnant before, while smoking and no folic acid use were less prevalent in these subgroups. Table 3 also shows that none of the women with subfertility (n=13; table 1), reported to smoke or consume alcohol at baseline. Within the subgroup of participants who became pregnant since PCC, the positive change in folic acid use was most notable (table 3, and appendix 1 for insight in change in pregnancy

Table 3. Subgroup analyses of complete cases for self-reported data on no folic acid supplementation, smoking, and alcohol use

Subgroups of complete cases*	% no folic acid supplementation		% smoking		% alcohol use ≥1 unit/ week	
	T1	T2	T1	T2	T1	T2
Total	33.5	20.6	11.7	14.6	25.6	22.6
Age†						
< 25 years	47.1	29.4	27.8	38.9	17.6	17.6
≥ 25 years	31.1	18.5	9.9	11.9	26.8	23.5
Ethnicity†						
Dutch	26.7	11.1	11.2	13.8	33.0	28.7
Other	46.0	32.0	13.7	17.6	10.2	10.2
Education†						
Low- intermediate	35.3	25.0	19.1	22.1	16.7	16.7
High	30.5	16.8	5.2	9.4	33.7	27.4
Pregnancy intention†						
< 6 months	23.3	10.1	10.0	13.1	26.4	20.9
> 6 months	70.6	64.7	17.1	20.0	21.2	30.3
Subfertility†						
Yes	38.5	15.4	0	7.7	0	0
No	32.3	20.6	12.2	14.7	27.9	24.7
Previous pregnancy						
Yes	42.6	25.5	17.0	19.1	14.9	17.0
No	30.1	18.7	9.7	12.9	29.8	24.8
Pregnant since PCC‡						
Yes	25.0	8.3	2.8	5.6	25.7	20.0
No	35.8	23.9	14.1	17.0	25.6	23.3
Questionnaire timing						
Prior to PCC	32.8	14.9	9.0	11.9	27.7	18.5
After PCC	34.0	24.3	13.5	16.3	24.3	25.2

* Complete cases: N= 177

† Missing data 5-10% instead of below <5%

‡ 'Pregnant since PCC' is derived from follow-up data

status). We also explored differences related to whether women filled in the questionnaire prior to the first consultation (n=88, 37%), or on the same day or later (n=149, 63%) and found that positive change in folic acid use and alcohol cessation seemed larger in the 'prior to PCC' group than in the 'after PCC' group.

The questionnaire on women's experience with PCC was filled in by 86 of the 117 (74%) participants who received this questionnaire. The average responsiveness score, over all experience items per individual, had a median score of 3.38 (IQR 3.00-3.74, range 3-4). The domain specific scores are provided in figure 2. Participants judged their experience with PCC in three additional questions. Firstly, on a scale of zero to ten, participants rated their experience with the PCC service positive with a median of 8.0 (range 4-10). Secondly, women were asked whether they would recommend the PCC service to other people. Only four women reported that they would not recommend PCC. Thirdly, participants could indicate in an open question what they would like to change about the PCC service. This question was answered by 37 participants. Five women answered 'no change'. Other responses were that PCC should include more examinations on general health and fertility, and that PCC needs a more personalized approach (e.g. it should response to specific questions and educational background of the participant; the information provided was often limited). In addition, women remarked that PCC was not always well organized and lacked familiarity. Some women were unsure what to expect and some would have appreciated to see their preferred health care provider.

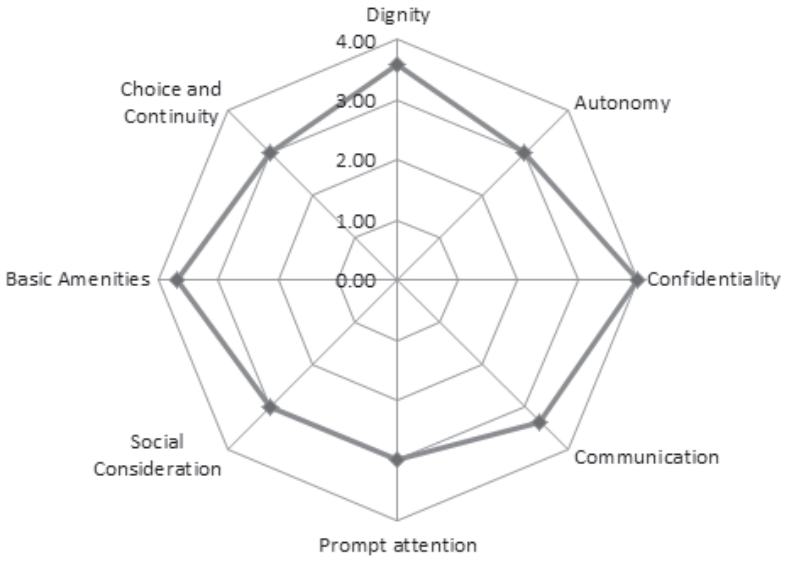

Figure 2. Responsiveness scores
Domain-specific scores on scale 1 to 4; 4 being most positive. Maximum 5/86 missing per domain.

DISCUSSION

In this study we have shown that both self-reported and biomarker-confirmed folic acid supplementation increased after PCC. Furthermore, self-reported binge drinking decreased after PCC. We have not been able to show a significant change in smoking, regular alcohol consumption, illicit substance use, and BMI. The direction of change, although not statistically significant, showed an improvement for all outcomes, except for smoking. In summary, our results suggest that a comprehensive PCC intervention, which consisted of a recruitment strategy and subsequent PCC consultations delivered by a GP or midwife, has beneficial effects on periconception health regarding preconception lifestyle.

Our primary outcomes on folic acid supplementation, smoking, and alcohol use are largely in accordance with the few other studies involving multifactorial preconception health promotion interventions in a general population of women planning to become pregnant. These previous studies have often also shown a positive effect on initiation of folic acid and reducing alcohol consumption, but less effect on cessation of smoking.[24-27] Changing an addiction such as smoking is likely to require more effort.

The biomarker data largely confirmed our results based on self-reported data regarding these three primary outcomes. In line with previous studies, serum folate levels of <20 nmol/L showed similar results as self-reported folic acid supplementation.[21 22] In contrast, erythrocyte folate levels of < 590 nmol/L were found less often, which may indicate that this cutoff level was not valid. We obtained results that resembled the self-reported and serum folate results, when we used higher cutoff levels (900-1000 nmol/L; data not shown) that have been referred to in the literature in relation to optimal supplementation (400 µg/day) and prevention of neural tube defects. [28 29] Regarding smoking, cotinine results were in line with self-reported results. Different cotinine cutoff levels have been used in other studies, suggesting that levels lower than our 25 µg/L might be more valid and that continuous data could illustrate smoking reduction instead of quitting.[30 31] Our results did not change using the lowest level of detection of 10 µg/L or using continuous data (data not shown). Identifying moderate levels of alcohol consumption with biomarkers is difficult, which could explain that we found no positive cases using CDT.[32] However, PEth may be able to detect low levels of alcohol exposure.[20] Our PEth results showed a similar trend as self-reported data on alcohol consumption, including a reduction in positive cases in the period after PCC in line with less self-reported binge drinking. Also, high PEth levels (>50µg/L) decreased in the 82 complete cases (T1 n=8, 0.10%; T2 n=3, 0.04%).

Due to small numbers, little can be said about the other preconception health outcomes self-reported illicit substance use. Obesity was prevalent in 20% of our cohort, yet the PCC consultation, which provided information on multiple risk factors, might be insufficient in enabling

women to lose weight. Furthermore, the short follow-up of three months could be inadequate to realize a decrease in prevalence of obesity. The increasing incidence of obesity and the known associations with adverse pregnancy outcomes urge interventions in preconception period, yet evidence on the best approach is lacking.[33]

Overall, the baseline prevalence of the behavioral risks in our cohort was lower or similar to other cohorts.[8-10 34] It is possible that our cohort reflected a population with relatively healthy lifestyle behaviors, since these women were actively planning and preparing for pregnancy by using PCC.[9 10 35] Other studies have also reported differences in prevalence among subgroups, which confirm our exploratory findings; characteristics such as younger age, ethnic minority background, lower educational attainment and a previous pregnancy seem to be associated with no use of folic acid supplementation and with smoking, but not with alcohol consumption.[8-10 15 22 36 37] Improvement of lifestyle behaviors in certain subgroups may require even extra attention, since interventions can exacerbate socio-economic related inequalities, for example in folic acid use, if not adapted to high-risk women.[37] Altogether, the need and potential for PCC have been illustrated, but the challenge remains to enhance promotion of pregnancy preparation with regards to: 1) outreach of PCC, 2) attaining more improvement of different health behaviors and health outcomes, and 3) reducing periconception and perinatal health inequalities. Recommendations from our sub-study on women's experience concerned availability of one's own health care provider and a more personalized approach to add more value. Literature shows little about patient experience with general PCC.[38]

Several strengths and limitations of this study could be recognized. One of its strengths is the assessment of biomarkers, including the relatively novel and promising analysis of PEth as a direct alcohol biomarker. Another strength is the real-time community-based approach, which made it possible to evaluate primary care PCC within the general population. We tried to overcome the problem of limited uptake of PCC by applying a recruitment strategy, yet the estimated sample size of 839 was not reached.[18] As a result, the study was possibly underpowered to demonstrate change in certain outcomes. The outcomes may also be biased by the low level of participation in general (44%) and by the high level of drop out within the biomarker data (56%) and anthropometric data (49%) in specific. There could also have been a Hawthorne effect, being an effect merely as a result of participating in a study.[39] In addition, variation in timing of questionnaire responses, potential differences in delivery of PCC, and variation in urgency in wanting to become pregnancy, complicate unraveling the actual effect of PCC in changing the outcomes. A comparative study design with longer follow-up time would have been favorable. Lastly, the study outcome definitions could be debated. We chose to define dichotomous outcomes due to the relatively small sample size, but as a result we might have missed small changes in preconception behaviors. The most common lifestyle behavior outcomes in preconception health research were chosen as primary outcomes, whilst by PCC relatively less

frequent risk factors might have been addressed and improved in our study population as well, as general PCC is comprehensive.[1 19] Therefore, the effect of PCC could possibly be even larger than our results suggest.

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ADDENDUM

Appendix 1. Supplementary tables - direction of change per outcome category and 'pregnancy intention'

Supplementary table 1. Direction of change of self-reported folic acid use

T1 \ T2	Self-reported folic acid use			
	no	yes	missing	total (%)*
no	33	24	26	83 (35.6)
yes	2	111	37	150 (64.4)
missing	1	1	2	4
total (%)*	36 (20.9)	136 (79.1)	63	237

* Of non-missing cases

Supplementary table 2. Direction of change of erythrocyte folate ≥ 590 nmol/L

T1 \ T2	Erythrocyte folate ≥ 590 nmol/L			
	no	yes	missing	total (%)*
no	0	5	15	20 (11.5)
yes	3	58	93	154 (88.5)
missing	0	6	6	12
total (%)*	3 (4.2)	69 (95.8)	114	186

* of non-missing cases

Supplementary table 3. Direction of change of serum folate ≥ 20 nmol/L

T1 \ T2	Serum folate ≥ 20 nmol/L			
	no	yes	missing	total (%)*
no	12	15	28	55 (30.2)
yes	3	49	75	127 (69.8)
missing	0	2	2	4
total (%)*	15 (18.5)	66 (82.5)	105	186

* of non-missing cases

Supplementary table 4. Direction of change of self-reported smoking

T1 \ T2	Self-reported smoking			
	no	yes	missing	total (%)*
no	145	6	52	203 (87.1)
yes	1	19	10	30 (12.9)
missing	1	0	3	4
total (%)*	147 (85.5)	25 (14.5)	65	237

* Of non-missing cases

Supplementary table 5. Direction of change of serum cotinine ≥25µg/L

T1 \ T2	Cotinine ≥25µg/L			
	no	yes	missing	total (%)*
no	70	1	89	160 (87.9)
yes	1	8	13	22 (12.1)
missing	2	0	2	4
total (%)*	73 (89.0)	9 (11.0)	104	186

* of non-missing cases

Supplementary table 6. Direction of change of self-reported ≥1 unit alcohol/ week

T1 \ T2	Self-reported ≥1 unit alcohol/ week			
	no	yes	missing	total (%)*
no	118	7	54	179 (77.8)
yes	12	31	8	51 (22.2)
missing	1	2	4	7
total (%)*	131 (76.6)	40 (23.4)	66	237

Supplementary table 7. Direction of change of self-reported binge drinking >6 units

T1 \ T2	Self-reported binge drinking >6 units			
	no	yes	missing	total (%)*
no	135	5	50	190 (82.6)
yes	19	11	10	40 (17.4)
missing	2	1	4	7
total (%)*	156 (90.2)	17 (9.8)	64	237

Supplementary table 8. Direction of change of CDT > 2.2%

T1 \ T2	Biomarker: CDT > 2.2%			
	no	yes	missing	total (%)*
no	80	0	102	182 (100)
yes	0	0	0	0 (0)
missing	2	0	2	4
total (%)*	82 (100)	0 (0)	104	186

Supplementary table 9. Direction of change of PEth > 6 µg/L

T1 \ T2	Biomarker: PEth > 6 µg/L			
	no	yes	missing	total (%)*
no	56	2	88	146 (79.8)
yes	7	9	21	37 (20.2)
missing	2	0	1	3
total (%)*	65 (85.5)	11 (14.5)	110	186

Supplementary table 10. Direction of change of self-reported illicit substance use

T1 \ T2	Self-reported illicit substance use			
	no	yes	missing	total (%)*
no	164	0	60	224 (97.4)
yes	3	1	2	6 (2.6)
missing	3	0	4	7
total (%)*	170 (99.4)	1 (0.6)	66	237

Supplementary table 11. Direction of change of BMI > 30 kg/m^2

T1 \ T2	BMI > 30 kg/m^2			
	no	yes	missing	total (%)*
no	88	1	87	176 (80.0)
yes	2	18	24	44 (20.0)
missing	2	1	9	12
total (%)*	92 (82.1)	20 (17.9)	120	232

Supplementary table 12. Direction of change for pregnancy intention

T1 \ T2	Pregnancy intention					
	currently pregnant	next 3 months	next 3-6 months	after > 6 months	missing	total (%)*
currently pregnant	2	0	1	0	1	4 (1.8)
next 3 months	21	41	13	3	36	114 (50.4)
next 3-6 months	9	14	19	6	11	59 (26.1)
after > 6 months	1	1	8	23	16	49 (21.7)
missing	1	1	0	3	6	11
total (%)*	34 (20.3)	57 (34.1)	41 (24.6)	35 (21.0)	70	237

* of non-missing cases