# Designing & Evaluating General Individual Preconception Care

## the Ready for a Baby program

SEVILAY TEMEL

**Designing & Evaluating**
**General Individual Preconception Care**
*- the Ready for a Baby program -*

***Sevilay Temel***

The research presented in this thesis was performed at the department of Obstetrics and Gynaecology, division of Obstetrics and Prenatal Medicine, Erasmus University Medical Centre, Rotterdam, the Netherlands

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**DESIGNING & EVALUATING**
**GENERAL INDIVIDUAL PRECONCEPTION CARE**

***- the Ready for a Baby program -***

*Het ontwikkelen en evalueren van algemene individuele preconceptiezorg*
*- het Klaar voor een Kind programma -*

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*Annem ve babam için*

*Voor mijn ouders*

**CONTENTS**

# Chapter 1

## General introduction

Partly based on 'Preconceptiezorg', Handboek vrouwspecifieke geneeskunde. 2013. Chapter 22:249-63.

In 2000, 2004 and again in 2010, the position of the Netherlands in the European perinatal mortality rate ranking (deaths from 22 weeks of gestational age until seven days postpartum) appeared unfavorable [1-3]. Eighty five percent [4] of the perinatal mortality cases are preceded by four adverse perinatal outcomes (the 'Big 4'): being congenital abnormalities, small for gestational age (birthweight <10$^{th}$ percentile for gestational age [5]), premature delivery (birth <37 weeks), and/or a low Apgar score (<7, 5 minutes after birth), with deprived neighbourhoods found to have an up to four times higher perinatal mortality rates than average [6, 7]. The most pronounced discrepancies in outcomes were found in Rotterdam, where perinatal mortality can be as low as 2 per 1,000 births in non-deprived neighbourhoods and as high as 34 per 1,000 births in deprived neighbourhoods [8].

## THE 'READY FOR A BABY' PROGRAM

Not only is the perinatal mortality rate worrying, but also perinatal morbidity was higher in the four largest cities in the Netherlands [9]. In the city of Rotterdam analysis of perinatal data showed that one out of six children had a suboptimal start to their lives [8]. A suboptimal start at birth results in greater risk of developmental and behavioral problems, with a negative influence on the child's entire life [10, 11].

These outcomes raised the question whether the provision of obstetrical care was satisfactory and meeting the needs of the populations at risk. In 2008, at a first meeting with experts in Rotterdam, the negative perinatal results were analyzed and discussed. Subsequently, small groups of experts discussed risk factors and possible approaches to the solution of these problems. On the basis of this first meeting, the first outlines of the 'Ready for a Baby' program became visible [12]. The program allowed for an integrated approach to implement several interventions to improve birth outcomes in Rotterdam. In January 2009, the Ready for a Baby program (see figure 1) was officially launched - an initiative by the Erasmus University Medical Center and the Rotterdam municipality. The main objective of this 10-year program was to improve perinatal health and to reduce perinatal mortality in all districts of Rotterdam to at least the current national average [13].

Preconception care (PCC) was the first link in this program and aimed to develop, to execute and to evaluate a preconception health intervention in two districts in the city of Rotterdam. For this purpose three approaches which combined individual and collective PCC, as indicated by the Dutch Health Council, were used [14]. The councils of the city districts North and South, the obstetric primary care providers, (non-medical) social

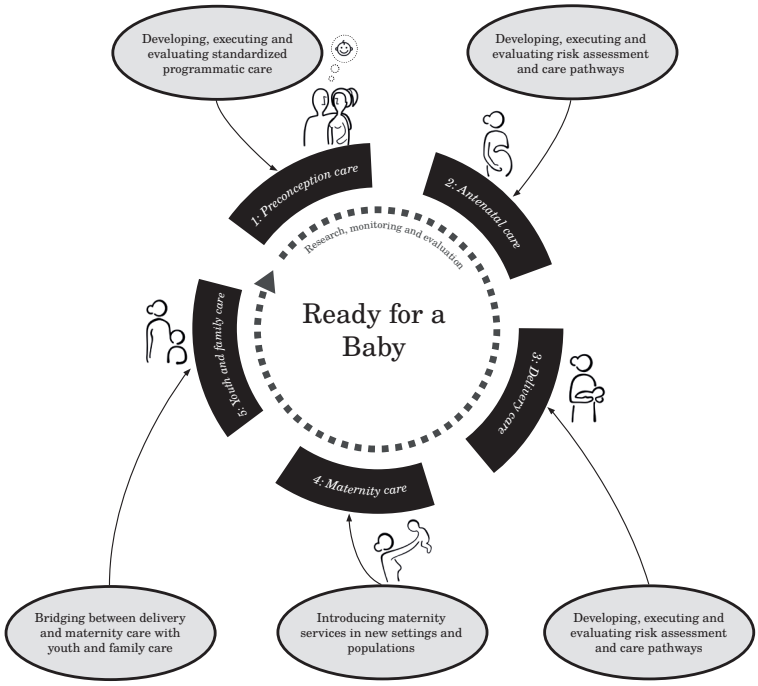


**Figure 1.** The Ready for a Baby program: overview of the obstetrical chain of care

welfare organizations, and migrant institutions were closely involved in the development and the implementation of the preconception health intervention study.

The second link, aimed at improving the quality of antenatal care by: 1) studying factors which contribute to the delay in entering antenatal care among women living in deprived areas, 2) developing preventive and risk-selecting activities during the first trimester of pregnancy which compromises both medical and psycho-social and socio-economic risk factors (e.g. the R4U, Rotterdam Risk Reduction Checklist) [15] with care pathways, and 3) developing a protocol or model for shared care for greater interdisciplinary collaboration between community midwives and obstetric caregivers in hospitals [16]. A close collaboration with the midwifery practices, the obstetricians, and the social welfare organizations was established.

In the third link, the objective was to improve the delivery care. In the same period that the Ready for Baby program started, the establishment of primary care birthing centres adjacent to hospitals were opened. The first one opened on a new top floor of the Sophia Children's Hospital of the Erasmus University on 1 October, 2009. Birth centres in Rotterdam provide women without a medical indication the possibility to give birth in a primary care setting adjacent to the hospital with nearby specialist care [17]. In order to improve the quality of care just before, during and after delivery, the aim was: (1) to

develop preventive and risk-selecting instruments which link both medical and psychosocial and socio-economic risk factors with care pathways, and (2) to develop protocols for all health care professionals involved: the community midwives, the maternity care providers, the obstetricians, and the family and youth care professionals.

The fourth link, maternity care, aimed to introduce maternity services to families who are not acquainted with this typical form of Dutch health service. After birth in a primary care birth center, a prolonged stay by mother and baby was possible with 24 h a day, professionally available maternity care. Moreover, maternity care assistants were educated and trained in culturally-diverse patient populations paying attention to culture, traditions and religion. Maternity care-providing organizations were involved in policy improvements and interventions to reach target populations by organizing community focus groups to try to understand the barriers in case of culturally-diverse women.

The fifth link, youth and family care, aimed to identify risk factors that may affect a child's health or upbringing at an early stage for which appropriates steps can be taken. Essential to this process is the fast and accurate communication of problems during pregnancy, birth or the period after delivery to the youth and family centres. During a visit to these centers staff could also suggest preconception counselling to mothers with previous 'Big4' children before planning a new pregnancy- defined as 'interconception care'.

Registration and evaluation were essential in order to measure whether the objectives of the program were being achieved. Developments were monitored across the city and project-based evaluations were carried out.

In this thesis the focus is on the PCC study.

## PRECONCEPTION CARE

The rationale of the PCC study within the Ready for a Baby program originates from increasing evidence showing the critical influence of embryogenic development and placentation during early pregnancy on pregnancy outcome [18-20]. PCC should therefore be regarded as a necessary additional component to the obstetric care system in the improvement of perinatal outcomes. In the Netherlands in 2007, the Health Council advised to integrate general PCC into the health care system [14]. General PCC is directed at all couples trying to conceive and takes place in primary care (general practitioner [GP] or midwife level). The Dutch situation is ideal to reach couples planning pregnancy on time, as 80% of the pregnancies are planned in the Western population [21] and every couple is registered with a GP who therefore could provide general PCC. There have been some initiatives regarding PCC in the Netherlands: several pilot studies have been performed [22, 23] and some midwifery practices offer PCC. Nevertheless,

to date, general PCC has not been integrated in the Dutch health care system. Multiple explanations can be given.

Firstly, only a limited number of systematic PCC programs have actually been evaluated; these have been mainly in secondary or tertiary care [24-26]. Many authors have reported only the number of women who attended PCC, or their reasons for referral, which mainly concerned previous reproductive or maternal medical complications. In the Netherlands, few studies focused on comprehensive general PCC as a single package [22, 23]. Studies focusing on process development and evaluation act as a basis for implementation of PCC. So far, however, these studies are lacking.

Secondly, as PCC is regarded as a window of opportunity, several proposed components of PCC are still being discussed. International variation exists in contents of PCC delivery [27-30]. The Dutch Health Council emphasized the importance of providing PCC in a single package, to guarantee that no component is being neglected. It divided PCC into individual and collective forms with respective target groups and set a content for PCC [14]. However, regular meetings within scientific associations, national committees and preconception health caregivers were advised to have shared commitment and responsibility as well as to have contents and forms of PCC up to date.

Thirdly, the clinical effectiveness of many specific components of PCC like folic acid intake on pregnancy outcome are proven and scientifically well documented [31, 32]. The question whether couples undergoing preconceptional interventions, like stopping alcohol intake, actually induces behaviour change and subsequently improves pregnancy outcome remains to be answered.

Finally, studies revealed barriers for the implementation, such as lack of provider time and lack of guidelines. From women's perspectives, lack of knowledge and perceived lack of risks are reported [33]. For example, preconceptional folic acid supplementation knowledge and use remain lower among non-Dutch women [34, 35]. Furthermore, it remains partly unclear what women think of PCC in general. Frey and Files investigated women's attitudes regarding PCC and concluded that the majority of women understood the importance of PCC but did not discuss these issues with their physician [36]. Another study found that most women have a positive view of preconception counselling [37]. Exploring women's knowledge, attitudes and behaviours will assist in the development of more accurate and tailored tools to implement (general) PCC.

## AIM OF THIS THESIS

Therefore, the main aim of the findings described in this thesis is to provide more insight into the above mentioned barriers. This thesis has three parts: Part I introduces the topic of this thesis and gives a point of departure from the literature and experts, Part II con-

tains the pilot studies with the overall process evaluation of the preconception health intervention study in the Ready for a Baby program, and Part III provides the general discussion and the Summary/Samenvatting.

The five objectives are:

1. To give insight in approaches for delivery and challenges of PCC
2. To study expert opinions about the content and form of PCC
3. To study the relationship between preconceptional lifestyle interventions and behavioural change and pregnancy outcome.
4. To determine the intention and knowledge of PCC among the general population.
5. To evaluate the development and implementation of the preconception health intervention study.

## OUTLINE OF THIS THESIS

In **Part I (chapters 1-4)** (see figure 2), we introduce the topic of this thesis and give an overview of approaches for delivery and challenges of PCC. We provide the experts' opinions on the content and form of PCC. We deliver a systematic review of the available effectiveness of lifestyle interventions amongst preconceptional women in the general population- in terms of behavioural change and pregnancy outcome.

In **Part II (chapters 4, 5 and 6),** we focus on the pilot projects and the process evaluation of the preconception health intervention study. We investigate in the determinants of the intention of PCC use and study knowledge regarding preconceptional folic acid

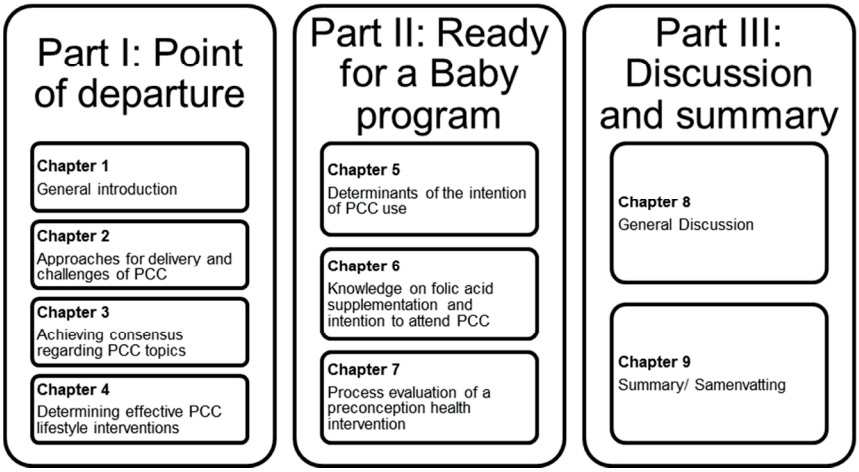


**Figure 2.** Outline of this thesis: objectives and chapters

intake and preconceptional consultation of GP/midwife. Furthermore, we evaluate the development and implementation of the preconception health intervention study.

In **Part III (chapters 7 and 8),** we provide an overall discussion of the main findings of this thesis, including recommendations for future research and implications for clinical practice and a summary and conclusion of this thesis.

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# Part I

## Point of Departure

# Chapter 2

## Preconception care; an essential preventive strategy to improve children's and women's health

Boukje van der Zee, Inez D. de Beaufort, Sevilay Temel, Guido de Wert, Semiha Denktas, Eric A. P. Steegers

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## ABSTRACT

Over the past few decades, reproductive health has not improved. Recently, the Netherlands was shown –particularly in large cities- to have relatively high perinatal death rates compared with other European countries. Preconception care offers new strategies for improving reproductive health. The authors consider the national implementation of preconception care consultations as well as other possible preconception care approaches. Two characteristics of preconception care are defined that would favour organizing it top-down (policies) in addition to bottom-up (caregivers); it is a new and complex link in a chain that connects both the affected individual's life course and different health care disciplines. Preconception care is a promising new approach to improve a woman and her family's health; failing to facilitate preconception care would be a failure of both professional and governmental responsibilities.

Over the past few decades, reproductive health has not improved. In the United States, maternal mortality has only modestly decreased in the past few decades [1], whereas it has even increased in the Netherlands [2]. In urban regions, perinatal health differs considerably from the national average, especially in deprived areas of larger cities. Reproductive health also concerns perinatal conditions related to the probability of perinatal death such as preterm birth, intrauterine growth restriction, congenital anomalies, and a sub-optimal start at birth. Previous research explained these poor perinatal outcomes by the over-representation of non-Western women, women of low socio-economic status, and women living in deprived areas of the city, factors that are associated with an accumulation of risk factors [3,4]. The lack of improvement in reproductive outcome despite improved quality of and better access to prenatal care strongly suggests that prenatal care alone is insufficient [5].

Preconception care is thought to be a promising approach to improve both newborn and maternal health [6,7]. Preconception care was described by Chamberlain as a specialty service for women who had previously experienced a poor reproductive outcome [8,9]. Nowadays, the importance of preconception health is becoming better understood and studies and guidelines are developing worldwide for components of preconception care. However, with the exception of Hungary, there seem to be no comprehensive national policies anywhere in the world.

First, we will define and list some benefits of preconception care. Second, we consider the implementation of preconception care. Special attention will be given to the situation in the Netherlands, where the perinatal death rates are higher compared with other European countries [10]. Consequently, we discuss alternative approaches to improving preconception health. We state that preconception care should be organized through top-down as well as bottom-up initiatives. We conclude with a number of challenges that may accompany the implementation of preconception care.

## DEFINING PRECONCEPTION CARE

The principal goals of preconception care are to optimize the health of the future child and to improve maternal health through primary intervention [11]. Preconception care entails risk assessment, health promotion, counselling, and intervention. Risk assessment is the systematic identification and evaluation of risk factors for so-called adverse pregnancy outcome. If risks are identified, this may require additional screening, diagnostic tests, and specialist consultations. Health promotion consists of informing and educating couples on a variety of health-promotion issues and measures, including periconceptional folic acid supplementation, avoiding alcohol, tobacco, and other

drugs, and the importance of proper nutrition. Intervention is carried out to modify or eliminate risk factors. Individual preconception care from a specialist is offered to women at increased risk of an adverse pregnancy outcome, such as women with a complicated medical, obstetrical, or family history, or who have chronic diseases and conditions like congenital cardiac defects. General individual preconception care can be offered to all women of reproductive age or focused at women planning to become pregnant [12]. In this article, we will deal with general individual preconception care focused on women planning to become pregnant.

Every couple potentially has at least one risk factor for an adverse pregnancy outcome [13], so every couple would benefit from preconception care. Preconception care can be seen as a window of opportunity to improve children's and women's health at the same time. We touch on these benefits and would like to refer to evidence for several components of preconception care from the recommendations from the Centers for Disease Control working group and, among others, three important journal supplements from the American Journal of Obstetrics and Gynecology, Maternal and Child Health Journal, and Women's Health Issues [1,14-16].

The primary beneficiary of preconception care is the child. Preconception care is important for optimal intrauterine growth and development. Current antenatal care generally does not start before the 12$^{th}$ week of pregnancy, thereby neglecting the first gestational weeks during which embryonic growth and development takes place and is associated with adverse pregnancy outcome [17-19]. Therefore, preconception care is the only way in which appropriate action can be taken in time to avoid risks with regard to early pregnancy. Above all, a woman's lifestyle prior to the pregnancy is the strongest predictor of her lifestyle during the pregnancy [20].

Secondly, preconception care may improve women's health before, during, and after pregnancy. An important spin-off is that the woman optimises her fertility by adopting a healthy lifestyle [21]. Individual advice is provided to enable women to make an informed choice about getting pregnant and, if necessary, changing their lifestyle to optimize their chances of a good pregnancy outcome. The Health Council of the Netherlands considers this informed choice an important aim of preconception care [11]. Preconception care may increase awareness of possible health risks, which may also contribute to continuing a healthy lifestyle later in life [22]. Similar considerations hold, *mutatis mutandis*, for the father, whose lifestyle may also influence the health of the child, and who has a shared responsibility for the child [23] and who may profit from a healthy lifestyle himself. The woman may benefit directly, for example, when her partner stops smoking, or indirectly by receiving his support.

Lifestyle guidelines that are provided during preconception care may result in greater compliance because of an increased motivation and responsibility for not only the individual's health, but also for the health of the future child.

## THE NETHERLANDS: A SINGLE PACKAGE

In the Netherlands in 2007, the Health Council advised integrating general preconception care into the health care system [11,24] The Council emphasized the importance of providing preconception care in a single package to guarantee that no component is neglected and all are easily accessible, enabling tailor-made care.

This, according to the Council, will require making preconception care part of a continuum, developing guidelines for patterns of referral, and keeping comprehensive records. Professional groups that could potentially be involved include midwives, general practitioners, gynaecologists, and maternal and child health services. The former Dutch minister of Health recognized the importance of implementing preconception care, and created a commission (Stuurgroep Zwangerschap en Geboorte) to explore the possibilities for implementing it. He recently acted upon the commission's recommendations, called on professional groups to define preconceptional guidelines, and agreed to include preconception care consultations into the health insurance packages starting from January 1, 2011 [25].

In the Netherlands, studies were conducted on how to improve preconception nutritional lifestyle [26,27], folic acid supplementation [28-30], and cystic fibrosis carrier screening [31]. A few pilot projects on comprehensive general preconception care were included in a single package [32-35]. In 2007, one of these pilot studies was conducted in the city of Rotterdam [36]. Through public campaigns, parents-to-be were encouraged to complete a pre-pregnancy checklist on the Internet (www.zwangerwijzer.nl) and send the results to a caregiver. Zwangerwijzer is a medically-validated, web-based instrument for self-completion and freely accessible. It identifies individual risk factors, and provides background information and advice about preventive measures [37,38].

Some couples may not have easy access to the Internet or may have difficulties using it, especially those with a low socio-economic status and who are non-Dutch speaking immigrants. They can visit a midwife practice, which organizes preconception consultations, or ask their general practitioner to assist with completing the form. An additional risk assessment by trained professionals is necessary to verify several items, and to further explore identified risk factors for an adverse pregnancy outcome. Using this information, the caregiver (generally the midwife or general practitioner) provides preconception advice and provides additional health promotion information. Depending on the risk factors, the couple may be referred to a specialist for preconception care (hospital care: gynecologist, clinical geneticist).

During the public campaign in Rotterdam, there was a significant increase in Zwangerwijzer website visits but not in the entry of the preconception consultations, probably because of the short campaign period.

In 2009, the municipal council of Rotterdam and the Erasmus University Medical Centre started a city-wide urban perinatal health program to improve perinatal health outcomes. Preconception care is a key element of this ten-year program. Two preconception projects in two districts with deprived neighbourhoods began in 2009 and 2010. Preconception care was adapted to the relatively low socioeconomic population; (1) collective campaigns using specific instruments (multi-lingual posters, leaflets, advertisements, and columns in the local media), followed by (2) a preconception education program tailored to specific target groups (short courses for men/women about healthy pregnancy and the importance of preconception care), and (3) individual preconception counselling combined with social services for parents-to-be provided by a midwife or general practitioner.

In the Netherlands, the costs and effects of a mass campaign and a single preconception consultation with regard to folic acid supplementation and smoking cessation, for all couples contemplating pregnancy, were estimated based on 200,000 women approached yearly and an uptake rate of 50%. Effectiveness and potential savings were based on hospital costs of neural tube defects and very low birth weight attributable to maternal smoking. If 50% of women sought preconception counselling and 15% gave up smoking after counselling, and 80% of women who had not done so started taking folic acid, 22 neural tube defects, 98 low-birth-weight infants, 10 very-low-birth-weight infants, and 7 perinatal deaths could be avoided. Preventing neural tube defects and smoking-related morbidity alone could recover approximately 30% of the costs of a preconception care mass campaign and consultation. The net costs were estimated at between 3 (uptake 50%) and 4.1 (uptake 75%) million Euros [39]. Recently, the former Dutch minister of Health estimated the annual costs of implementing preconception care consultations, if all future pregnant women were interested, at 7 million Euros [25].

In light of the many other preventable adverse outcomes and the potential for preconception care to prevent significant lifetime costs of affected children, preconception care is, therefore, likely to be cost-effective in the Netherlands [39].

## OTHER POTENTIAL APPROACHES

In Europe, there were a number of studies regarding general preconception care (Hungary, Belgium, Italy, Poland, France, UK, and Portugal) [11,40]. In 2008, the first 'Central and Eastern European Summit on Preconception Health and Prevention of Birth Defects' was organized in Hungary, and in October 2010 the first 'European Congress on Preconception Care and Preconception Health' took place in Belgium.

In the United States, several organisations actively promote general preconception care (Centers for Disease Control, March of Dimes, American College of Obstetrics and

Disease Control) [41,43], which led to two national summits [44,45]. An Expert Panel convened by the CDC published recommendations on preconception care [16]. In Canada, efforts led to national guidelines [46].

The organisation and content of preconception care depend on the infrastructures of the national health care, insurance systems, and socio-economic determinants of morbidity and mortality. There are large differences between countries. For example, in the Netherlands, 85% of the pregnancies are planned [11], whereas in the US only 50% are planned [47]. This could be why preconception care in the US was presented as a separate strategy but rather focuses on preconception care as part of a continuum of women's health care strategies. Its aim is to 'catch' women with reproductive potential any time they meet with a health care provider [42]. With regard to awareness and health promotion, it would be possible to extend the target population and provide information to high school students [48].

Continued mass campaigns seem necessary to increase awareness of the importance of preconception health and some basic knowledge, such as the need for periconception folic acid supplementation. In the Netherlands, the number of neural tube defects fell from 12.3 per 10,000 children in 1997 to 6.3 per 10,000 children in 2004 [11]. This decrease is partly associated with an increase in the use of folic acid. In 1997, a one-time mass media campaign was organised in the Netherlands to promote the use of folic acid. Appropriate folic acid use rose from 15% in 1996 to 36% by the end of 1998 [49]. Folic acid supplementation in the Netherlands is lower among non-Dutch women or women with a low level of education than among highly-educated Dutch women [49]. Although the campaign was successful, the aim of the campaign has not been entirely achieved. Establishing changes in attitude probably requires programs that run for a longer period [50].

To reach the target population and focus, for example, on lower-educated women, it might be useful to use marketing tools like audience segmentation, as was presented by Elizabeth Mitchell during the 2010 European Congress on Preconception Health and Preconception Care in Brussels [51]. By using audience segmentation, a broad population is divided into smaller segments based on common characteristics. Interventions are better targeted because they can be tailor made.

## TOP-DOWN INSTEAD OF BOTTOM-UP

Although preconception care has progressed over the past three decades, there is still room for improvement. There are two characteristics of preconception care that, in our view, favour organizing preconception care from the top (policy) in addition to initiatives

organized from the bottom (caregivers). To begin with, general preconception care is a relatively new concept and, therefore, requires another mindset; parents-to-be as well as physicians are still insufficiently aware of pregnancy-related risk factors, possibilities for prevention, and of properly timed, specific risk-reducing behaviour [32].

Secondly, preconception care has a multifaceted character and should be part of an interlinked chain that creates connections both in the life course (from preconception care through to prenatal, neonatal, and youth care) of the individual and between health care disciplines (general practitioners, midwives, obstetricians, clinical geneticists, and maternal and child health professionals). These connections are necessary to avoid bureaucratic barriers and to guarantee a continuum of optimal care.

These characteristics may complicate the organization of preconception care from the bottom because many disciplines are involved, and reaching consensus about all aspects may be difficult and time consuming. Comprehensive national policies are needed to support the bottom-up initiatives. Governments should create the conditions to make initiatives work; for example, by obliging insurance companies to cover the costs of a preconception visit and creating awareness. Therefore, governments should organize continued mass campaigns to promote preconception health and preconception health care, which are expected to be as successful as the folic acid campaign discussed above [50].

## CHALLENGES

There are a number of challenges and questions to be addressed. Challenges in implementing preconception care concern organizational, practical, and ethical issues [52]. A very general organizational question is how to best organise preconception care to obtain optimal health results. Clearly, there is no single format. Because it is new, there is a need to explore and evaluate different approaches in different countries.

With regard to the ethical challenges, the question that sometimes pops up in the Netherlands is whether preconception care spoils the naturalness, insouciance, and joy of becoming pregnant and having a child. This objection is often referred to as the argument of *medicalization* of getting pregnant and of pregnancy [11]. Medicalization is a so-called container notion, used to express many different feelings and concerns about pregnancy and related preventive care. A careful analysis of the term is beyond the scope of this paper, but it should, in our view, not be used as a general ethical shield against any form of preconception consultation. After all, preconception care, like other types of preventive medicine, may have substantial health benefits for those concerned.

A practical and moral challenge springs from the fact that providing preconception information and advice will not guarantee that a person acts on this information [53]. For

different reasons (strong habits, addiction, disbelief), they may not succeed in changing their behaviour. Sometimes programs should to be provided to assist them, e.g. quitting smoking or making dietary changes. Nonetheless, some parents-to-be may not want to change their behaviour. The questions are notoriously difficult and controversial, like what their moral responsibility is towards their future child and what interference, if any, is justifiable when it comes to possible dangers for future children. The issue of the precise limits and allocation of responsibility should, however, not paralyse the debate or the implementation of preconception care. In many cases, parents-to-be are grateful for the information, and the option to do what is best for the health of their child. Another important question concerns factors that are not related to life style, but factors over which the individual has no control, such as possible 'inborn' genetic risks. Informing people about genetic risks may confront them with complex moral dilemmas. The Health Council of the Netherlands suggests dealing with this problem by first providing only general information on possible genetic risk factors, then letting women (couples) decide whether they want more detailed information and perhaps testing; for instance, to determine whether one carries a particular autosomal recessive disease.

Another challenge is finding the best way to reach the most vulnerable subpopulations such as immigrants and those with a low socio-economic status [54]. For this purpose, non-conventional methods and additonal initiatives should be investigated. In the two preconception projects in Rotterdam, social peer group networks and community social workers were involved, and channels specific to the target groups were activated; e.g. these included migrant organisations with peer group educators.

## CONCLUSIONS

All women should have an equal opportunity to receive adequate preconception care, taking into account the situation in their country. As preconception care improves women's health and that of future generations, not providing preconception care would be a failure of professional and governmental responsibilities.

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# Chapter 3

## The Dutch national summit on preconception care: a summary of definitions, evidence and recommendations

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## ABSTRACT

**Objectives** Preconception care is a primary preventive approach in which prepregnancy risk factors are addressed in order to prevent adverse pregnancy outcomes. Although benefits of preconception care are acknowledged, consensus on concepts of preconception care and approaches for implementation in the Netherlands are currently lacking. Due to the comprehensiveness and multidisciplinary nature of preconception care consensus could be a prerequisite to develop or implement approaches to deliver preconception care.

**Methods** A literature-based consensus meeting was organized to achieve consensus about (I) the definition, (II) categories, (III) target groups, (IV) prepregnancy risk factors and interventions and (V) risk assessment instruments.

**Discussion** Preconception care is only delivered in a small scale and consensus on the content and how the care should be delivered is not well documented. Consensus regarding the content and delivery of preconception care is necessary to upscale preconception care and to commit both curative and public health in their responsibility in preconception care.

**Conclusions** This paper presents a summary of the reached consensus and the identified knowledge gaps during the meetings.

## INTRODUCTION

Preconception care (PCC) is widely recognized as a way to optimize women's health through biomedical and behavioural change prior to conception, ultimately to improve pregnancy outcomes. In terms of prevention, PCC is primary prevention for the future baby and secondary prevention for prospective mothers. When these appropriate secondary and primary preventive measures are taken public health benefits are achievable by prevention and treatment of identified risk factors (e.g. smoking, alcohol abuse, obesity and infectious diseases) and improvement of perinatal health potentially leading to improvement of health later in life.

Despite recognition of the importance of PCC in the Netherlands within curative care and governmental policy makers [1], PCC is still only delivered on a small scale and not in a uniform manner. Lack of consensus regarding the content and the delivery of the care seems to be an underlying cause. This consensus is important to provide caregivers with a foundation for further implementation of PCC. Consensus is also a necessary first step in creating of awareness among caregivers regarding their societal responsibilities in primary and secondary prevention.

Therefore, a consensus meeting was organized to identify gaps and essential targets to contribute to policy thinking for implementation of PCC. Point of departure was a comprehensive literature study. This paper summarizes results of the meetings. These results can be used to create commitment and responsibility amongst curative caregivers and public health policy makers to keep the debate going in the content of PCC.

## METHODS

A comprehensive literature study was performed to provide a starting point to address five core subjects: 1) the definition of PCC, 2) categories of PCC, 3) relevant target groups and methods for outreach, 4) risk factors which should be taken up in PCC (an evidence update as of 2008) and effective interventions (evidence as of inception of databases), and 5) risk assessment instruments. Despite increasing evidence of paternal influence on pregnancy outcome and the crucial influence of men on their partners' health behaviours, this meeting – and therefore the literature study - firstly focussed on PCC for women [2-4]. This meeting does not have its focus specifically on lifestyle risk factors, however we would like to point out that we recently have published another systematic review regarding effectiveness of PCC interventions on lifestyle risk factors in the Preconception Phase [5]. The meeting, organised by the Erasmus MC in Rotterdam, consisted of two one day sessions (January 2012 and April 2012). Propositions for con-

sensus – based on the literature - were presented as a starting point for the discussion. Participants included:

- Care givers (midwives, general practitioners, gynaecologists, clinical geneticists, an occupational health physician);
- Representatives from professional organizations of the care givers (Regional Organisational Support for Primary health care [ROS]);
- Governmental representatives (the Ministry of Health Welfare and Sport, the Commission for Perinatal Health [College Perinatale Zorg], a Municipal Health Service [GGD Rotterdam-Rijnmond]);
- Health insurance companies and the Health Care Insurance Board;
- Funders of scientific research (the Netherlands Organisation for Health Research and Development [Zon MW]);
- Providers of health care expertise (the Health Council of the Netherlands [Gezondheidsraad], the National Institute for Public Health and the Environment [RIVM], the Dutch National Genetic Resource and Information Center [Erfocentrum], the Dutch Foundation of Preconception Care, Organisation for Applied Scientific Research [TNO], the Dutch birth registry (Netherlands Perinatal Registry [PRN]);
- Patient-consumer federation (the Dutch Genetic Alliance of Parent and Patient organizations [VSOP]);
- Other relevant disciplines (department of medical ethics, epidemiology).

Sessions were chaired by independent experts on PCC. Achieved consensus, lack of consensus and knowledge gaps were recorded. These records were verified by participants after each session.

## EXPERTS DISCUSSION

Results will be presented per core subject in a fixed format: an introduction, the proposal, achieved consensus (in case of agreement), lack of consensus (if any) and identified knowledge gaps resulting in recommendations for future research.

### I. Definition of PCC

*Introduction*

Various definitions for PCC have been formulated. The definition is an important take off point in the debate around the content of PCC. In 1992 the following definition was included in PubMed's Mesh database: "*An organized and comprehensive program of health care that identifies and reduces a woman's reproductive risks before conception through risk assessment, health promotion, and interventions [6].* In 2005 the Centers for

Disease Control and Prevention (CDC) and the March of Dimes recognized the need to state that PCC is a continuum of care throughout the various stages of the reproductive life of women. This was incorporated in their definition: *"A set of interventions that aim to identify and modify biomedical, behavioural, and social risks to a woman's health or pregnancy outcome through prevention and management, emphasizing those factors that must be acted on before conception or early in pregnancy to have maximal impact [7]."* In 2007 the Health Council of the Netherlands presented a definition in line with the CDC: *"Preconception care is the entire range of measures designed to promote the health of the expectant mother and her child, which, in order to be effective, must preferably be adopted prior to conception [1]."*

*Proposition*

To adapt the definition of the CDC and the March of Dimes, due to the different elements of risk factors, defined outcomes and the defined timeframe.

*Consensus*

- There was agreement with the proposition.
- To add that: PCC should be regarded as a programme and that PCC includes psychosocial risks, non-medical risks (e.g. financial problems and domestic violence) counselling and informed decision-making.
- To replace 'woman's health' with 'parental health'.
- To replace 'pregnancy outcome' with 'the health of their future child', prolonging the timeframe targeted by PCC.
- A note should be added to the definition about the potential of PCC to reduce perinatal mortality and morbidity.
- The consensus meeting resulted in the following definition: *"A set of interventions and/or programmes that aims to identify and enable informed decision-making to modify biomedical, behavioural, and (psycho)social risks to parental health and the health of their future child, through counselling, prevention and management, emphasizing those factors that must be acted on before conception and in early pregnancy, to have maximal impact and/or choice.*

  ** Preconception care may be a good opportunity to reduce perinatal mortality and morbidity.*

*Knowledge gaps/recommended future research*

- Although major steps are to be made in the implementation of PCC for women first, it is desirable to achieve consensus on PCC for men, in the future.

- Perinatal mortality and morbidity is a more important outcome for policy makers. Therefore trials should also address pregnancy outcomes (besides behavioural change) as an outcome measure of the effectiveness of PCC (see Figure 1).

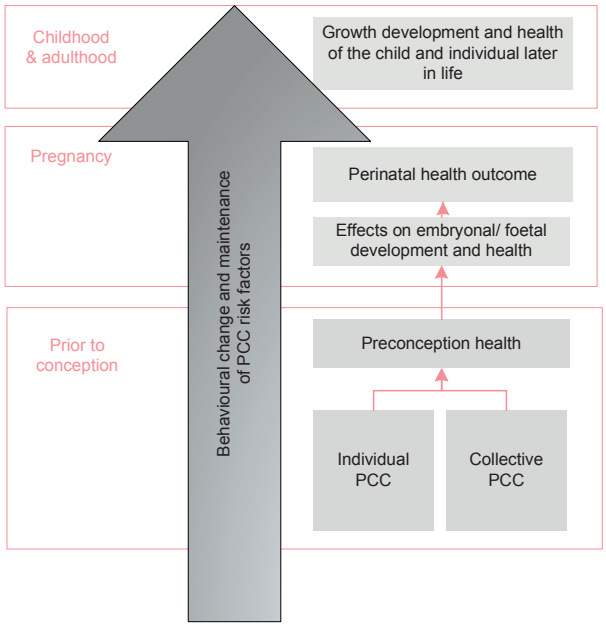


**Figure 1.** Outcomes of PCC

Preconception risk factors potentially and behavioral change may influence feto-maternal health throughout the periconception period, pregnancy as well as during childhood and adulthood. Health during reproductive age will subsequently affect the outcomes of subsequent pregnancies and the health of future generations.

## II. Categories of PCC

*Introduction*

PCC is meant to improve the health of mother and child in various ways. The Dutch Health Council provides the following categorization of methods for PCC delivery:

- *Collective measures* are aimed at the general population to improve preconception health. An example is campaigns on the use of folic acid.
- *General individual PCC* is detection and management or intervention on risk factors, in couples planning a pregnancy within the general population. The general nature resides from the fact that these couples mostly do not have a known or predefined preconception risk(profile).

- *Specialist individual PCC* is provided for a) couples with a known or predefined risk for an adverse pregnancy outcome (e.g. Diabetes) or b) couples who are referred from general individual PCC after risk assessment (e.g. when diabetes is detected).

Recognition of the different forms of PCC is important in the implementation of PCC. Categorization provides a basis to identify professionals with core responsibilities in a category, to tailor a feasible recruitment approach and applicable target group.



*Proposition*

- Not to change the categorization of PCC.
- Addition of care pathways to the elements of PCC. They can facilitate implementation of individual PCC in a uniform and locally tailored manner. Care pathways are a means of achieving multidisciplinary agreements on organization and efficient shared care. They should be evidence based and in line with local guidelines and available care facilities [8].

*Consensus*

- Care pathways were recognized to be valuable, specifically where they address socio-medical risk factors. Professional organizations should have a leading role in the development in care pathways, specifically to achieve multidisciplinary agreements.

*Disagreement*

- There is unclarity regarding which health care professional has a core responsibility in which category. The line between general individual PCC and specialized PCC is not very evident. There are caregivers that could address both general and specialized individual PCC. The difficulty lays in the education and/experience in addressing specialistic risk factors. As PCC has a very broad content; it seems merely impossible for one caregiver to address all risk factors.

*Knowledge gaps/recommended future research*

- There is a need to define the role of different professions within the Dutch Healthcare system within different categories of PCC. The collaboration between public and curative health, and delegation of tasks (e.g. to qualified physician assistants or nurses) should be explored further. This task can be fulfilled by the Commission for Perinatal Health (CPZ) which has now appointed a committee that will develop a consensus based multidisciplinary guideline. This guideline will explicate specific roles of health care workers.

## III. Reaching target groups

*Introduction*

So far, no (inter)national consensus exists as to whom PCC should be offered. The target population can be divided into four major groups: (1) the general population, (2) all men and women of reproductive age (3) men and women aiming to conceive and (4) men and women with predefined high risk groups (e.g. due to previous pregnancy complications, genetic risks, chronic illness or medication use).

Reaching women and men before the onset of pregnancy is crucial for effective PCC. Women neither actively seek PCC consultation, nor do they accept the offer to attend a consultation [9]. In every day practice clinicians do not often initiate a PCC consultation, nor do they recommend it to women [10,11]. The curative setting and the public health setting in contact with women of childbearing age should be aware of the importance of preconception health promotion. However there is a lack of awareness or perhaps sense of responsibility under these professionals about their responsibility and potential role in preconception health promotion.

Research on why the outreach of PCC is limited and how this shortcoming can be addressed, is scarce. Several studies have indicated that an important problem with reaching parents to be on time is that many women do not plan pregnancies [12,13]. Another challenge is adapting the PCC approach to reach specific target groups. The importance is recognized by trials evaluating outreaches of PCC programs [14-16]. Above all, research on effective (tailored) methods to reach target groups for PCC are lacking [17,18].

*Proposition*

- Increased awareness and specification of their role in executing PCC should be contemplated by the following care givers/ organizations: governmental organisations, care providers (midwives, general practitioners, pediatricians, gynecologists and medical specialists in general), youth and family centers, peer educators, social welfare services, and schools.

*Consensus*

- There was consensus on the fact that preconception health promotion needs broad support from actors with different relations to the target group. The following actors in general were identified additional to the professionals above, either as a direct link to the target population or as a medium: municipal health service, paramedics (e.g. dieticians and dentists), pharmacists, occupational health physicians, all health promotional institutes in general that address people of childbearing age, institutes focusing on migrants, the social network around future parents (e.g. aunts,

grandmothers), policy makers and means of communication (e.g. internet). The need for involvement and collaboration of curative health professionals and public health professionals is therefore acknowledged.

- Tailored approaches should be applied by actors for the different target groups of PCC. Specifically teenagers are a group of interest because early sensitisation could promote timely behavioural change or utilisation of PCC services later in life.



*Knowledge gaps/recommended future research*

- The consensus meeting concentrated on identifying actors to enlarge awareness and outreach of preconception health promotion amongst target groups. Feasible approaches should be developed per actor; per target group.
- There is a gap in practice as to how the above mentioned actors optimally could have a role.

A potential schematic approach to reach women with Diabetes Mellitus is shown in Figure 2.

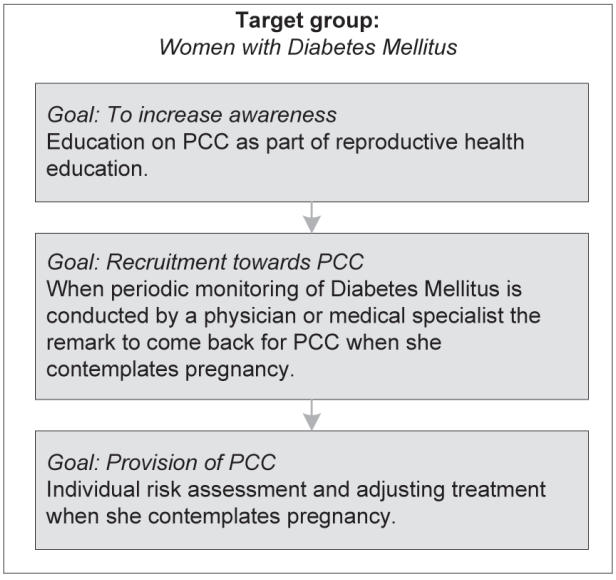


**Figure 2.** Target approach to reach women with Diabetes Mellitus
This figure shows a potential approach to improve preconception health and to target women with Diabetes Mellitus to utilize PCC when they contemplate pregnancy later in life.

## IV. Risk factors and interventions as part of PCC

*Introduction*

For the delivery of PCC there has to be consensus on the content. This should be based on known risk factors for adverse pregnancy outcomes and effective interventions to address them in the preconception period. A risk factor- and intervention review was conducted to form a basis for the discussions.

*Risk factors*

A review by Jack et al., was conducted in 2008 to provide evidence for risk factors to be taken up in PCC [19]. To update this review for the consensus meeting a search was conducted in PubMed, as of 2008. Selection was performed according to predefined criteria: the study assesses risk factor(s) which are present in the preconception period and the study reports an association with an adverse pregnancy outcome. Three reviewers independently assessed eligibility and performed data extraction. The search resulted in 2214 articles of which 178 articles were included.

*Interventions*

A systematic search was conducted to assess efficacy of available PCC interventions in PubMed, Embase and Web of Science from 1900 to January 2012. Selection was performed according to predefined criteria: the study assesses interventions, addressed in the preconception phase for an adverse pregnancy outcome. Two reviewers independently assessed eligibility of 678 articles and performed data extraction on 104 included articles.

Table 1 gives an update of the quality of the evidence for the risk factors per domain with interventions where available. Strength of evidence was assessed according to the Canadian Task Force on Preventive Health Care [20].

**Table 1.** Quality of the evidence for preconception risk factors and interventions to improve maternal and/or infant health and consensus on uptake in PCC

| Risk domain | Risk factors | Outcome | Intervention | Consensus |
|---|---|---|---|---|
| *Health care promotion* | Interpregnancy intervals (<6 months and >60 months) | II-2 | | + |
| | Lack of physical exercise | II-2 | I-a | + |
| | Unplanned pregnancy | III | | + |
| *Immunizations* | Human Papilloma Virus (HPV) | II-2 | | - |
| | MMR | II-3 | II-2 | + |
| | Hepatitis B | III | | - |
| | Varicella | III | | + |
| | Influenza | III | | - |
| | DTP | III | | + |
| *Infection* | Syphilis | I-a | | + |
| | HIV | I-b | | + |
| | Periodontal disease | I-b | | + |
| | Bacterial vaginosis | I-b | | + |
| | Asymptomatic bacteriuria | II-1 | I-a | + |
| | Herpes Simplex Virus (HSV) | II-1 | | + |
| | Chlamydia | II-2 | | + |
| | Toxoplasmosis | II-2 | | + |
| | GBS | II-2 | | + |
| | Tuberculosis | II-2 | | + |
| | Hepatitis C | III | | + |
| | Cytomegalovirus (CMV) | III | | + |
| | Parvovirus | III | | + |
| | Malaria | III | | + |
| | Gonorrhoea | III | | + |
| *Chronic medical conditions* | Diabetes mellitus type 1 or 2 | I-a | I-a | + |
| | Thyroid disease | II-1 | | + |
| | Phenylketonuria (PKU) | II-1 | | + |
| | Seizure disorders | II-2 | | + |
| | Hypertension | II-2 | | + |
| | Systemic Lupus Erytromatosus (SLE) | II-2 | | + |
| | Chronic renal disease | II-2 | | + |
| | Cardiovascular disease | II-2/II-3 | | + |
| | Thrombophilia | II-3 | | + |
| | Asthma | II-3 | | + |
| | Rheumatoid arthritis (RA) | III | | + |

**Table 1.** Quality of the evidence for preconception risk factors and interventions to improve maternal and/or infant health and consensus on uptake in PCC (continued)

| Risk domain | Risk factors | Outcome | Intervention | Consensus |
|---|---|---|---|---|
| *Psychiatric conditions* | Depression and anxiety disorders | II-2 | | + |
| | Bipolar disorder | II-2 | | + |
| | Schizophrenia | II-2 | | + |
| *Maternal exposure* | Alcohol | I-a | I-a | + |
| | Tobacco | I-a | | + |
| | Illicit substances | II-2 | | + |
| *Genetic risks* | Genetic disorder(s) or carrier ship in one of the prospective parents | II-2 | | + |
| | Ethnicity based risks | II-3 | | + |
| | Positive family history | II-3 | | + |
| | Recurrent miscarriages | III | II-2 | |
| | Known genetic conditions | II-3 | | |
| *Nutrition* | Inadequate folate intake | I-a | I-a | + |
| | BMI > 30 kg/m$^2$ | I-b | I-a | + |
| | BMI < 18 kg/m$^2$ | II-2 | | + |
| | Insufficient vitamin B12 | II-1 | | + |
| | Inadequate dietary intake | II-2 | I-a | + |
| | Western Dietary pattern | II-2 | | + |
| | Excessive vitamin E intake | II-2 | | + |
| | Insufficient Vitamin D | II-3 | | + |
| | Insufficient or excessive vitamin A intake | III | | + |
| | Eating disorders | III | | + |
| *Environmental exposures* | Occupational exposure (e.g. chemicals, solvents) | II-2 | | + |
| | Household exposures (e.g. PCB's, solvents, metals (lead)) | III | | + |
| *Psychosocial stressors* | Inadequate financial resources | II-2 | | + |
| | Interpersonal violence | II-2 | | + |
| *Medication* | Prescribed medication | II-1 | | + |
| | Herbs/herbal products/ weight loss products | II-1 | | + |
| | Over the counter drugs | III | | + |
| *Reproductive history* | Prior preterm birth | I-a | | + |
| | Prior miscarriage | I-a | | + |
| | Prior fetal growth restriction | II-2 | | + |
| | Prior caesarean delivery | II-2 | | + |
| | Prior stillbirth | II-2 | | + |
| | Uterine anomalies | II-3 | | + |

**Table 1.** Quality of the evidence for preconception risk factors and interventions to improve maternal and/or infant health and consensus on uptake in PCC (continued)

| Risk domain | Risk factors | Outcome | Intervention | Consensus |
|---|---|---|---|---|
| *Special groups* | Immigrant and refugee populations | II-2 | | |
| | Women who survived cancer | II-2 | | |
| | Women with disabilities | III | | |

**Quality of evidence**

I-a: at least 1 properly conducted randomized controlled trial BEFORE pregnancy
I-b: at least 1 properly conducted randomized controlled trial not necessarily before pregnancy
II-1: well-designed controlled trials without randomization
II-2: cohort or case-control studies
II-3: multiple time series with or without intervention or dramatic results in uncontrolled experiments
III: opinions: clinical experience, descriptive statistics, case reports or reports of experts committees



*Proposition*

- Identified risk factors and available interventions with a level of evidence of I-A to II-3 should be included as part of evidence based PCC.
- Identified risk factors with a level of evidence of I-A to II-3, but without evidence based interventions, should be prioritized for development of interventions.

*Consensus*

- Table 1 shows the consensus achieved per risk factor, regarding the uptake as part of PCC.
- There were remarks considering the uptake of the following risk factors in PCC:
  - *Group B streptococcus* (*GBS):* Due to the recurrence of GBS colonisation after treatment, it is not considered beneficial to screen all women preconceptionally for GBS. However, PCC can identify women with previous GBS infection or neonatal complications due to GBS colonization. For these women a management plan for their pregnancy and delivery can be formulated.
  - *HPV immunization:* Although HPV carrier status is common, fetomaternal transmission rates and consequent neonatal outcomes are infrequent; there was consensus not to incorporate HPV carrier detection and immunization in PCC.
  - *Hepatitis B immunization:* Where Hepatitis B infection is present in one of the future parents, routine clinical care was thought to be sufficient together with the local policy in pregnancy regarding vaccination of the neonate after birth.
- Although the review did not point out the following risk factors; the experts noted the following risk factors to be taken up as part of PCC:
  - *Chronic medical conditions:* such as inflammatory bowel disease (Colitis, Crohn's disease), women with organ transplants, previous thrombotic event or embolism.
  - *Genetic risks:* consanguinity.

- *Exposures:* Occupational exposure to working shifts and stress, sauna, diving and passive smoking as part of household exposure.
- *Psychosocial stressors:* adverse childhood events.
- *Reproductive history:* subfertility, prior pregnancy complications, prior congenital anomalies, prior neonatal complications and advanced maternal age (defined as older than 36 years).
- The discussion about risks that should be addressed by the PCC provider set aside, prospective parents may have questions (e.g. with regards to fertility and sexual health). PCC providers should assess needs and inform or refer where necessary.

· The current proposal focuses on individual risk factors. The participants agreed that the effect of risk accumulation should be recognized. Risk accumulation is the phenomenon that combinations of risk factors augment the total risk of the individual to a larger extent than the sum of the individual risks [21].

*Knowledge gaps/recommended future research*

· More research is needed regarding the Population Attributable Risks (PAR) of preconception risk factors and combined effects of risk factors.

· A remark can be made by the risk factor 'unplanned pregnancy.' It is unclear whether this considers unplanned pregnancies that are welcome or not welcome. This might be an important factor affecting pregnancy outcome as risky behaviour is more likely to happen when a pregnancy is unwanted. More insight is necessary in the contributory risk component in unplanned pregnancy: unwantedness versus the unplanned nature.

· As the possible content of PCC is growing, there is a need for prioritization in the interventions for a woman's specific risk profile. There is no method to identify the best core of action and a fixed format is not feasible due to inter-individual differences. PCC providers are subjected to 'common sense' in the prioritization of risk factors. This should be based on the impact of risk factors and the feasibility of interventions.

## V. Risk assessment instruments

*Introduction*

Assessing preconception risk factors within all domains is time consuming and to stimulate a uniform risk assessment; risk assessment instruments are necessary.

Available risk assessment instruments were identified:

· ZwangerWijzer is the most widely used instrument in the Netherlands [22,23]. It is a validated tool based on the Preconception Health Assessment form developed by Cefalo and Moos [24]. It is self-administered online questionnaire that assesses and informs about medical-, genetic-, environmental- , occupational-, nutritional-, and

lifestyle risk factors. The identified risks can be emailed to a caregiver – to provide an agenda for individual PCC. A supportive program provides the caregiver with a preconception patient record with protocols to address each identified risk factor [25].

- Slimmer Zwanger is a personal screening and coaching program provided by mobile phone app [26]. The application assesses nutrition and lifestyle behaviours by a self-administered questionnaire. The application then provides motivational text messages and e-mail messages to change risky behaviours. Effectiveness is currently being assessed.

*Proposition*

- To include generic risk assessment instruments suitable for the local setting in PCC.

*Consensus*

- Instruments with a wide range of detecting risk factors to limit the amount of questionnaires are preferable.
- Risk assessment instruments can lead to awareness and therefore can function as an intervention themselves.

*Knowledge gaps/recommended future research*

- Appropriate evidence-based standardised risk assessment instruments remain to be developed or existing tools should be optimized (e.g. multilingual) and validated.

## SUMMARY

In conclusion, consensus was achieved on the majority of the key elements of PCC, including the definition, the categorisation, institutes and health care professionals which should play a role in reaching target groups, the content and delivery and the need for development of evidence-based risk assessment instruments. These elements give further insight in what should be resolved in order to enlarge the scale at which PCC is delivered. Furthermore, these can be used as starting points for policy makers and other relevant actors that take responsibility to develop implementation strategies for PCC.

In order to develop a tailored PCC program, the needs of specific populations should be known and resources should be in line with setting specific characteristics.

This consensus paper is based on current evidence. Biannual update on the evidence of preconception risk factors and management is recommended to keep the debate going. This debate is necessary to hold the commitment amongst the broad scope of professionals in the curative setting and the public health care setting to collaborate regarding PCC.

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# Chapter 4

## Evidence based preconceptional lifestyle interventions

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## ABSTRACT

Although the evidence for the associations between preconceptional risk factors and adverse pregnancy outcomes is extensive, the effectiveness of preconceptional interventions to reduce risk factors and to improve pregnancy outcomes remains partly unclear. The objective of this review is to summarize the available effectiveness of lifestyle interventions prior to pregnancy for women in terms of behavior change and pregnancy outcome. A predefined search strategy was applied in electronic databases and citation tracking was performed. Study selection was performed by two independent reviewers according to predefined criteria for eligibility: the intervention was performed preconceptionally on women regarding alcohol use, smoking, weight, diet/nutrition, physical activity, folic acid status (fortification and supplementation) to achieve behavior change and / or improve pregnancy outcome. Quality and strength of evidence were assessed by two independent reviewers. 4,604 potentially relevant records were identified of which 44 records met the inclusion criteria.

Overall, there is a relatively short list of core interventions for which there is substantial evidence of effectiveness when applied in the preconception period.

## INTRODUCTION

Worldwide efforts are made to reduce adverse pregnancy outcomes. As many women do not realize they are pregnant until the fifth week of pregnancy - when essential fetal processes have already commenced - the first antenatal visit is relatively late to address perinatal risk factors [1]. As these risk factors can mostly be identified, managed or treated when they are detected preconceptionally to prevent or limit fetal exposure, preconception care (PCC) has been identified as a promising form of care to improve pregnancy outcomes [2,3].

PCC is defined as *"A set of interventions that aim to identify and modify biomedical, behavioral, and social risks to a woman's health or pregnancy outcome through prevention and management, emphasizing those factors that must be acted on before conception or early in pregnancy to have maximal impact* [4]. *(p. S198)*.

Effective PCC interventions could be an opportunity to improve pregnancy outcomes. Although the amount of evidence for preconceptional risk factors associated with adverse pregnancy outcomes is growing, PCC is still largely based on the assumption that elimination of the risk factor will reduce the chances of adverse perinatal outcomes rather than on evidence for the effectiveness of the preconceptional interventions itself. Risk factors in PCC are very diverse, reflecting the diverse pathophysiology in the peri-conceptional period. Risk factors, from both parents, can be of genetic, environmental or behavioral origin. Therefore a broad approach in PCC is necessary to optimize perinatal health.

In many countries preconceptional health assessment focuses on women with pre-defined risk factors, such as diabetes. PCC is offered much less frequently to women in the general population without previously identified risk factors. Assessment of the general lifestyle and behavioral risks such as alcohol consumption, smoking, the use of drugs and nutritional diet and folic acid supplementation seems to be mostly offered to these women with predefined risk factors. More evidence is needed regarding the effectiveness of interventions aimed at general lifestyle risk factors which are applicable to a large proportion of the couples aiming to conceive. This evidence would help not only women with predefined risks but would also be a boost for implementation of PCC for the general population.

Furthermore, evidence for preconceptional health interventions is necessary to embed PCC as an available Health Service - for professionals and for couples wishing to conceive – amongst the general population. Also, concrete evidence is necessary to motivate policy makers, insurers and health care providers themselves. Although it is challenging to reach target groups for PCC, PCC is regarded to be a very welcome health service by couples wishing to conceive [5].

In order to address these general risk factors in PCC, evidence-based preconceptional interventions, to reduce or eliminate these general risk factors, are needed. Besides a Cochrane review in 2009 [6], restricted to randomized controlled trials (RCT's) no systematic review compromising observational studies has been conducted to address preconceptional lifestyle interventions for women. A systematic review including observational studies is deemed valuable as the majority and most prominent studies are observational due to the behavior changes which are included in PCC.

The objective of this review is to provide an up to date overview of the effectiveness of predefined lifestyle interventions on behavior change and improved pregnancy outcomes amongst preconceptional women in the general population.

## METHODS

### Search strategy

Studies were identified initially with an electronic search in the following databases: MEDLINE, EMBASE and Web of Science (from inception to March 2012, restricted to the following languages: English, Dutch, German, French, and Spanish; and humans). The electronic search encompassed keywords referring to the preconceptional time period, health care promotion or intervention, the mother/ father or couple, and predefined risk factors. The detailed search is available in the appendix (Appendix 1). Furthermore, citations of identified reviews were screened for eligible records.

### Study selection

The following criteria for eligibility were applied to select studies: (1) the study included any kind of intervention (e.g. varying form individual consultation to group education sessions performed preconceptionally) regardless of duration or amount of visits of preconceptional women, (2) the intervention focused on health promotion or on modification of any of the following risk factors: alcohol, smoking, weight, diet/nutrition, physical activity, folic acid fortification and folic acid supplementation (in relation to other anomalies than neural tube defects [NTDs]), and (3) reported outcome(s) were behavior change and/or risk factor modification and/or pregnancy outcome (e.g. miscarriages, birth defects, premature birth, birth weight, low birth weight and/or small for gestational age, and perinatal deaths). Regarding birth defects, development of NTDs was not regarded as an outcome for folic acid supplementation as this is already considered evidence-based in numerous studies [7]. Although fertility is an important outcome of preconceptional interventions, this was regarded as a subgroup of interventions and was not included in this systematic review. Records were assessed for eligibility based on title and abstract. The full manuscripts of these abstracts and of potentially relevant

articles identified with citation tracking were then evaluated to determine whether inclusion criteria were met. Additionally, identified reviews were screened for potentially relevant references. Study selection was performed independently by two reviewers (ST and SVV) with a third reviewer (SD) for adjudication of discrepancies.

### Data extraction

Predefined characteristics that were extracted were: title; author(s); aim; intervention (how, when and by whom) per group (if applicable); study design; inclusion and exclusion criteria; participant recruitment (time period of study, country, recruitment site, patient sampling method if specified); methods of randomization/ case or control selection/ matching if applicable; data collection/follow-up (prospectively or retrospectively, sources of data, method and timeframe of assessment and blinding when specified); flow chart of participants; loss to follow-up (number and reasons stated); baseline characteristics of the study population; setting of the intervention; definitions of pre-specified outcomes (of interest to this review) and the corresponding results (if applicable confounder adjusted estimates were given, with confounders for which was adjusted stated). Items were (largely) extracted from the STROBE Statement and the Cochrane Handbook [8,9]. In case of questions regarding these items, authors of the articles in question were contacted for clarification.



### Study quality and assessment of the strength of evidence

A quality assessment checklist was constructed based on the results of a systematic review evaluating tools for assessing quality and susceptibility to bias in observational studies and the Cochrane handbook regarding quality assessment for RCTs [9,10]. Nine criteria were used across five quality domains. The criteria for quality assessment can be found in the appendix (Appendix 2).

Studies were considered as highly susceptible to bias if two or more of the five domains were scored as susceptible to bias, or if three or more of the five domains were scored as unclear.

The strength of the evidence for each intervention was assessed by two reviewers (ST, SVV) according to predefined criteria adapted from the Canadian Task Force for Preventive Medicine [11]. In case of disagreement, a third reviewer (SD) was asked to resolve discrepancy. The applied classification for the strength of evidence can be found in the appendix (Appendix 2).

### Data analysis

Due to presumed clinical heterogeneity no attempt for a meta-analysis was pre-specified.

## RESULTS

### Study identification and selection

From the search for articles related to preconceptional lifestyle interventions in women and behavior change and/or risk factor modification and/or pregnancy outcome, 105 full-text articles were retrieved from 4,604 references (2,777 from Medline; 1,127 from Embase; 671 from Web of Science; and 29 references from reviews). After exclusion of 61 full-text articles for stated reasons, 44 articles fulfilled the selection criteria (Figure 1).

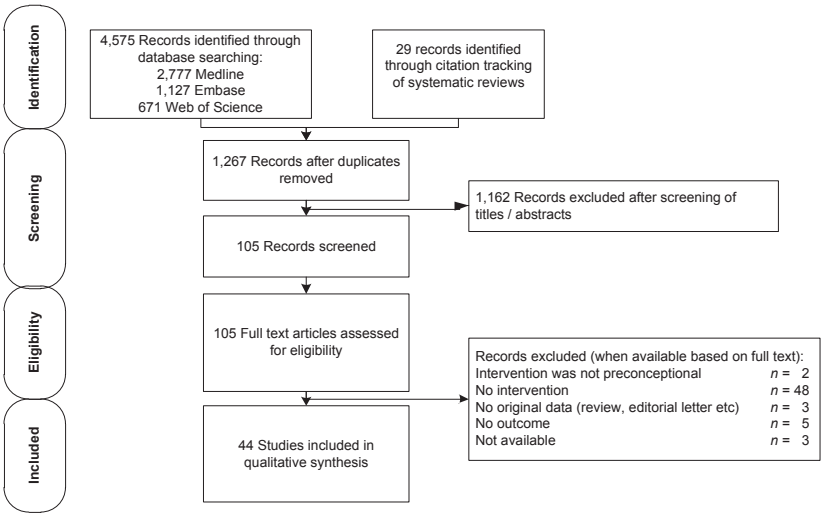


**Figure 1.** Flowchart: identification, screening and selection process of studies for inclusion in review

Table 1 summarizes the included studies. Results are classified as followed. Firstly, studies were grouped by the core risk factor that the interventions address and report. Multiple risk factor studies with multiple outcomes were classified separately. Rationale for this approach is to give a structured overview and classification between studies addressing and reporting a single risk factor versus multiple risk factor studies. Secondly, interventions were classified into individual (individual consultation of a patient/ couple), group based (consultation of patients/ couples performed in groups), or collective interventions (interventions targeted at a group of people as a whole, e.g. iodising salt in prevention of hypothyroidism) [12].

The majority of studies focused on individual interventions [13-38]; three studies focused on group interventions [39-41], one study focused on a mix of individual and group intervention [42] and 14 studies focused on collective interventions [43-56]. Of

**Table 1.** Characteristics of Studies Reporting on the Effectiveness of Preconceptional Interventions Included in This Systematic Review (N=44; 1987-2012; Australia, Canada, China, Denmark, Finland, France, Germany, Hungary, Israel, the Netherlands, Norway, UK, USA, USSR.)

| Study | | | | | Outcome | | |
|---|---|---|---|---|---|---|---|
| | Subject area | Intervention type | Study design | Study population (no.) | Behavioral change | Pregnancy outcome | High susceptibility to bias |
| Floyd, 2007 [36] | Alcohol | Individual | RCT | 830 | Self-reported | Not reported | |
| Czeizel, 1999 [29] | Smoking | Individual | Cohort | 8,837 | Biomarkers | Not reported | |
| Hughes, 2000 [38] | Smoking | Individual | RCT | 94 | Self-reported and biomarkers | Not reported | |
| De Weerd, 2001 [35] | Smoking | Individual | Cohort | 111 | Self-reported and biomarkers | Not reported | Yes |
| Caan, 1987 [34] | Nutrition | Individual | CC | 642 | Not reported | Yes | |
| Cena, 2008 [39] | Nutrition | Group | RCT | 155 | Self-reported | Not reported | |
| Doyle, 1999 [42] | Nutrition | Mixed individual and group | Cohort | 153 | Self-reported | Not reported | |
| Medical Research Council Vitamin Study Research Group, 1991 [13] | Folic acid | Individual: folic acid advice and provision | RCT | 1,817 | Not reported | Yes | Yes |
| Czeizel, 1992 [14] | Folic acid | Individual: folic acid advice and provision | RCT | 7,905 | Not reported | Yes | Yes |
| Czeizel, 1993 [15] | Folic acid | Individual: folic acid advice and provision | RCT | 7,905 | Not reported | Yes | Yes |

**Table 1.** Characteristics of Studies Reporting on the Effectiveness of Preconceptional Interventions Included in This Systematic Review (N=44; 1987-2012; Australia, Canada, China, Denmark, Finland, France, Germany, Hungary, Israel, the Netherlands, Norway, UK, USA, USSR.) (continued)

| Study | | | | Outcome | | | |
|---|---|---|---|---|---|---|---|
| | Subject area | Intervention type | Study design | Study population (no.) | Behavioral change | Pregnancy outcome | High susceptibility to bias |
| Czeizel, 1993 [16] | Folic acid | Individual: folic acid advice and provision | RCT | 4,753 | Not reported | Yes | |
| Czeizel, 1994 [17] | Folic acid | Individual: folic acid advice and provision | RCT | 7,905 | Not reported | Yes | Yes |
| Czeizel, 1996 [18] | Folic acid | Individual: folic acid advice and provision | RCT | 5,453 | Not reported | Yes | |
| Czeizel, 1998 [19] | Folic acid | Individual: folic acid advice and provision | RCT | 4,862 | Not reported | Yes | Yes |
| Rolschau, 1999 [21] | Folic acid | Individual: folic acid advice and provision | RCT | 14,021 | Not reported | Yes | |
| Ulrich, 1999 [22] | Folic acid | Individual: folic acid advice and provision | RCT | 8,184 | Not reported | Yes | |
| de Weerd, 2002 [28] | Folic acid | Individual: folic acid advice and provision | Cohort | 111 | Self-reported and biomarkers | Not reported | |
| Czeizel, 2003 [20] | Folic acid | Individual: folic acid advice and provision | RCT | 7,905 | Not reported | Yes | Yes |

**Table 1.** Characteristics of Studies Reporting on the Effectiveness of Preconceptional Interventions Included in This Systematic Review (N=44; 1987-2012; Australia, Canada, China, Denmark, Finland, France, Germany, Hungary, Israel, the Netherlands, Norway, UK, USA, USSR.) (continued)

| Study | Outcome | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Subject area** | **Intervention type** | **Study design** | **Study population (no.)** | **Behavioral change** | **Pregnancy outcome** | **High susceptibility to bias** |
| Czeizel, 2004 [23] | Folic acid | Individual: folic acid advice and provision | CCT | 6,138 | Not reported | Yes | |
| Watkins, 2004 [24] | Folic acid | Individual: folic acid advice and provision | Cohort | 1,093 | Self-reported and biomarkers | Not reported | |
| Robbins, 2005 [25] | Folic acid | Individual: folic acid advice and provision | RCT | 322 | Self-reported | Not reported | |
| Schwarz, 2008 [26] | Folic acid | Individual: folic acid advice and provision | RCT | 446 | Self-reported | Not reported | |
| Morgan, 2009 [27] | Folic acid | Individual: folic acid advice and provision | Cohort | 322 | Self-reported | Not reported | |
| Chan, 2001 [43] | Folic acid | Collective: public campaign | Cohort | 512 | Self-reported | Not reported | |
| Myers, 2001 [44] | Folic acid | Collective: public campaign | Cohort | 222,314 | Not reported | Yes | |
| Gindler, 2001 [45] | Folic acid | Collective: public campaign | Cohort | 23,806 | Not reported | Yes | |
| Gucciardi, 2002 [46] | Folic acid | Collective: fortification | Cohort | 3,207 (cases) | Not reported | Yes | |

**Table 1.** Characteristics of Studies Reporting on the Effectiveness of Preconceptional Interventions Included in This Systematic Review (N=44; 1987-2012; Australia, Canada, China, Denmark, Finland, France, Germany, Hungary, Israel, the Netherlands, Norway, UK, USA, USSR.) (continued)

| Study | Subject area | Intervention type | Study design | Study population (no.) | Outcome | | |
|---|---|---|---|---|---|---|---|
| | | | | | Behavioral change | Pregnancy outcome | High susceptibility to bias |
| Honein, 2001 [47] | Folic acid | Collective: fortification | Cohort | 13,786 (cases) | Not reported | Yes | |
| Persad, 2002 [48] | Folic acid | Collective: fortification | Cohort | 107,851 | Not reported | Yes | |
| Ray, 2002 [49] | Folic acid | Collective: fortification | Cohort | 218,977 | Not reported | Yes | |
| Williams, 2002 [50] | Folic acid | Collective: fortification | Cohort | 5,630 (cases) | Not reported | Yes | |
| CDC, 2004 [51] | Folic acid | Collective: fortification | Cohort | 5,200 (cases) | Not reported | Yes | |
| Liu, 2004 [55] | Folic acid | Collective: fortification | Cohort | 825 | Self-reported and biomarkers | Not reported | |
| Canfield, 2005 [53] | Folic acid | Collective: fortification | Cohort | 9,729,763 | Not reported | Yes | |
| Botto, 2006 [52] | Folic acid | Collective: fortification | Cohort | 1.5 million | Not reported | Yes | |
| Yazdy, 2007 [56] | Folic acid | Collective: fortification | Cohort | 45,926,398 | Not reported | Yes | |
| de Wals, 2007 [54] | Folic acid | Collective: fortification | Cohort | 1.9 million | Not reported | Yes | |
| Lumley, 2006 [30] | Multiple risk factors | Individual | RCT | 786 | Not reported | Yes | |

**Table 1.** Characteristics of Studies Reporting on the Effectiveness of Preconceptional Interventions Included in This Systematic Review (N=44; 1987-2012; Australia, Canada, China, Denmark, Finland, France, Germany, Hungary, Israel, the Netherlands, Norway, UK, USA, USSR.) (continued)

| Study | Outcome | | | | | | |
|---|---|---|---|---|---|---|---|
| | Subject area | Intervention type | Study design | Study population (no.) | Behavioral change | Pregnancy outcome | High susceptibility to bias |
| Elsinga, 2008 [31] | Multiple risk factors | Individual | RCT | 633 | Self-reported | Yes | |
| Hammiche, 2011 [37]; Hammiche, 2010; van Mil, 2010 | Multiple risk factors | Individual | Cohort | 419 | Self-reported and biomarkers | Not reported | |
| Ockhuijsen, 2012 [32] | Multiple risk factors | Individual | Cohort | 101 | Self-reported and biomarkers | Not reported | |
| Williams, 2012 [33] | Multiple risk factors | Individual | CSS | 9,457 | Self-reported | Not reported | |
| Hillemeier, 2008 [40] | Multiple risk factors | Group | RCT | 362 | Self-reported and biomarkers | Not reported | |
| Weisman, 2011 [41] | Multiple risk factors | Group | RCT | 315 | Self-reported | Not reported | |

RCT=Randomized Controlled Trial; CC=Cases control trial; CCT= Cohort controlled trial; CSS= Cross sectional study

the 44 studies identified, 25 of those studies reported on pregnancy outcome [13-23, 30, 34, 44-54, 56], 18 studies reported on behavior change regarding the risk behavior(s) [24-29, 32-33, 35-43, 55], and one study reported on both pregnancy and behavior change outcome [31]. Behavior change was most often based on self-reported outcomes [25-27, 31, 33, 36, 39, 41-43]; one study measured behavior change with biomarkers only [29] and eight studies measured behavior change using a combination of self-report and biomarkers [24, 28, 32, 35, 37-38, 40, 55]. 19 RCTs [13-22, 25-26, 30-31, 36, 38-41], 22 cohort studies [24, 27-29, 32, 35, 37, 42-56], one case control study [34], one cohort controlled trial [23], and one cross sectional study [33] were identified. Results are presented in Web Table 1 and discussed per (risk) behavior in the following section.

**Data extraction**

*Alcohol.* One RCT reported on the effectiveness of a program to reduce alcohol-exposed pregnancies by reducing risky drinking (eight drinks/week or >five drinks on one occasion) in women in which conception could occur [36]. Floyd et al. assessed the effectiveness of a prevention program consisting of four counselling sessions with personalized feedback and goal setting regarding risky drinking. Participants also received a counselling session on contraception. The comparison group received written information regarding alcohol risks and women's health. The study population N=830 consisted of women of childbearing age not planning pregnancy and were engaged in risky drinking. Women who received motivational counselling sessions and counselling about contraception had significantly higher odds to be at reduced risk for an alcohol-exposed pregnancy up to the nine months after the intervention (OR 2.11; 95% CI 1.47-3.03). This outcome is based on self-reported behavior change.

Since the trial was conducted in a population with a high-predefined risk of alcohol consumption, results are limited in generalizability. Regarding other criteria the study quality was good resulting in a low risk of bias overall. Considering the aims of the review, this study was not conducted specifically with women planning a pregnancy. The strength of evidence is I-a.

*Smoking.* Three studies reported on the effectiveness of the advice to quit smoking: one RCT [38] and two cohort studies [29,35].

One study assessed the effectiveness of a preconceptional health program in terms of behavior changes with a biomarker. Czeizel et al. 1999 assessed smoking cessation rates with urinary cotinine. The intervention, smoking cessation advice at a preconceptional consultation, resulted in a decrease of smoking rates after three months (17.9% vs. 12.4%). In Hughes et al., the effectiveness of a 'stage of change' oriented scripted handout and counselling at the hospital's cessation clinic was assessed. The comparison group received information about the impact of pre-pregnancy smoking. de Weerd et

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| **ALCOHOL** | | | | | |
| ***Individual interventions*** | | | | | |
| *Floyd, 2007 [1]* | Aim: To reduce the risk of an alcohol exposed pregnancy (AEP) in preconceptional women by focusing on both risk drinking and ineffective contraception use.<br>Intervention: The intervention group received four motivational counselling sessions (advice to reduce risky drinking, with personalised feedback and goal setting) by 21 trained counsellors and a contraception counselling visit about effective contraception use by six contraceptive care providers (physicians and family planning nurses) after the 2nd counselling session. The intervention took place within 14 weeks. Each session was 45-60 minutes.<br>The comparison group received written information on alcohol and women's health after randomization. Care provider: not specified. | Design: Randomized controlled trial.<br>In- exclusion criteria: (1) Women aged 18-44 years; (2) no condition causing infertility; (3) not pregnant or planning pregnancy in the next nine months; (4) had vaginal intercourse in the previous three months without effective contraception with a fertile man; (5) engaged in risky drinking (see 'Outcomes' for definition); and (6) available for the follow-up period.<br>Recruitment: Between 2002-2005 in the United States. Participant recruitment by flyers, newspapers, radio announcements, and presentations in jails and treatment centers (drug and alcohol treatment centers, suburban primary care practices, hospital-based gynecology clinic, a Medicaid health maintenance organization).<br>Randomization: Computer generated.<br>Data collection/Follow-up: Prospectively. Both groups were assessed at baseline, at three and at nine months in-person. With an abbreviated assessment at six months by telephone.<br>Instruments: questionnaire and daily journal.<br>Outcome assessor blinded. | Study population: Eligible n=1,035.<br>Included n=830 (intervention group n=416; comparison group n=414).<br>Loss to follow-up: n=125 in the intervention group; n=112 in the comparison group. Reasons not specified.<br>Baseline characteristics: intervention vs. comparison group mean age 29.8 years vs. 29.5 years; single 51.4% vs. 50.5%; DSM IV criteria for alcohol dependence 55.3% vs. 56.5%; drug use in the past 12 months 93.5% vs. 91.5%.<br>Setting: Community-based, where the intervention was delivered is not specified. | Outcomes: Odds for reduced risk drinking (>eight drinks/week or >five drinks on one occasion) and AEP (risky drinking and ineffective contraception).<br>Results:<br>Women in the intervention group had higher odds to be at reduced risk for risk drinking:<br>- At three months follow-up (*aOR 1.79; 95% CI 1.28-2.51);<br>- At six months follow-up (*aOR 1.64; 95% CI 1.15-2.33); and<br>- At nine months follow-up (*aOR 1.54; 95% CI 1.09-2.18).<br>Women in the intervention group had higher odds to be at reduced risk for an AEP:<br>- At three months follow-up (*aOR 2.32; 95% CI 1.69-3.20);<br>- At six months follow-up (*aOR 2.15; 95% CI 1.52-3.06); and<br>- At nine months follow-up (*aOR 2.11; 95% CI 1.47-3.03).<br><br>*aOR= adjusted OR, confounders: number of male intercourse partners, scores on alcohol questionnaires. | I-a |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| **SMOKING** | | | | | |
| ***Individual interventions*** | | | | | |
| *Czeizel, 1999 [2]* | Aim: To evaluate the effect of ten years preconception care on smoking cessation.<br>Intervention: All women attending a Hungarian Family Planning Program (HFPP) received a check-up of reproductive health, a three months preparation for conception (smoking cessation, alcohol drinking, drug and medication use) and better protection in early pregnancy with immediate prenatal care. Care provider: qualified nurses. | Design: Cohort study.<br>In- exclusion criteria: Voluntary of non-pregnant and non subfertile women.<br>Recruitment: Between 1984 and 1994 in Hungary. Recruitment sites were from the Hungarian Preconceptional clinics by physicians, midwives, nurses and social workers.<br>Data collection/ Follow-up: Prospectively. Four visits to a preconception care clinic (of which the third and fourth occurred during pregnancy) with laboratory testing and data collection of pregnancy outcome by birth certificate. | Study population: Eligible n=not reported. Included n=8,837 of which n=6,060 confirmed pregnancies.<br>Loss to follow-up: Not reported.<br>Baseline characteristics: Mean age 25.8 years ± 3.4, 85% was primiparous, 60% had the highest class of education.<br>Setting: Outpatient clinic. | Outcomes: Smoking cessation (verified by urine cotinine).<br>Results: At initial consultation 17.9% was a smoker vs. 12.4% three months later. | II-2 |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Hughes, 2000 [3]* | Aim: To assess a "stage of change" oriented smoking cessation intervention for infertile and pregnant women, compared with standard of care. Intervention: The intervention group received scripted advice, "stage-of-change" specific information booklet discussion on the effects of smoking on fertility, and a referral to a smoking cessation clinic was offered. The control group received 'standard care' about the impact of smoking. Care provider: physicians and nurses. | Design: Randomized controlled trial.<br>In- exclusion criteria: (1) Women who had smoked ≥three cigarettes in the past six months; and (2) not attending for genetic counselling or habitual abortion.<br>Recruitment: Between 1996-1999 in Canada. Newly referred patients at infertility and prenatal clinic were recruited.<br>Randomization: Computer generated, block randomization.<br>Data collection/ Follow-up: Prospectively. Questionnaire (baseline and 12 months) and exhaled carbon monoxide measurements (at six and twelve months) for both groups. | Study population: Eligible n=not specified. Included n=94 infertile women (intervention group n=47; comparison group n=47) and n=110 pregnant women (intervention group n=56; comparison group n=54).<br>Loss to follow-up: None.<br>Baseline characteristics: Infertile, intervention vs. comparison group mean age 32.13 years vs. 32.15 years; age first smoked 14.93 years vs. 15.09 years; age regular smoked 17.33 years vs. 17.30 years; number of months infertile 38.08 vs. 37.83; current number of cigarettes smoked 12.19 vs. 13.80, number of quit attempts 2.40 vs. 3.40, "stage-of-change" at enrolment 2 vs. 3.<br>Pregnant, intervention vs. comparison group mean age 26.34 years vs. 25.43 years; age first smoked 13.66 years vs. 14.51 years; age regular smoked 15.20 years vs. 16.36 years; current number of cigarettes smoked 13.43 vs. 12.00, number of quit attempts 3.62 vs. 2.41, gestation at enrolment (w) 18.91 vs. 20.55; "stage-of-change" at enrolment 3 vs. 4.<br>Setting: Infertility and prenatal clinic at three university teaching hospitals. | Outcomes: Self-identified "stage-of-change" and rate of maintenance of cessation after twelve months.<br>Results:<br>Intervention and comparison were similarly effective amongst infertile and pregnant women; the rate of maintained cessation rose significantly from 4% to 24% over twelve months, with a mean delta "stage-of-change" 0.28. | I-a |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *De Weerd, 2001 [4]* | Aim: To evaluate a smoking cessation advice given before pregnancy on smoking behavior.<br>Intervention: Smoking cessation advice (content not specified) during a preconceptional consultation three-four monthly. Care provider: not specified. | Design: Cohort study.<br>In- exclusion criteria: Non-pregnant women scheduled for a preconception care appointment in the fertility clinic.<br>Recruitment: Between 1997 and 1999 in the Netherlands. Women scheduled for an appointment were approached by letter for inclusion. Patient sampling: consecutively.<br>Data collection/ Follow-up: Prospectively. Questionnaire and serum cotinine at baseline and four-six weeks later and every three-four months until the sixth, eighth and twelfth week of pregnancy. | Study population: Eligible n=not specified. Included n=111 of which 16 self-reported smokers and 24 smokers based on cotinine in the serum ((cotinine >5µg/L).<br>Loss to follow-up: n=33 in the initially included population. Reasons not specified.<br>Baseline characteristics: not specified.<br>Setting: Tertiary care. | Outcomes: Smoking cessation or reduction by self-report and by cotinine levels.<br>Results: No self-reported smoking cessation, however 88% of self-reported smokers and 75% of cotinine validated smokers reduced smoking. | II-2 |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| **NUTRITION** | | | | | |
| ***Individual interventions*** | | | | | |
| *Caan, 1987 [5]* | Aim: To evaluate the postpartum component of the California WIC program and effects on birth outcomes.<br>Intervention: Intervention group received WIC support (food supplementation and nutrition education) during prior pregnancy and five to seven months postpartum. The comparison group received WIC support (food supplementation and nutrition education) during prior pregnancy and up to two months postpartum. Care provider: trained professionals at the local Californian WIC agencies. | Design: Case-control study.<br>In- exclusion criteria: (1) Women that had received WIC support during their first pregnancy (based on nutritional and medical risk of themselves or of their children); (2) gave birth to their first infant after August 1981; and (3) not to have breast fed her first infant.<br>Recruitment: Between 1981 and 1983 in the United States. Recruitment sites were 48/86 local WIC agencies. Patient sampling: consecutively.<br>Data collection/ Follow-up: Retrospectively and prospectively. Demographic and clinical data were obtained at enrolment and from old WIC records. The women were then prospectively followed throughout their 2nd pregnancy until shortly after delivery. Data on birth outcome was collected. Source and method of data collection not specified in either group. | Study population: Eligible n =897. Included n=642 (cases n=333; controls n=309).<br>Loss to follow-up: n=178 due to missing outcome data and n=16 because of foetal death or multiple birth.<br>Baseline characteristics: Cases vs. controls Race: Whites 17% vs. 26%, Blacks 8% vs. 10%, Hispanics 65% vs. 37%, Southeast Asians 7% vs. 26%, Native Americans 3% vs. 2%; parity one liveborn 46% vs. 38%, >one liveborn 54% vs. 63%; birth weight of first child (g) 3349 vs. 3277; birth interval (days) 618 vs. 533.<br>Setting: 48/86 urban and rural local WIC agencies. | Outcomes: The impact of five to seven months of WIC support compared to up to two months of WIC support on infant outcomes (birth weight, birth length, birth weight adjusted for gestational age) and maternal outcomes (quetelet index on onset of 2nd pregnancy).<br>Results:<br>Infant outcomes:<br>Five to seven months of WIC participation was associated with a positive effect on:<br>- Birth weight (grams):* 3468±30,0 vs. 3337±31.1; p=0,003<br>- Birth weight (grams) adjusted for gestational age:*3461±26, 6 vs. 3341±27, 8; p=0,003.<br>- Birth length (inch):*19,8±0,076 vs. 20,1±0,008; p=0,01.<br><br>Maternal outcomes:<br>Five to seven months of WIC participated women had a **4.5% lighter body mass.<br><br>* Correction was applied for parity, pregravid maternal weight height, infant sex, birth weight of last infant, race, and smoking status.<br>** Correction was applied for race. Maternal age, number of household members, interbirth interval, birth weight of the first infant, weight status during first pregnancy, and smoking status of the mother. | II-2 |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| ***Group interventions*** | | | | | |
| *Cena, 2008 [6]* | Aim: To evaluate the effectiveness of a learner-centered, folate-focused nutrition lesson on folate intake and food-related behaviors, that is targeted toward low-income, nonpregnant women of childbearing age.<br>Intervention: The intervention group underwent a learner-centered nutrition lesson with group discussions, participatory activities, worksheets, visual aids, cooking demonstrations, and instructor explanations regarding recommended folate intake and supplementation. The control group received a lesson about resource management.<br>The assigned lessons (2.5 hours of length, in English or Spanish) were conducted by trained Food Stamp Nutrition Educators (FSNE) after baseline data collection. | Design: Randomized controlled trial.<br>In- exclusion criteria: (1) Non-pregnant women with a low-income (<185% of federal poverty level); (2) aged 18-45 years; (3) English or Spanish understanding and reading; and (4) primary purchaser of food for herself or her family.<br>Recruitment: Starting in 2006 (duration unclear) in the United States. The study's 15 recruitment sites were Food Stamp Program offices; WIC clinics; low-income schools; and community programs that serve low-income families or individuals.<br>Randomization: Recruitment sites were randomly assigned.<br>Data collection/ Follow-up: Prospectively. For both groups, at baseline and four weeks after each lesson, by questionnaires. | Study population: Eligible n=203. Included n=155 (intervention group n=77; comparison group n=78).<br>Loss to follow-up: N=2. Group and reason not specified.<br>Baseline characteristics: mean age 31.6±0.5 years (controls approximately 2 years older); ethnicity Hispanic (n=89), White (n=56), Native American/Alaskan native (n=6), Asian/ Pacific Islander (n=2), and mixed (n=4). Group not specified.<br>Setting: At the recruitment sites or at the local FSNE program office. | Outcomes: Change in folate intake (natural food folate, synthetic folic acid from fortified foods, synthetic folic acid from supplements, total synthetic folic acid, and total folate from all sources) and food related behaviors from baseline (before assigned lesson) to follow-up (four weeks after lesson).<br>Results:<br>- Participants who attended the folate-focused nutrition lesson had significantly greater increases in *baseline-adjusted natural food folate intake (p=0.009) and *baseline-adjusted total folate from all sources (p=0.045).<br>- Other results (synthetic folic acid from fortified foods, synthetic folic acid from supplements, and total synthetic folic acid) were not significantly different.<br><br>*Adjustment occurred for: age, ethnicity, county of residence, receipt of food stamps, and WIC participation | I-a |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| ***Mixed individual and group interventions*** | | | | | |
| *Doyle, 1999 [7]* | Aim: To evaluate the effectiveness of a nutrition counselling program during the interpregnancy interval for women with further pregnancy intention.<br>Intervention: Nutritional assessment followed by four to six weekly consultations by dieticians and co-workers from corresponding ethnic backgrounds about to strive to attain Reference Nutritional Intakes (RNI); monthly educational group events, including budget cooking demonstrations, talks on nutrition and a visit to the nearby supermarket to discuss choosing healthy alternatives; and two newsletters with key nutrition messages, a feature of one of the recruited mothers and news about the progress of the study. | Design: Cohort study.<br>In- exclusion criteria: (1) Mothers who had delivered a singleton baby weighing <2.5 kg (independent of gestational age); (2) who intended to have further pregnancies; (3) and whose diets were assessed as being inadequate.<br>Recruitment: Between 1995 and 1996 in the United States. Women were recruited during postpartum hospital stay.<br>Data collection/ Follow-up: Prospectively. Seven-day diet diary at baseline in the hospital and six months later. | Study population: Eligible n=153. Included n=111.<br>Loss to follow-up: n=70 women did not fill in the follow-up dietary diary.<br>Baseline characteristics: mean age 29.1; ethnic origin African 27%, Asian 12%, Caucasian 41%, and West Indian 20%.<br>Setting: Mother and Baby clinic. | Outcomes: Changes in dietary intake (Reference Nutritional Intakes) before and after the dietary intervention period.<br>Results:<br>Post-intervention:<br>- A significant increase in the intake of protein, zinc, niacin equivalents and vitamin B6.<br>- A small increase in the proportion of mothers who met the dietary reference values for energy and for 11 of the 15 nutrients considered (significance not tested).<br>- A significant trend towards a higher nutrient density for protein, minerals and most vitamins, particularly niacin equivalents and vitamin B6. | II-2 |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| **FOLIC ACID** | | | | | |
| ***Individual interventions: folic acid advice and provision*** | | | | | |
| *Medical Research Council Vitamin Study Research Group, 1991 [8]* | Aim: To assess the efficacy of folic acid and/ or multivitamin supplementation in the prevention of neural tube defects (NTDs)<br>Intervention: The following groups were composed: (A) mineral+ folic acid, (B) mineral + folic acid + multivitamin, (C) mineral + placebo, (D) mineral + multivitamin (no folic acid). After randomisation, women were asked to take a single capsule each day until 12 weeks of pregnancy (estimated from the first day of last menstrual period). Care provider: not specified. | Design: Randomized controlled trial.<br>In-exclusion criteria: (1) Women with a previous pregnancy affected by NTDs (not associated with the autosomal recessive disorder or Meckel's syndrome); (2) planning another pregnancy; (3) not already taking vitamin supplements; and (4) not having epilepsy.<br>Recruitment: Between 1983 and 1991 from 33 participating centres (17 in the UK and 16 in six other countries).<br>Randomization: At random, method not specified.<br>Data collection/ Follow-up: Prospectively, double blind. At baseline, urine and blood samples for all groups. Clinical follow-up for all groups was three monthly until the twelfth week of pregnancy. At each visit a note of their general health was made; number of capsules taken was counted; and blood and urine samples were taken. Outcome of pregnancies and health in first years of life was assessed with annual questionnaires for all groups. | Study population: Eligible n=not specified. Included n=1,817 (group A n=449, group B n=461, group C n=454, group D n=453).<br>Loss to follow-up: Not reported.<br>Baseline characteristics: Not specified, however groups were comparable regarding age and a NTD in a prior pregnancy.<br>Setting: At 33 international hospitals. | Outcomes: Comparison of miscarriage rates (not defined) in groups A+B vs. C+D.<br>Results:<br>No significant differences were seen: RR=1.06; 95% CI 0.79-1.43, p=0.70. | I-a |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Czeizel, 1992 [9]; Czeizel, 1993 [10] ; Czeizel, 1994 [11]; and Czeizel, 2003 [12]* | Aim: To assess the efficacy of preconceptional multivitamin use in reduction of first occurrence of NTDs and other congenital defects.<br>Intervention: All women attending a Hungarian Family Planning Program (HFPP) received a check up of reproductive health, a three month preparation for conception, including vitamin or trace-element supplementation and protection of very early pregnancy with immediate prenatal care. At the first meeting, the intervention group received a box with multivitamin tablets (0.8 mg folic acid, twelve vitamins, four minerals and 3 trace elements) with recommendation for 1 tablet a day preconceptional up to at least the second missed menstrual period. The control group was recommended to take a tablet with trace elements (manganese, copper, zinc and a low dose of vitamin C) daily until pregnancy.<br>Care provider: qualified nurses. | Design: Randomized controlled trial.<br>In- exclusion criteria: (1) Women < 35 years planning pregnancy; (2) no delayed conception (>12 months of sexual activity without contraception) or infertility; (3) no pregnancy yet; (4) voluntary participation; and (5) a promise of compliance with the HFPP.<br>Recruitment: Between 1984 and 1996 in Hungary. Recruitment sites were the 26 Hungarian family planning clinics.<br>Randomization: Patients were asked if they agreed to their allocation on the basis of the randomization table.<br>Data collection/ Follow-up: Prospectively. Clinical follow-up was three monthly until pregnancy. Self-reported supplement use by questionnaires and number of tablets left was assessed. Pregnancy was confirmed by a sensitive serum pregnancy test and by ultrasonography. At the 12$^{th}$ week of pregnancy women were referred for routine antenatal care. Pregnancy outcomes were collected from certificates filled in by women and verified by their physician. Follow-up regarding congenital abnormalities included a physical examination performed 'blind' by two paediatricians. For both groups the same data collection method was applied. The trial was double blind. | Study population: N= 7,905 participants in n=5,502 women a pregnancy was confirmed (n=2,793 in the intervention group; n= 2,660 in the control group).<br>Loss to follow-up: 49/5,502 pregnancy outcomes could not be clarified.<br>Baseline characteristics: intervention vs. trace element group: age (mean years; ±SD) 27, ±3 vs. 27± 3; primiparous 88% vs. 89%; prepregnancy body weight 57.1kg ±7.7kg vs. 57.3 ±7.3 kg.<br>Setting: Outpatient clinics. | Outcomes: Pregnancy outcome: termination rates, miscarriage rate (undefined), still birth (> 28 weeks GA), live birth rate, low birth weight rate (not defined), preterm birth rate (not defined).<br>Results:<br>Birth outcomes:<br>- First trimester termination: n=6 (0.2%) vs. n=6 (0.2%); second trimester termination after diagnosis of fetal defect: n=3 (0.1%) vs. n=13 (0.5%).<br>- Miscarriage: n=301 (10.8%) vs. n=251 (9.4%) ($X^2$=2.69, p=0.10)<br>- Stillbirth n=11 (0.4%) vs. n=9 (0.3%).<br>- Live birth: n=2410 (86.3%) vs. n=2337 (n=87.9).<br>- Low birth weight rate: n-178 (7.5%) vs. n=166 (7.2%) ($X^2$=1.86, p=0.17).<br>- Preterm birth n=178 (7.5%) vs. n=166 (7.2%) ($X^2$=0.21, p=0.64).<br>Congenital anomalies: in the article of Czeizel, 1992; Prevalences of congenital malformations intervention group (n=2104 in this subset) vs. comparison group (n=2052 in this subset):<br>- Cardiovascular malformation: n=6 vs. n=9.<br>- Cleft lip and/or palate: n=4 vs. n=5.<br>- Hypospadias: n=1 vs. n=1.<br>- Obstructive defects of urinary system n=1 vs. n=2.<br>- Congenital postural deformity: n=2 vs. n=0.<br>- Limb reduction defect: n=1 vs. n=5;<br>- Foramina parietale permagna: n=0 vs. n=2.<br>- Exomphalos and gastroschisis: n=1 vs. n=1.<br>- Hemangioma in the face: n=3 vs. n=1.<br>- Other: n=4 vs. n=7. | I-A |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Czeizel, 1993 [13]* | Aim: To assess the effect of periconceptional multivitamin supplementation on NTDs and other congenital abnormalities.<br>Intervention: All women attending a Hungarian Family Planning Program (HFPP) received a check up of reproductive health, a three month preparation for conception, including vitamin or trace-element supplementation and protection of very early pregnancy with immediate prenatal care.<br>At the first meeting, the intervention group received a box with multivitamin tablets (0.8 mg folic acid, twelve vitamins, four minerals and 3 trace elements) with recommendation for 1 tablet a day preconceptional up to at least the second missed menstrual period.<br>The control group was recommended to take a tablet with trace elements (manganese, copper, zinc and a low dose of vitamin C) daily until pregnancy.<br>Care provider: qualified nurses. | Design: Randomized controlled trial.<br>In- exclusion criteria: (1) Women < 35 years planning pregnancy; (2) no delayed conception (>12 months of sexual activity without contraception) or infertility; (3) no pregnancy yet; (4) voluntary participation; and (5) a promise of compliance with the HFPP.<br>Recruitment: Between 1984 and 1992 in Hungary. Recruitment sites were the 26 Hungarian family planning clinics.<br>Randomization: Patients were asked if they agreed to their allocation on the basis of the randomization table.<br>Data collection/ Follow-up: Prospectively. Clinical follow-up was three monthly until pregnancy. Self-reported supplement use by questionnaires and the number of tablets left was assessed. Pregnancy was confirmed by a serum pregnancy test and by ultrasonography. Pregnancy outcomes were collected from certificates filled in by women and verified by their physician. Follow-up regarding congenital abnormalities included a physical examination performed 'blind' by two paediatricians.<br>Data collection method and timeframe was equal in both groups. The trial was double blind. | Study population: Eligible n=4,753 confirmed pregnancies (intervention group n=2,420; comparison group n=2,333). Included n=4,156 women (intervention group n=2,104; comparison group n=2,052) and n=3,713 infants (intervention group n=1,876; comparison group n=2,032).<br>Loss to follow-up: 13% in the intervention group and 12% in the comparison group did not report pregnancy outcomes.<br>Baseline characteristics: intervention vs. comparison group mean maternal age 26.8 vs. 26.7 years; primiparous women 94.5% vs. 94.0%<br>Setting: Outpatient clinics. | Outcomes: Number of major and mild congenital abnormalities.<br>Results:<br>- The rate of major congenital abnormalities other than NTDs and genetic syndromes was 9.0/1000 in pregnancies with known outcome in the vitamin group and 16.6/1000 in the trace element group (RR=1.85; 95% CI 1.02-3.38), difference 7.6/1000.<br>- The rate of all major congenital abnormalities other than NTDs and genetic syndromes diagnosed up to the eight month of life was 14.7/1000 informative pregnancies in the vitamin group and 28.3/1000 in the trace element group (RR=1.95; 95% CI 1.23-3.09), difference 13.6/1000. | I-a |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Czeizel, 1996 [14]* | Aim: To assess the effect of periconceptional multivitamin supplementation on NTDs and other congenital abnormalities.<br>Intervention: All women attending a Hungarian Family Planning Program (HFPP) received a check up of reproductive health, a three month preparation for conception, including vitamin or trace-element supplementation and protection of very early pregnancy with immediate prenatal care. At the first meeting, the intervention group received a box with multivitamin tablets (0.8 mg folic acid, twelve vitamins, four minerals and 3 trace elements) with recommendation for 1 tablet a day preconceptional up to at least the second missed menstrual period. The control group was recommended to take a tablet with trace elements (manganese, copper, zinc and a low dose of vitamin C) daily until pregnancy.<br>Care provider: qualified nurses. | Design: Randomized controlled trial.<br>In- exclusion criteria: (1) Women < 35 years planning pregnancy; (2) no delayed conception (>12 months of sexual activity without contraception) or infertility; (3) no pregnancy yet; (4) voluntary participation; (5) a promise of compliance with the HFPP; and (6) infants with no minor anomalies.<br>Recruitment: Between 1984 and 1992 in Hungary. Recruitment sites were the 26 Hungarian family planning clinics.<br>Randomization: Patients were asked if they agreed to their allocation on the basis of the randomization table.<br>Data collection/ Follow-up: Prospectively. Clinical follow-up was three monthly until pregnancy. Self-reported supplement use by questionnaires and number of tablets left was assessed. Pregnancy was confirmed by a blood pregnancy test and by ultrasonography Pregnancy outcomes were collected from certificates filled in by women and verified by their physician. Follow-up regarding congenital abnormalities included a physical examination performed 'blind' by two paediatricians. Data collection method and timeframe was equal in both groups. The trial was double blind. | Study population: Eligible n=5,502 confirmed pregnancies (intervention group n=2,819; comparison group n=2,683). Included n=5,453 women (intervention group n=2,793; comparison group n=2,660) and 4,862 infants (intervention group n=2,471; comparison group n=2,391).<br>Loss to follow-up: Dropout rate 0.9% in both groups. Reasons not specified.<br>Baseline characteristics: intervention vs. comparison group mean maternal age 26.9 vs. 26.9; primiparous women 88.3% vs. 89.9%.<br>Setting: Outpatient clinics. | Outcomes: Number of major congenital abnormalities.<br>Results:<br>- Major congenital abnormalities rate in the intervention group: RR=0.51; 95% CI 0.36-0.71, p<0.0001.<br>- After the exclusion of NTDs, the rate for a major congenital abnormality in the intervention group: RR=0.54; 95% CI 0.39-0.76, p=0.0003. | I-a |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Czeizel, 1998 [15]* | Aim: To assess the effect of periconceptional multivitamin use on birth defects.<br>Intervention: All women attending a Hungarian Family Planning Program (HFPP) received a check up of reproductive health, a three month preparation for conception, including vitamin or trace-element supplementation and protection of very early pregnancy with immediate prenatal care. At the first meeting, the intervention group received a box with multivitamin tablets (0.8 mg folic acid, twelve vitamins, four minerals and 3 trace elements) with recommendation for 1 tablet a day preconceptional up to at least the second missed menstrual period. The control group was recommended to take a tablet with trace elements (manganese, copper, zinc and a low dose of vitamin C) daily until pregnancy.<br>Care provider: qualified nurses. | Design: Randomized controlled trial.<br>In- exclusion criteria: (1) Women < 35 years planning pregnancy; (2) no delayed conception (>12 months of sexual activity without contraception) or infertility; (3) no pregnancy yet; (4) voluntary participation; and (5) a promise of compliance with the HFPP.<br>Recruitment: Between 1985 and 1993 in Hungary. Recruitment sites were the Hungarian family planning clinics.<br>Randomization: Patients were asked if they agreed to their allocation on the basis of the randomization table.<br>Data collection/ Follow-up: Prospectively. Clinical follow-up was three monthly until pregnancy. Self-reported supplement use by questionnaires and number of tablets left was assessed. Pregnancy was confirmed by a blood pregnancy test and by ultrasonography. Pregnancy outcomes were collected from certificates filled in by women and verified by their physician. Follow-up regarding congenital abnormalities included a physical examination performed 'blind' by two paediatricians. For both groups the same data collection method was applied. The trial was double blind. | Study population: Eligible n=not specified. Included n=4,862 (intervention group n=2,471; comparison group n=2,391).<br>Loss to follow-up: Intervention group 0.9%, comparison group 0.9%. Reasons not specified.<br>Baseline characteristics: Not reported.<br>Setting: 26 Hungarian family planning clinics. | Outcomes: Birth defects.<br>Results: Daily maternal periconceptional multivitamin use was associated with:<br>- A non-significant risk reduction for orofacial clefts: OR=0.77; 95% CI 0.22-2.69.<br>- A non-significant increased risk for cleft lip with or without cleft palate: OR=1.29; 95% CI 0.32-5.22.<br>- A non-significant risk reduction for cleft palate only: OR=0.19; 95% CI 0.01-4.03.<br>- A significant risk reduction for heart defects: OR= 0.42; 95% CI 0.19-0.98.<br>- A non-significant risk reduction for outflow tract defects: OR= 0.48; 95% CI 0.04-5.34.<br>- A significant risk reduction for conotruncal defects: OR= 0.29; 95% CI 0.09-0.97.<br>- A non-significant risk reduction for limb deficiencies: OR=0.19; 95% CI 0.03-1.18.<br>- A non-significant risk reduction for hypertrophic pyloric stenosis: OR=0.24; 95% CI 0.05-1.14.<br>- A significant risk reduction for urinary tract defects: OR= 0.21; 95% CI 0.05-0.99.<br>- A significant risk reduction for obstructive and renal agenesis: OR=0.12; 95% CI 0.02-0.69. | I-a |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Rolschau, 1999 [16]* | Aim: To study the effect of two doses of folic acid supplementation on birth outcomes.<br>Intervention: After randomization, the intervention group received free folic acid supplements (2.5 mg) for daily use. The comparison group received free folic acid supplements (1,0 mg) for daily use.<br>Care provider: midwives, obstetricians, paediatricians, departments of obstetrics and most general practitioners. | Design: Randomized controlled trial.<br>In- exclusion criteria: (1) Women aged 18-35; (2) planning pregnancy or already pregnant; (3) registered resident in the county of Funen; (4) not having a prior baby with a NTD; and (5) no multiple pregnancy or abortion.<br>Recruitment: Between 1983 and 1986 in Denmark. Recruitment sites were population-based by campaigns (mailings, media, and involved health care professionals).<br>Randomization: Not specified. Not all women were randomized.<br>Data collection/ Follow-up: Prospectively. A registration form was completed by the general practitioner/ midwife/ doctor and kept by the pregnant woman. Length of follow-up: up to the infant's medical examination at 5 months. For both groups the same data collection method was applied. | Study population: Eligible n=14,533 pregnancies in 8,184 women. Randomized n=8,184 women (intervention group n=2,310; comparison group n=. Included n=14,021 women and n=13,860 single born infants.<br>Loss to follow-up: Not accounted for.<br>Baseline characteristics: Not reported.<br>Setting: GP or midwife practices and the Obstetric Department of Odense University Hospital. | Outcomes: Birth weight, incidence of preterm, low birth weight (≤2,500 gram) and small for gestational age (weight for gestational age <2SD than the average, excluding congenital anomalies and stillborn).<br>Results:<br>Intervention vs. comparison group vs. no folic acid:<br>- Birth weight at gestational age: no significant differences in gestational weight (results not given); when folic acid was started preconceptionally gestational birth weight was higher.<br>- Preterm birth (excluding congenital abnormalities and perinatal deaths): no difference between different doses.<br>- Low birth weight: 40.9% vs. 51.5% and 59.8%, p=0.01. There was no difference between users of 2.5 mg and 1.0 mg folic acid<br>- SGA: 14.7‰ when folic acid was started preconceptionally and 17.4‰ when started during the first 19 weeks of pregnancy. No difference was observed between 2.5 mg and 1.0 mg folic acid. | I-a |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Ulrich, 1999 [17]* | Aim: To study the prevalence of congenital abnormalities in a subset of Rolschau 1999.<br>Intervention: See Rolschau 1999. | Design: Subset of the study of Rolschau 1999, a randomized controlled trial.<br>In- exclusion criteria: See Rolschau 1999.<br>Recruitment: See Rolschau 1999.<br>Randomization: Only randomized women in Rolschau 1999 were included in this subset.<br>Data collection/ Follow-up: Complementary to the data collection for Part I of the study (see Rolschau 1999) information on congenital malformations was extracted for both groups from (1) the European Registration of Congenital Anomalies and Twins (Eurocat) and, (2) hospital records. | Study population: Eligible=see Rolschau 1999. Included n=8,293 infants born from 8,184 pregnancies.<br>Loss to follow-up: Not accounted for.<br>Baseline characteristics: Not reported.<br>Setting: See Rolschau 1999. | Outcome: Selected congenital anomalies (neural tube defects (omitted from our report) cardiovascular anomaly, limb reduction defects, urinary tract anomalies, oral clefts, talipes, hypospadias).<br>Results: 2.5 mg folic acid vs. 1.0 mg folic acid:<br>- Cardiovascular anomalies: 15/4165 vs. 12/4128 vs. 13/2742.<br>- Limb reduction defects: 1/4165 vs. 2/4128 vs. 2/2742.<br>- Urinary tract anomalies: 9/4165 vs. 4/4128 vs. 2/2742.<br>- Oral clefts: 13/4165 vs. 7/4128 vs. 6/2742.<br>- Talipes: 3/4165 vs. 6/4128 vs. 6/2742.<br>- Hypospadias: 5/4165 vs. 7/4128 vs. 5/2742. | I-a |
| *de Weerd, 2002 [18]* | Aim: To assess whether counselling to start or continue with folic acid supplementation improves folate status.<br>Intervention: Assessing prepregnancy risk factors during the intake visit. After 4-6 weeks, at the counselling visit preconceptional advice was given to take multivitamin containing 400µg of folic acid daily until eight weeks of conception and provision of the tablets as part of a preconceptional health program containing health promotion (smoking cessation, nutritional habits, and information on the antenatal care system). Care provider: physicians. | Design: Cohort study.<br>In- exclusion criteria: Women planning pregnancy and visiting preconception care clinic (because of previous obstetric complications or other maternal risk factors) or fertility clinic.<br>Recruitment: Between 1997 and 1999 in the Netherlands. Recruitment sites were the fertility clinic or preconception care clinic.<br>Data collection/ Follow-up: Prospectively. A questionnaire at baseline and blood samples (red cell and serum folate levels) before the first consultation and every three - four months after counselling and in the sixth, eighth and twelfth week of pregnancy. | Study population: Eligible n=168. Included n=111.<br>Loss to follow-up: n=33. Reasons not specified.<br>Baseline characteristics: mean age (±SD) 32.5 ±3.5 years; nulliparous 59.5%; White race 97.3%; education level low 13.3%, middle 40%, high 23.8%.<br>Setting: University hospital. | Outcomes: Changes in self-reported folic acid supplementation (any frequency) and red cell folate level (user status was defined as ≥590 nmol/L) and serum folate (user status defined as levels ≥20 nmol/L).<br>Results:<br>- Self-reported supplement use four months after counselling: 54% (compared to 56% of the women at baseline).<br>- Red cell folate level amongst non-users four months after counselling: 680 nmol/L (SD 52 nmol/L) (compared to 540 nmol/L SD± 30 nmol/L). P<0.01.<br>- After one year no significant changes were seen in folate status compared to initial precounselling folate levels: women that already used supplementation precounselling maintained their folate use. | II-2 |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Czeizel, 2004 [19]* | Aim: To assess the effect of periconceptional multivitamin supplementation containing folic acid (0.8 mg) on congenital abnormalities.<br>Intervention: The comparison group did not use supplementation. Care provider: qualified nurses. | Design: Cohort controlled trial.<br>In- exclusion criteria: (1) Not sterile or subfertile women; (2) capable of conception within one year; (3) not currently pregnant; and (4) women that didn't use supplements longer than 7 days and did not conceive within one year were excluded from the supplemented cohort.<br>Recruitment: Between 1993 and 1996 in Hungary. Recruitment sites for supplemented women were 26 Hungarian Preconceptional clinics; unsupplemented women were recruited from antenatal care clinics between the 8th and 12th week of pregnancy.<br>Matching: Unsupplemented women were matched to supplemented women 1:1 and based on age, socioeconomic status, place of residence and year of pregnancy.<br>Data collection/ Follow-up: Prospectively. Clinical follow-up was three monthly until pregnancy. Self-reported supplement use by questionnaires and by counting number of tablets left. Pregnancy was confirmed by a blood pregnancy test and by ultrasonography. Pregnancy outcomes were extracted from a pregnancy outcome certificate. Congenital defects were detected in neonatal follow-up up to the twelfth month and in autopsy reports of infant deaths or stillborn infants. | Study population: Eligible n=3,981 supplemented women. Included n=6,138 pregnant women (n=3,069 supplemented and n=3,069 unsupplemented) of which n=3,056 informative offspring were evaluated in both cohorts.<br>Loss to follow-up: Pregnancy outcomes could not be clarified in 54 supplemented and 47 unsupplemented women.<br>Baseline characteristics: not reported.<br>Setting: Outpatient clinics. | Outcomes: Occurrence of congenital abnormalities (urinary tract anomalies, cardiovascular anomalies, pyloric stenosis, limb deficiencies, and oral facial clefts) in live born or still born or terminated pregnancies in 2nd and 3rd trimester.<br>Results:<br>Supplemented vs. unsupplemented:<br>- Cardiovascular malformations: n=31 vs. n=50 (OR=0.60; 95%CI 0.0.38-0.96); Ventricular septum defect: n=5 vs. n=10 (OR=0.26; 95%CI 0.08-0.73); Conotruncal defects (transposition of great vessels, Fallot): n=3 vs. n=1 (OR=3, 95% CI 0.24-15.0); Atrial septum defects Type II: n=9 vs. n=13 (OR=0.69; 95% CI 0.27-2.76).<br>- Urinary tract congenital anomalies: Renal dysgenesis: n=2 vs. n=0; Cystic kidney: n=2 vs. n=0; Obstructive congenital anomalies: n=2 vs. n=19 (OR=0.52; 95%CI 0.24-1.13).<br>- Congenital pyloric stenosis: n=0 vs. n=2.<br>- Limb deficiencies: n=1 vs. n=3 (OR=0.33; 95%CI 0.01-3.71).<br>- Orofacial clefts: n=4 vs. n=3 (OR=1.33; 95%CI 0.23 – 9.11). | II-2 |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Watkins, 2004 [20]* | Aim: To determine if folic acid consumption is influenced by providing free folic acid supplements or fortified breakfast cereal.<br>Intervention: After obtainment of informed consent, women received folic acid pills (400 mcg), educational materials about folic acid, and super-fortified cereal (fortified with 400 mcg of folic acid per serving). Care provider: clinic staff. | Design: Cohort study.<br>In- exclusion criteria: Non-pregnant women aged 18-45 years.<br>Recruitment: Between 2000 and 2001 in Georgia. Clinic staff recruited women from six family clinics.<br>Data collection/ Follow-up: Prospectively. Brief survey and blood sample (analyzed for serum folate and vitamin B12) after each clinic visit. | Study population: Eligible n=1,825. Included n=1,093.<br>Loss to follow-up: N=928 visited only once. Reasons not specified.<br>Baseline characteristics: age 87.5% <35 years; race/ethnicity 54.1% White, 40.5% Black, 4.9% Other; 48.9% high school graduate or less; 32.4% smoker.<br>Setting: Six family planning clinics. | Outcomes: Change in the self-reported use of folic acid and change in mean serum folate levels.<br>Results: The interventions did not significantly influence self-reported folic acid consumption (OR= 1.18; 95% CI 0.76-1.83) or mean serum folate levels (results not shown, p-values >0.1). | II-2 |
| *Robbins, 2005 [21]* | Aim: To assess the efficacy of a physician-based intervention during routine gynaecologic visits on women's folic acid supplementation.<br>Intervention: The intervention group received a brief folic acid counselling (30-60 seconds) and 30 folic acid tablets from the gynaecologist at start, a reminder phone call from a research nurse 1 to 2 weeks after the counselling and a pamphlet. The comparison group received a brief physician counselling (30-60 seconds) on 1 or 3 non-pregnancy related preventive health behaviors (breast self-examination, seat belt use, or sunscreen use); a pamphlet on folic acid and a coupon for a free bottle of 30 folic acid tablets, and a stamped addressed envelope to mail the coupon. | Design: Randomized controlled trial.<br>In-exclusion criteria: (1) Non-pregnant women aged 18-45 years capable of becoming pregnant; (2) attending a routine gynaecologic visit (not for preconception care); (3) understanding English; and (4) no pregnancy with neural tube defect or no tubal ligation or no hysterectomy in the past.<br>Recruitment: Timeframe unclear. Women were recruited via four clinics (two were academic and 2 were private practices) in the United States.<br>Randomization: Randomly at patient level – method not described.<br>Data collection/ Follow-up: Prospectively. Self-reported folic acid use at baseline and assessed by phone interview 2 months later. | Study population: Eligible n=not specified. Included n=322 (intervention group n=160; comparison group n=162).<br>Loss to follow-up: N=43: n=40 could not be contacted for the follow-up telephone interview and n=3 refused to complete the follow-up.<br>Setting: 2 academic and 2 private clinics. | Outcomes: Changes in daily (7 days/week) and weekly (at least 1 day/week) folic acid use.<br>Results:<br>- Weekly folic acid intake increased in the intervention group by 68% vs. 20% in the comparison group (p=0.008).<br>- No significant differences were found in daily intake. | I-a |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Schwarz, 2008 [22]* | Aim: To evaluate the efficacy of a computer-assisted counselling with provision of free folate tablets in increasing women's use of folate supplements.<br>Intervention: After the baseline survey and randomization, the intervention group received a 15-minute computerized counselling about periconception folate supplementation with nine questions and answers in the form of short video segments. Each subject was provided with 200 tablets (400 mcg) of folate with written instructions to use daily. The comparison group received counselling on emergency contraception. Emergency contraception was provided with instructions. Care provider: research assistants. | Design: Randomized controlled trial.<br>In- exclusion criteria: (1) English-speaking women aged 18-45 years; (2) women were excluded if she was currently pregnant/ she had undergone a hysterectomy or tubal ligation/ intrauterine device in place/ vasectomised partner; and (3) as were women without a phone.<br>Recruitment: Between March and July 2005 in the United States. Recruitment sites were the waiting areas of two urgent care clinics.<br>Randomization: Computer-generated randomization.<br>Data collection/ Follow-up: Prospectively. At baseline a computerized survey with 85 items which took 15-minutes while waiting to see a clinician. Follow-up by a phone survey with 30 items six months post enrolment. Outcome assessor blinded. | Study population: Eligible n=1,391. Randomized n=446 (intervention group n=227, comparison group n=219).<br>Loss to follow-up: n=219. Reasons not specified, however women were less likely to complete the follow-up if they were enrolled at the county clinic, had lower incomes, had not completed a college education, and were self-identified as black.<br>Baseline characteristics: not specified.<br>Setting: Semiprivate space in urgent care clinics. | Outcomes: Folate supplements use at six months follow-up.<br>Results: Folate supplement use in the intervention group vs. the comparison group: 32% vs. 21%, RR=1.54; 95% CI=1.12-2.13; p=0.007. | I-a |
| *Morgan, 2009 [23]* | Aim: To determine if vitamin consumption is influenced by providing a free bottle of multivitamins.<br>Intervention: Verbal counselling, provision of written materials (such as a brochure), and free 100-count bottles of multivitamins containing 400 mcg folic acid. Care provider: usually nurses. | Design: Cohort study.<br>In- exclusion criteria: Non-pregnant women of childbearing age.<br>Recruitment: In 2004 in the United States. Recruitment sites were from 24 participating local county health departments. Patient sampling: a proportional-to-size sampling design gathered 3,500 consent forms of which 14% were randomly chosen.<br>Data collection/ Follow-up: Prospectively. Eight to ten months after the intervention a phone call for an eight-question survey and sometimes a written survey (after six phone attempts) was conducted. | Study population: Eligible n=500 (sampled from 3,500). Included n=322.<br>Loss to follow-up: N=178 did not completed the survey. Reasons not specified.<br>Baseline characteristics: ethnic origin 60.3% White, 26.6% Latino/Hispanic, 7.5% African American, 2.8% American Indian and 3.4% Other/unknown; age 51.6% <25 years, 34.8% 25-34 years, 13.6% >34 years.<br>Setting: 24 local county health departments. | Outcomes: Change in the self-reported daily use of multivitamins at eight to ten months follow-up.<br>Results:<br>A greater than two-fold increase (PR=2.1; p<0.001) of daily multivitamin use (25% vs. 53%). | II-2 |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| ***Collective interventions: public campaign*** | | | | | |
| *Chan, 2001 [24]* | Aim: To study the effect of a folate campaign towards targeted health professionals and women of reproductive age.<br>Intervention: Key messages of the folate campaign were:<br>1) folate/ folic acid intake by women of reproductive age reduces NTD's in the offspring;<br>2) green leafy vegetables, fruit, cereals contain the most folate;<br>3) folate/ folic acid intake is important in the periconceptional phase.<br>These messages were incorporated into information leaflets for professionals, consumer pamphlets in seven languages, guidelines, newsletter, study curricula, presentations towards professionals.<br>Health professionals approached for the campaign were general practitioners, pharmacists, dieticians, nurse and medical staff of the child and youth health service.<br>The campaign was coordinated by a multidisciplinary committee of the Women's and Children's Hospital and the Public and Environmental Health Service of the Department of Human Services. | Design: Cohort study.<br>In- exclusion criteria: (1) Women aged 15-44 years; (2) postnatal; and (3) that delivered in 1995 and 1996.<br>Recruitment: Between 1994 and 1998 in Australia. Recruitment occurred through random dialling and post-delivery consecutively.<br>Data collection/ Follow-up: Retrospectively. Folic acid intake by computer assisted telephone interviews undertaken by random dialing by a market research company pre-campaign (1994) and during the campaign (1995, 1996 and 1998) and folate use with postnatal self-report questionnaires (delivery: 1996-1998). | Study population: Eligible n=not specified. Included n=512.<br>Loss to follow-up: Not applicable.<br>Baseline characteristics: Not reported.<br>Setting: Community based (posters and pamphlets were distributed in community health centres, pharmacies, in health food shops, shopping centres, local libraries, child day care, preschools, and high schools) and hospital based (doctors office, hospitals). | Outcomes: Folate consumed before and in the first three months of pregnancy.<br>Results:<br>- Women reported to have increased folate rich food consumption: in 1995 12.0% vs. 18.2% in 1996.<br>- Women reported to have increased periconceptional folic acid supplementation: in 1995 10.1%, in 1996 26.7%, in 1998 46.1%. | II-2 |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Myers, 2001 [25]* | Aim: To evaluate the effect of a public health campaign with periconceptional maternal daily consumption of 400 mcg of folic acid and the risk for imperforate anus in the offspring.<br>Intervention: Intake of daily one pill containing 400 mcg of folic acid from the time of premarital examination of women and until the end of the first trimester of pregnancy. Care provider: village health care workers. | Design: Cohort study.<br>In- exclusion criteria: (1) All women who registered with the pregnancy monitoring system; and (2) and had an informative pregnancy.<br>Recruitment: Between 1993 and 1995 in China. Recruitment site was from the pregnancy monitoring system.<br>Data collection/ Follow-up: Prospectively. Free bottles of folic acid to women; three blinded pediatricians independently reviewed birth reports of liveborn and stillborn infants of at least 20 weeks' gestation; and a clinical geneticist validated the diagnoses. | Study population: Eligible n=223,722. Included n=222,314 (n=126,783 women taking periconceptional folic acid; n=95,531 not taking periconceptional folic acid).<br>Loss to follow-up: Not applicable.<br>Baseline characteristics: North vs. South region: mean age 25.2 vs. 25 years.<br>Setting: Premarital examination clinic and at home of the participants. | Outcomes: Association of imperforate anus (the absence of an anal opening) with maternal periconceptional folic acid supplementation.<br>Results:<br>Periconceptional daily 400 mcg folic acid supplementation was, after controlling for maternal age, associated with a risk reduction of 41% in imperforate anus of the child (OR=0.59; 95% CI 0.33-1.07). | II-2 |
| *Gindler, 2001 [26]* | Aim: To evaluate the effect of a public health campaign with periconceptional maternal daily consumption of 400 mcg of folic acid and the occurrence of miscarriages.<br>Intervention: Intake of daily one pill containing 400 mcg of folic acid from the time of premarital examination of women and until the end of the first trimester of pregnancy. Care provider: village health care workers | Design: Cohort study.<br>In- exclusion criteria: (1) Women residing in Jiaxing City who had a premarital examination;(2) nulliparous; and (3) who registered with the pregnancy monitoring system.<br>Recruitment: Between 1993 and 1995 in China. Recruitment site was from the pregnancy monitoring system.<br>Data collection/ Follow-up: Prospectively. Free bottles of folic acid to women; information about each woman's pill-taking; urine pregnancy test one to two weeks after a missed menstrual period; and a booklet with data on past pregnancy history, the prenatal period and delivery. Additionally, dates of all menses and dates and results of pregnancy tests for each woman were collected. | Study population: Eligible n=not specified. Included n=23,806 (n=21,935 women taking periconceptional folic acid; n=1,871 not taking periconceptional folic acid).<br>Loss to follow-up: Not applicable.<br>Baseline characteristics: periconceptional folic acid use vs. no use of folic acid: age at pregnancy 23.5 vs. 23.8 years; BMI mean 20.4 vs. 20.5; high school education 5.3% vs. 11.4%; farmer 55.6% vs. 54.8%.<br>Setting: Premarital examination clinic and at home of the participants. | Outcomes: Association of miscarriages (a spontaneous fetal death <20 weeks of gestation, following a positive pregnancy test) with maternal periconceptional folic acid use.<br>Results:<br>Compared with women who had no folic acid use, the RR of miscarriage for women with periconceptional folic acid use was 1.03; 95% CI 0.89-1.20. | II-2 |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| ***Collective interventions: fortification*** | | | | | |
| *Gucciardi, 2002 [27]* | Aim: To study trends in the total incidence of open NTDs capturing the fortification period.<br>Intervention: Folic acid fortification of grain is mandatory as of 1998. | Design: Cohort study.<br>In- exclusion criteria: (1) All live births, stillbirths and therapeutic abortions with NTDs registered in the databases and hospital data; and with no therapeutic abortions in free-standing abortion clinics.<br>Recruitment: Between 1986 and 1999 in Canada. Recruitment occurred from the Canadian Congenital Anomalies Surveillance System and hospital data. The registries are population based.<br>Data collection/ Follow-up: Retrospectively. Collection of the total incidence of NTDs by combining the numbers of NTDs occurring in live births, stillbirths and therapeutic abortions. | Study population: Eligible total births n=not specified. Included total NTDs n=3,207 (live births n=1,503; stillbirths n=425; therapeutic abortions n=1,279).<br>Loss to follow-up: Not applicable.<br>Baseline characteristics: Not reported.<br>Setting: Population based. | Outcomes: Changes in NTDs birth incidence per 10,000 (live births and stillbirths only).<br>Results:<br>- Total NTD incidence rate increased by 38% from 1986 to 1995 (11.7 to 16.2/10000 pregnancies, p<0.001); decreased by 47% from 1995 to 1999 (8.6/10000 pregnancies, p<0.001).<br>– NTD birth incidence decreased by 50% from 1986 to 1999 (10.6 to 5.3/10000 births, p<0.001).<br>- Rate of NTDs in live births declined by 50% from 8.6/10000 live births in 1986 to 4.3/10000 live births in 1999 (p<0.001).<br>- The rate of stillbirths with a NTD decreased by 53%, from 33.6/1000 stillbirths in 1986 to 15.9/1000 stillbirths in 1999 (p<0.001).<br>- From 1986 to 1995 the rate of therapeutic abortions in which a NTD or hydrocephalus was detected rose 190%, from 17.5 to 50.7 per 10000 abortions (p<0.001). By 1999 it had fallen by 43% to 28.7/10000 abortions (p<0.001). This resulted in a decrease in the ratio of NTD-affected births to therapeutic abortions from 3:1 in 1986 to 1:1 in 1999. | II-2 |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Honein, 2001 [28]* | Aim: To study the effect of folate food fortification with folic acid on NTD birth prevalence.<br>Intervention: Folic acid fortification of grain is mandatory as of 1998. The comparison group was born prior to the fortification period. | Design: Cohort study.<br>In- exclusion criteria: (1) Infants with spina bifida/ anencephaly or any congenital abnormality; and (2) born in 45 states which registered congenital anomalies on the certificate.<br>Recruitment: Between 1990 and 1999 in the United States. Recruitment occurred from birth certificate data for live births. The registry is population based.<br>Data collection/ Follow-up: Retrospectively. Cases with infants with spina bifida and anencephaly were collected from birth certificate information. | Study population: Eligible total births n=not specified. Included total NTDs n=13,786. ( spina bifida n=9,054; anencephaly n=4,732).<br>Loss to follow-up: Not applicable.<br>Baseline characteristics: Not reported.<br>Setting: Population based. | Outcomes: Comparison of pre- (infants born from October 1995-1996) and post-fortification (infants born from October 1998-1999) spina bifida, anencephaly and total NTD prevalence rates.<br>Results:<br>- Decline in birth prevalence of spina bifida post-fortification compared to pre-fortification: 23% (PR=0.77; 95% CI 0.70-0.84).<br>- Decline in birth prevalence of anencephaly post-fortification compared to pre-fortification: 11% (PR=0.89; 95% CI 0.78-1.01).<br>- Decline in total NTDs post-fortification compared to pre-fortification: 19% (PR= 0.81; 95 CI 0.75-0.87). | II-2 |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Persad, 2002 [29]* | Aim: To assess changes in annual incidence of open NTDs, in Nova Scotia after the introduction of folic acid fortification.<br>Intervention: Folic acid fortification of grain is mandatory as of 1998. | Design: Cohort study.<br>In- exclusion criteria: (1) All live births, stillbirths and terminated pregnancies with open NTDs over a 10-year period; and (2) registered in the databases.<br>Recruitment: Between 1991 and 2000 in Canada. Recruitment occurred from the Nova Scotia Atlee Perinatal Database and from the Fetal Anomaly Database. The registry is population based.<br>Data collection/ Follow-up: Retrospectively. Collection of annual incidence rates of open NTDs, spina bifida, and anencephaly pre- (1991-1997) and post-fortification (1998-2000). | Study population: Eligible total births n=not specified. Included total births n=107,851; open NTDs n=239.<br>Loss to follow-up: Not applicable.<br>Baseline characteristics: Not reported.<br>Setting: Population based. | Outcomes: Annual incidence changes of open NTDs, and of the subgroups spina bifida and anencephaly, per 1000 births (live births, stillbirths and terminations) pre- and post-fortification.<br>Results:<br>- The total annual incidence of open NTDs fell by 54% after folic acid fortification, from 2.58/1000 births on average during 1991-1997 to 1.17/1000 births during 1998-2000: RR=0.46; 95% CI 0.32-0.66; p<0.001.<br>- Subgroup analysis of spina bifida, the mean annual incidence decreased from 1.51/1000 births before to 0.62/1000 births after fortification: RR=0.40; 95% CI 0.25-0.67; p<0.001.<br>- Subgroup analysis of anencephaly, the mean annual incidence decreased from 0.93/1000 births to 0.38/1000 births after fortification: RR=0.41; 95% CI 0.22-0.77; p=0.0004. | II-2 |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Ray, 2002 [30]* | Aim: To assess the effect of folic acid food fortification before and after on the prevalence of open NTDs.<br>Intervention: Folic acid fortification of grain is mandatory as of 1998. | Design: Cohort study.<br>In- exclusion criteria: (1) All antenatal and postnatal diagnosed open NTDs among women residing in Ontario; (2) and registered in the MSS database.<br>Recruitment: Between 1994 and 2000 in Canada. Recruitment occurred from the Ontario MSS database. The registry is hospital based.<br>Data collection/ Follow-up: Retrospectively. Collection of antenatal diagnosed open NTDs (based on ultrasonography or fetal autopsy after therapeutic termination) and postnatal diagnosed open NTDs (based on all live born and stillborn affected infants after 20 weeks' gestation) pre- (1994-1997) and post-fortification (1998-2000). | Study population: Eligible women and total births n=not specified. Included screened women n=218,977 and n=117,986 pre- and after fortification respectively; cases of open NTDs n=248 and n=69 pre- and after fortification respectively.<br>Loss to follow-up: Not applicable.<br>Baseline characteristics: Pre- vs. post-fortification: mean maternal age 30.1 years (SD 0.16) vs. 30.3 years (SD 0.081).<br>Setting: Population based. | Outcomes: Decrease in the prevalence of open NTDs, and of the subgroups anencephaly and spina bifida, per 1000 pregnancies post-fortification.<br>Results:<br>- The prevalence of open NTDs decreased from 1.13/1000 (n=248) pregnancies before fortification to 0.58/1000 (n=69) pregnancies thereafter: PR=0.52; 95% CI 0.40-0.67, p<0.0001.<br>- The prevalence of anencephaly decreased from 0.38/1000 (n=84) pregnancies before fortification to 0.16/1000 (n=19) pregnancies thereafter: PR=0.42; 95% CI 0.26-0.69, p<0.0002.<br>- The prevalence of spina bifida decreased from 0.75/1000 (n=164) pregnancies before fortification to 0.42/1000 (n=50) pregnancies thereafter: PR=0.57; 95% CI 0.41-0.78, p<0.0001. | II-2 |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Williams, 2002 [31]* | Aim: To assess the effect of folic acid food fortification before and after on the prevalence of spina bifida and anencephaly.<br>Intervention: Folic acid fortification of grain is mandatory as of 1998. | Design: Cohort study.<br>In- exclusion criteria: (1) All antenatal and postnatal diagnosed open NTDs among women residing in Ontario; (2) and registered in the MSS database. The registry is population based.<br>Recruitment: Between 1995 and 1999 in the Unites States. Recruitment occurred from 24 birth defects population-based surveillance systems.<br>Data collection/ Follow-up: Retrospectively. Collection of the prevalence of NTDs (live births, stillbirths, fetal deaths, and elective terminations) using data from nine surveillance systems with prenatal ascertainment and data from 13 surveillance systems without prenatal ascertainment and electively terminated cases during the three periods: 1) pre-fortification 1995-1996 or 2) during optional fortification 1997-1998 or 3) during mandatory fortification 1998-1999. | Study population: Eligible total births n=not specified. Included n=5,630 cases of spina bifida and anencephaly.<br>Loss to follow-up: Not applicable.<br>Baseline characteristics: Not reported.<br>Setting: Population based. | Outcomes: Decrease in the prevalence of spina bifida and anencephaly post-fortification.<br>Results:<br>Prevalences from the pre- to the mandatory fortification period:<br>- Spina bifida decreased 31%: PR=0.69; 95% CI 0.63-0.74.<br>- Anencephaly decreased 16%: PR=0.84; 95% CI 0.75-0.95.<br>- Spina bifida decreased 40%: PR=0.60; 95% CI 0.51-0.71 among the nine programs with prenatal ascertainment and 28%: PR=0.72; 95% CI 0.65-0.80 among the thirteen programs without prenatal ascertainment. | II-2 |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *CDC, 2004 [32]* | Aim: To assess the effect of folic acid food fortification before and after on the prevalence of NTDs.<br>Intervention: Folic acid fortification of grain is mandatory as of 1998. | Design: Cohort study.<br>In- exclusion criteria: (1) All antenatal and postnatal diagnosed NTDs among women residing in Ontario; (2) and registered in the MSS database.<br>Recruitment: Between 1995 and 2000 in the United States. Recruitment occurred from 23 population-based surveillance systems.<br>Data collection/ Follow-up: Retrospectively. Collection of the prevalence of NTD-affected pregnancies (live births, stillbirths, fetal deaths, and elective terminations) using data from eight surveillance systems with prenatal ascertainment and data from fifteen surveillance systems without prenatal ascertainment pre- (1995-1996) and post-fortification (1999-2000). | Study population: Eligible total births n=not specified. Included n=7,080 and n=5,200 cases of spina bifida and anencephaly.<br>Loss to follow-up: Not applicable.<br>Baseline characteristics: Not reported.<br>Setting: Population based. | Outcomes: Decrease in the prevalence of NTD-affected pregnancies post-fortification.<br>Results:<br>- Estimated number of NTD-affected pregnancies declined from 4,000 in 1995-1996 to 3,000 in 1999-2000.<br>Data from systems with prenatal ascertainment showed:<br>- Before fortification the total annual number of NTD-affected pregnancies was 4,130: n=2,490 spina bifida and n=1,640 anencephaly.<br>- After fortification the total annual number of NTD-affected pregnancies was 3,020: n=1,640 spina bifida and n=1,380 anencephaly.<br>à 27% decline.<br>Data from systems without prenatal ascertainment showed:<br>- Before fortification the total annual number of NTD-affected live births, stillbirths, and fetal deaths at >20 weeks' gestation was 2,950: n=1,980 spina bifida and n=970 anencephaly.<br>- After fortification the total annual number of NTD-affected live births, stillbirths, and fetal deaths at >20 weeks' gestation was 2180: n=1,340 spina bifida and n=840 anencephaly.<br>à 26% decline. | II-2 |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Liu, 2004 [33]* | Aim: To evaluate the effectiveness of the public health strategy of food fortification with folic acid and to determine possible adverse effects resulting from fortification.<br>Intervention: Folic acid fortification of white flour, pasta, and cornmeal is mandatory as of 1998. | Design: Cohort study.<br>In- exclusion criteria:<br>- Women: non-pregnant of childbearing age (19-44 years) not taking folic acid supplements.<br>- Seniors: aged 65 years and over without a vitamin B12 deficiency or anaemia, and not taking vitamin B12 or supplements containing folic acid.<br>Recruitment: Between 1997 and 1998 in Canada. Recruitment occurred through a random telephone survey prior to folic acid fortification.<br>Data collection/ Follow-up: Prospectively. In person interviews recollected vitamin supplement use, a Willet food frequency dietary questionnaire was taken to assess intake over the past year, and blood samples pre- and post-fortification were taken. Women and seniors were followed-up to two years after the start of fortification. | Study population: Eligible n=not specified. Included pre- fortification n=233 women, n=202 seniors; post-fortification n=204 women, n=186 seniors.<br>Loss to follow-up: Women n=29; seniors n=16. Reasons not specified.<br>Baseline characteristics: Not reported.<br>Setting: Population based. | Outcomes: NTD prevalence, red blood cell folate and dietary folate intake pre- vs. post-fortification.<br>Results:<br>- The total annual rate of NTDs fell by 78% after the implementation of folic acid fortification (pre fortification: 4.36/1000 births; post fortification 0.96/1000 births; RR=0.22; 95% CI 0.14-0.35; p<0.0001). NTDs amongst terminated pregnancies were stable throughout the pre- and post-fortification period.<br>- Significant increases in RBC folate levels for women and seniors after mandatory fortification (625 mol/L [SD 601-649] vs. 818 [SD 784-854]; p<0.001).<br>- The proportion of women aged 19-44 years taking a vitamin supplement containing folic acid increased from 17% to 28% (p<0.003). | II-2 |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Canfield, 2005 [34]* | Aim: To assess changes in birth defect prevalences since folic acid fortification.<br>Intervention: Folic acid fortification of grain is mandatory as of 1998. | Design: Cohort study.<br>In- exclusion criteria: (1) Infants registered in one of the 23 states affiliated to the National Birth Defects Prevention Network; (2) with one of the selected birth defects (anencephaly, spina bifida without anencephaly, common truncus, transposition of the great arteries, tetralogy of Fallot, ventricle septal defects, cleft palate only, cleft lip without cleft palate, pyloric stenosis, renal agenesis, bladder exostrophy, obstructive genitourinary defects, reduction defects of the upper and lower limbs, omphalocele, Down syndrome); and (3) live born or born after pregnancy terminations in 8 states.<br>Recruitment: Between 1995 and 2000 in the United States. Recruitment occurred from population-based registries.<br>Data collection/ Follow-up: Retrospectively. Collection of prevalence rates of birth defects pre-fortification (1995-1996) and post-fortification (1999-2000). | Study population: Eligible total births n=not specified. Included total births n=9,729,763; cases n=96,087.<br>Loss to follow-up: Not applicable.<br>Baseline characteristics: Not reported.<br>Setting: Population based. | Outcomes: Prevalence rate of congenital abnormalities (PR) (N per 10000 live births) pre- and post-fortification.<br>Results: PR combined with availability of prenatal screening:<br>- Anencephaly PR=0.84; 95% CI 0.76 – 0.94.<br>- Spina Bifida PR=0.85; 95% CI 0.69-0.97.<br>- Common truncus PR=0.88; 95% CI 0.72-1.08.<br>- Transposition of the great arteries PR=0.88; 95% CI 0.81-0.96.<br>- Tetralogy of Fallot PR=0.96; 95% CI 0.88-1.04.<br>- Ventricular Septum Defect PR=0.97; 95% CI 0.94-1.00.<br>- Cleft Palate PR=0.88; 95% CI 0.82-0.95<br>- Cleft lip and/or palate PR=0.95; 95% CI 0.90-1.00<br>- Pyloric stenosis PR=0.95; 95% CI 0.90-0.99<br>- Renal agenesis PR=0.92; 95% CI 0.84-1.01<br>- Bladder exostrophy PR=1.13; 95% CI 0.82-1.55.<br>- Obstructive genitourinary defects PR =1.12; 95% CI 1.07-1.16.<br>- Upper limb reduction defects PR =0.89; 95% CI 0.80-0.99.<br>- Lower limb reduction defects PR=0.97; 95% CI 0.84-1.11.<br>- Omphalocele PR=0,79; 95% CI 0.66-0.95.<br>- Down syndrome PR=1,06; 95% CI 1,01-1,11. | II-2 |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Botto, 2006 [35]* | Aim: To evaluate international rates and trends of 14 major defects in areas with official recommendations to fortificate or where fortification occurs.<br>Intervention: Folic acid national policy of recommendations or actual food fortification. This varied in type and timing per country. | Design: Multicentre cohort study.<br>In- exclusion criteria: Unknown outcomes of pregnancies and subjects with occult spinal dysraphism, including spina bifida occulta, thickened filum terminale, diastematomyelia, caudal regression syndrome, intradural lipoma, lipomeningomyelocele, split notochord, and other forms of myelodysplasia were excluded.<br>Recruitment: Through 2003 in Europe, Australia, Canada and the United States. Recruitment occurred from 15 surveillance data. The registries are population based.<br>Data collection/ Follow-up: Retrospectively. Collection of rates and trends for 14 major birth defects pre-recommendation or fortification and post-recommendation or fortification. | Study population: Eligible total births n=not specified. Included total births n=1.5 million yearly (from Europe n=1,000,000; from Canada and the USA n=370,000; from Australia n=87,000).<br>Loss to follow-up: Not applicable.<br>Baseline characteristics: not reported.<br>Setting: Population based. | Outcomes: Decrease in the prevalence of selected birth defects (live births, terminations), including NTDs, per 1000 births for the time period before and after the year of introduction of national policy of recommendations or fortification.<br>Results:<br>- Significant changes in trends were seen for NTDs in areas with fortification but not in areas with supplementation recommendations alone: varying decrease from 10 to 35% in the data of Australia (PPR=0.90; 95% CI 0.82-0.99), Western Australia (PPR=0.70; 95% CI 0.61-0.81); Canada (PPR=0.71; 95% CI 0.53-0.94); and USA (PPR=0.65; 95% CI 0.56-0.76).<br>- For other major birth defects, there was an overall lack of major trend changes after recommendations or fortification. | II-2 |
| *Yazdy, 2007 [36]* | Aim: To study the impact of folic acid fortification on orofacial clefts.<br>Intervention: Folic acid fortification of grain is mandatory as of 1998. | Design: Cohort study.<br>In- exclusion criteria: (1) Infants born with orofacial clefts; and (2) not born between 1997 and 1998.<br>Recruitment: Between 1990 and 2002 in the United States. Recruitment occurred from US birth certificates data. The registry is population based.<br>Data collection/ Follow-up: Retrospectively. Comparing the prevalence of orofacial clefts among births before (1/1990-12/1996) and after fortification (10/1998-12/2002). | Study population: Eligible total births n=not specified. Included total births n=45,926,598; cases n=38,232.<br>Loss to follow-up: Not applicable.<br>Baseline characteristics: Not reported.<br>Setting: Population based. | Outcomes: Association between folic acid fortification and orofacial clefts.<br>Results:<br>Orofacial clefts declined following folic acid fortification: PR=0.94; 95% CI 0.92-0.96. The decline occurred in the subgroup of non-Hispanic Whites, non-smokers, and women who received prenatal care in the first trimester. | II-2 |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *de Wals, 2007 [37]* | Aim: To assess changes in the prevalence of NTDs before and after folic acid fortification.<br>Intervention: Folic acid fortification of grain is mandatory as of 1998. | Design: Cohort study.<br>In- exclusion criteria: (1) All live births, stillbirths and terminated pregnancies diagnosed with NTDs among women; (2) residing in seven of the ten Canadian provinces; and (3) subjects with no occult spinal dysraphism, including spina bififda occulta, thickened filum terminale, diastematomyelia, caudal regression syndrome, intradural lipoma, lipomeningomyelocele, split notochord, and other forms of myelodysplasia.<br>Recruitment: Between 1993 and 2002 in Canada. Recruitment occurred from multiple sources ranging from provincial databases, registry databases and medical records. The registries were area- and hospital based.<br>Data collection/ Follow-up: Retrospectively. Collection of annual incidence rates of NTDs pre- (before 1997) and post-fortification (after 2000). | Study population: Eligible total births n=1.9 million. Included cases n=2,446.<br>Loss to follow-up: Not applicable.<br>Baseline characteristics: not reported.<br>Setting: Population based. | Outcomes: Decrease in the prevalence of NTDs per 1,000 births (live/ stillborn and terminated pregnancies) after fortification.<br>Results:<br>- The prevalence of NTDs decreased from 1.58/1,000 births before fortification to 0.86/1,000 births during the full-fortification period, 46% reduction; 95% CI 40-51.<br>- The decrease was greater for spina bifida (53%) than for anencephaly and encephalocele (38% and 31%, respectively). | II-2 |
| **MULTIPLE RISK FACTORS** | | | | | |
| ***Individual interventions*** | | | | | |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Lumley, 2006 [38]* | Aim: Assessment of the effect of pre-pregnancy information, advice and counselling on birth weight on subsequent pregnancy outcomes.<br>Intervention: After recruitment, all women had a home visit with a discussion of their first pregnancy, labour and birth, and postpartum experience. In addition, the intervention group received an identification of any current social, health or lifestyle problems; discussion of preparation and timing for the next pregnancy; taking a family/genetic history and arranging a referral if necessary; arranging for rubella immunisation if not immune; offers of referral for any specific health problem identified; and discussion of the points on a WAIT, STOP, and GO reminder card. The comparison group only received a visit about postpartum experiences.<br>Care provider: midwives. | Design: Randomized controlled trial.<br>In- exclusion criteria: (1) Postpartum women attending government funded local Maternal and Child Health centres; (2) with high risk of poor birth outcomes (due to socioeconomic reasons); and (3) without attending for specialist care.<br>Recruitment: Between 1982 and 1991 in Australia. Recruitment sites were the Maternal and Child Health Centres by nurses.<br>Randomization: Balanced block in blocks of two, four or six.<br>Data collection/ Follow-up: Information about the previous pregnancy and birth was collected at the first home visit. Data on the subsequent pregnancy outcome was collected by home visit, telephone and mail. Follow-up continued until the end of 1994. | Study population: Eligible n=1,688 (intervention group n=842; comparison group n=846). Included n= 786 (intervention group n=392; comparison group n=394).<br>Loss to follow-up: n=173 intervention group; and n=191 comparison group. Reasons not specified.<br>Baseline characteristics: Intervention vs. comparison group maternal age <20 2.6% vs. 4.6%, 20-24 20.9% vs. 17.9%, 25-29 32.4% vs. 36.9%, 30-34 34.2% vs. 33.1%, 35-39 9.2% vs. 6.9%; region of birth Australia 64.5% vs. 70.8%, Asia/Middle East 19.1% vs. 18%, Africa 1.5% vs. 1.0%.<br>Setting: A pre-pregnancy walk-in service and at home. | Outcomes: Primary outcome: difference in birth weight compared to index pregnancy. Secondary outcomes: gestational age at birth, low birth weight (<2,500gram), birth weight <10$^{th}$ percentile, perinatal deaths and birth defects.<br>Results:<br>- Birth weight was significantly 97.4 gram lower among infants in the intervention group.<br>- No significant differences were found for preterm birth (OR 1.44; 95% CI 0.73-2.91), low birth weight (OR 1.85; 95% CI 0.91-3.91) or birth weight <10$^{th}$ percentile (OR 1.14; 95% CI 0.55-2.38).<br>- Compared to the comparison group the intervention group had more preterm births <32 weeks (10 vs. 1), more birth weights <2000 g (16 vs. 2), and more perinatal deaths due to birth anomalies (5 vs. 2). | I-A |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Elsinga, 2008 [39]* | Aim: To assess whether attendance of preconceptional health counselling change women's behavior and the percentage of adverse outcome.<br>Intervention: After women's approval, the intervention group received counselling with information on general risk factors and on their personal risk factors identified in the risk-assessment questionnaire. The control group received standard care. Care provider: general practitioners. | Design: Randomized controlled trial.<br>In- exclusion criteria: (1) Women aged 18-40; (2) contemplating pregnancy within one year; and (3) in cases were invitation was undesirable women were not invited.<br>Recruitment: Between 2000 and 2003 in the Netherlands. Recruitment occurred from the patients in the practices of general practitioners by annual invitations sent to an eligible sample.<br>Randomization: At the level of general practitioner practices. Method not specified.<br>Data collection/ Follow-up: Prospectively. Risk assessment questionnaire (27 questions with questions on pregnancy complications, pregnancy outcome, and seven questions on socioeconomic factors, anxiety, family planning, and folic acid use) was sent at baseline and within two months after delivery. | Study population: Eligible n=353. Included in the intervention group n=211 women and n=150 pregnancies; in the comparison group n=422 women and n=1,914 pregnancies.<br>Loss to follow-up: Not reported.<br>Baseline characteristics: intervention vs. comparison group age: 20-30 26,8% vs. 28,5%, age 30 ->40 73,2% vs. 71,5%; country of birth in the Netherlands 94,7% vs. 87,8%; educational level high 45,1% vs. 37,6.<br>Setting: General practitioner practices. | Outcomes:<br>Smoking**, alcohol consumption*, binge drinking*, start of folic acid use*, adverse pregnancy outcomes (premature birth (<37 weeks); low birth weight (<2,500grams); small for gestational age (growth <p 2,3); and congenital anomalies.<br>* up to 3 months before the pregnancy<br>** in or up to 3 months before pregnancy<br>Results:<br>Intervention vs. comparison group:<br>- Smoking cessation**:18% vs. 10% unadjusted OR=3,04; 95%CI 0,95-9,69.<br>- Folic acid use*: 86% vs. 53%; *adjusted OR=4,93; 95%CI 2,81-8,66.<br>- Alcohol consumption*: 32% vs. 45%; *adjusted OR=1,79 95%CI 1,08–2,97.<br>- Percentage of adverse outcome: 16,2% vs. 20,2%; OR=0.77; 95%CI 0.48-1.22.<br><br>*Adjusted for age, educational level and country of birth | I-a |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Hammiche, 2011[40]; Hammiche, 2010; van Mil, 2010* | Aim: To assess the efficacy of tailored preconception counselling to modify dietary and lifestyle behaviors in mainly subfertile couples planning pregnancy.<br>Intervention: A tailored dietary and lifestyle consultation during a clinical consultation (focusing on folic acid use, medication, alcohol, caffeine, drugs, physical exercise, infection risk, body mass index, waist circumference, waist to hip ratio, blood pressure, vitamin B12, avoidance of raw milk cheeses /raw meat or fish, and rubella vaccination status) followed by a voluntary 2nd counselling after three months. Background of the counsellor is unspecified. | Design: Cohort study.<br>In- exclusion criteria: Couples planning pregnancy.<br>Recruitment: Between 2007 and 2009 in the Netherlands. Women were recruited at the outpatient Academic Obstetrics and Gynaecology clinic.<br>Data collection/ Follow-up: Prospectively. At baseline and three months after the consultation by questionnaires, anthropometric measurements, and biomarkers. Data was used to formulate a personal Preconception Dietary Risk score (PDR score) and a Rotterdam Reproductive Risk Score (R3 score). | Study population: Eligible n=not specified. Included n=419 couples.<br>Loss to follow-up: 309 couples did not attend the voluntary follow-up consultation.<br>Baseline characteristics: median age 31 year; 56% Dutch ethnicity; 35% high educated; and 93.8% of the couples were subfertile.<br>Setting: Tertiary outpatient Academic Obstetrics and Gynaecology clinic. | Outcomes: Change in dietary and lifestyle behaviors and changes in the PDR- and R3-score in women.<br>Results:<br>- Intake of fruit increased from 65 to 80%.<br>- Recommended intake of fish increased from 39 to 52%.<br>- Median PDR score decreased from 2.6 (95% CI 2.4-2.9) to 2.4 (95% CI 2.1-2.6)<br>- Median R3 score decreased from 4.7 (95% CI 4.3-5.0) to 3.1 (95% CI 2.8-3.4) due to less alcohol use (-14.6%), more physical exercise and folic acid use. Low educated women showed a larger reduction than better educated women. | II-2 |
| *Ockhuijsen, 2012 [41]* | Aim: To assess the efficacy of interventions aimed at altering behavior patterns related to smoking and obesity in a preconception care service integrated in an IVF program.<br>Intervention: Counselling (not specified) during clinical visits and by telephone. Care provider: nurses. | Design: Cohort study.<br>In- exclusion criteria: (1) Couples on the waiting list for an IVF treatment; (2) who had visited the preconception clinic; (3) and were able to read Dutch.<br>Recruitment: Between 2007 and 2008 in the Netherlands. Recruitment site was from the IVF unit.<br>Data collection/ Follow-up: Prospectively. Self-reported and measured weight and self-reported smoking status. Follow-up by telephone call or visit every 4 weeks. The length of follow-up was up to 1 year. | Study population: Eligible n=130. Included n=101.<br>Loss to follow-up: n=25 (obese group n=15; smoking group n=10). Reasons not specified.<br>Baseline characteristics: 30 women had a BMI >30 kg/m$^2$ (mean value of 33.8; SD 3.6); 23 women smoked.<br>Setting: An IVF unit at a university hospital. | Outcomes: Mean weight reduction (self-reported and weighed combined) in kg and smoking cessation.<br>Results:<br>Weight loss:<br>- 15/30 women (50%) lost weight (mean 6.1 kg; SD 3.6); 11 of these 15 women reached the goal of losing 5% or more of their original weight.<br>Smoking cessation:<br>- 7/23 women (30%) quit smoking<br>- 6/23 women (26%) reduced the number of cigarettes. | II-2 |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Williams, 2012 [42]* | Aim: To assess the effect of preconception care on positive maternal behaviors before and during pregnancy.<br>Intervention: Any form of contact (content not further specified) preconceptionally to prepare for a healthy pregnancy and baby was compared to no contact to prepare for a pregnancy. Care provider: health care worker. | Design: Cross-sectional study.<br>In- exclusion criteria: (1) Women that had delivered a live birth 2-6 months ago; and (2) reported drinking or smoking during follow-up that did not report this at base line were excluded.<br>Recruitment: Between 2004 and 2008 in the Unites States. Recruitment occurred from state birth certificates. The registry is population based.<br>Data collection/ Follow-up: Retrospectively. Data from the Pregnancy Risk Assessment Monitoring System (PRAMS) was used; additional data was retrieved by mailed questionnaires. Non-responders were contacted by telephone. | Study population: Eligible n= 30,481. Included n=9,457.<br>Loss to follow-up: Not reported.<br>Baseline characteristics: Not specified per group; the population that received preconception care contained more women >20 years of age, more non-Hispanic white and black women, more years of education ≥12 years, more were married, more were privately insured, more have a normal weight, more have a prior live birth, more have a prior intended pregnancy, more have diabetes or a poor prior birth outcome.<br>Setting: Not specified. | Outcomes: Prepregnancy daily multivitamin consumption, smoking cessation (not smoking on an average day within the prior three months to pregnancy) and cessation of alcohol consumption (not drinking with the last three months prior to pregnancy).<br>Results: Receipt of preconception care was significantly associated with:<br>- Daily consumption of multivitamins one month before pregnancy (AOR 4.35; 95% CI 4.00-4.73).<br>- Cessation of drinking during the three months before pregnancy (AOR 1.34; 95% CI 1.16-1.54). | II-2 |
| ***Group interventions*** | | | | | |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Hillemeier, 2008 [43]* | Aim: To assess the efficacy of a preconceptional health program (the Strong Healthy Women intervention).<br>Intervention: Two weeks after the baseline risk assessment, the intervention group underwent six 2-hour group sessions spread out over a 12-week period (topics were pregnancy and conception, managing stress, physical activity, nutrition (including folic acid supplementation), preventing gynaecologic infection, tobacco exposure, and alcohol use. The comparison group did not receive the group sessions. Care provider: group facilitators who were trained for this project by the study investigators. | Design: Randomized controlled trial.<br>In- exclusion criteria: (1) Residence within the 28 county target study region; (2) women aged 18-35; (3) not pregnant at time of enrolment; (4) capable of becoming pregnant; and (5) English speaking.<br>Recruitment: Time frame unclear, in the United States. Recruitment occurred from the community via triangular community based approach with active (personal communication) and passive recruitment (media, mailings, posters and flyers).<br>Randomization: In a 2-to-1 ratio (intervention to comparison group).<br>Data collection/ follow-up: Prospectively. Participants received a baseline and follow-up health risk assessment at 14 weeks (self-administered 20-minute questionnaire, anthropometric measurements, and biomarkers). | Study population: Eligible n==692 (intervention group n=473; comparison group n=219). Included n=362 (intervention group n=252; comparison group n=110).<br>Loss to follow-up: 47% in the intervention group and 50% in the comparison group did not attend the follow-up risk assessment. Reasons not specified.<br>Baseline characteristics: intervention vs. comparison group married or living with partner 59% vs. 48%; mean age 26.52 years (SD 5.02) vs. 24.74 years (SD 4.64); high school education 36% vs. 31%; race White/non-Hispanic 92% vs. 91%, Other 8% vs. 9%; poor poverty status 27% vs. 29%.<br>Setting: 15 low-income rural communities, location not further specified. | Outcomes: Behavior change related primarily to nutrition and physical activity.<br>Results:<br>Statistically significant behavior changes included greater likelihood of:<br>- Reading food labels to identify nutritional values (OR 2.264; p-value 0.001).<br>- Using a daily multivitamin that contains folic-acid (OR=6.595; p-value <0.001).<br>- Meeting recommended levels of physical activity levels (OR=1.867; p-value 0.019).<br>Significant dose effects were found for:<br>- Reading food labels (OR=1.161; p-value 0.015)<br>- Daily use of multivitamin with folic-acid (OR=1.448; p-value <0.001).<br>- Anthropometric measurements (BMI, waist circumference, and blood pressure) and biomarkers (serum glucose, HDL cholesterol, and total cholesterol) were not significantly different in pre- and post-analysis. | I-a |

**Web Table 1.** Findings From Studies Reporting on the Effectiveness of Preconceptional Interventions per (Risk) Behavior (N=44) (continued)

| | Intervention | Methods | Population and setting | Outcomes | Strength of evidence |
|---|---|---|---|---|---|
| *Weisman, 2011 [44]* | Aim: To assess the long-term effects of the Strong Healthy Women intervention.<br>Intervention: See Hillemeier 2008. | Design: Follow up of the RCT Hillemeier 2008.<br>In- exclusion criteria: See Hillemeier 2008.<br>Recruitment: See Hillemeier 2008.<br>Data collection/ Follow-up: Telephone interviews (including, reading food labels for nutritional values, using a daily multivitamin with folic acid, meeting prevailing recommended physical activity levels, consuming fruits and vegetables at least daily, weight [measured at baseline and self-reported at follow-up], and BMI [computed using baseline measured height and weight, and self-reported weight at follow-up]) 6- and 12- months after group sessions in Hillemeier 2008. Birth records from women who gave birth to singletons during the 12-months follow-up period. | Study population: Eligible n=362 from the original trial. Included n=315 at 6 months; n=302 at 12 months (intervention group n=218, comparison group n=84); and n=45 data on birth outcomes.<br>Loss to follow-up: n=47 at six-months; n=60 at twelve months. Primary reason was failure to locate women; refusal was rare (4.7%).<br>Baseline characteristics at time of the 12-month follow-up period: intervention vs. comparison group married or living with partner 63.4% vs. 54.8%; mean age 28.2 years (SD 5.0) vs. 26.3 years (SD 4.7); high school education 37% vs. 31%; race White/non-Hispanic 93% vs. 88%, Other 7% vs. 12%; poor poverty status 27% vs. 29%.<br>Setting: See Hillemeier 2008. | Outcomes: (1) Maintenance of significant pretest-posttest changes; (2) impact on weight, BMI and daily folic acid use; and (3) impact on weight gain during pregnancy.<br>Results:<br>At 12 months follow-up women of the intervention group were more likely:<br>- To use multivitamin with folic acid daily (OR 2.15; 95% CI 1.19-3.88).<br>- To have a lower weight (OR -4.33; 95% CI -8.16- -0.49).<br>- To have a lower BMI (OR -0.75; 95% CI -1.39- -0.11).<br>- Intervention effect on physical activity, consumption of fruit and vegetables was not maintained during the follow-up periods (OR 1.00; 95% CI 0.57-1.76, OR 0.68; 95% CI 0.39-1.21, OR 0.99; 95% CI 0.57-1.71).<br>- Intervention effect on reading food labels for nutritional values decreased between the 6- and 12-month follow-up (OR 1.97; 95% CI 1.07-3.65 and OR 0.70; 95% CI 0.40-1.23). | I-a |

al. evaluated provision of advice to stop smoking. Both studies were performed in a hospital-based population; Hughes et al. also included pregnant women. Outcomes were self-reported behavior change and were verified with exhaled carbon monoxide measurements in the Hughes et al. and with the biomarker cotinine in de Weerd et al. With only advice to stop smoking, 88% of the self-reported smokers reduced smoking; however, none ceased smoking. The stages of change oriented counselling in Hughes et al. was not proven effective short-term; however, after 12 months women in the intervention group were significantly more likely to maintain smoking cessation than those in the control group.

Although the selection of the study population was unclear in Czeizel et al, overall susceptibility to bias was low. The study of de Weerd et al. is susceptible to an attrition bias: how loss to follow-up is dealt with is unknown. As data collection was based on a letter, items of quality assessment were unclear. Both, Hughes et al. and de Weerd et al. sampled patients within a hospital-based setting. The strength of evidence is I-a [38], and II-2 [29,35].

*Nutrition.* *Three* studies focused on the effectiveness of a nutritional intervention program: one RCT [39] and two case-control studies [34,42]. Caan et al. assessed the effect of long-term enrolment in the WIC supplemental food program with short-term enrolment amongst women with low-income and nutritionally at risk in their interpregnancy interval. Long-term (five to seven months) of WIC support was associated with a positive effect on birth weight and birth length. Cena et al. assessed the effect of nutrition lessons regarding folate amongst low-income non-pregnant women. The comparison group underwent a lesson about resource management. Nutrition lessons lead to increased self-reported intake of dietary folate.

Doyle et al. assessed the effectiveness of a preconception nutrition counselling program (individual consultations; educational group events and nutritional newsletters) amongst women with pregnancy intention and history of prior low birth weight baby and an inadequate dietary intake. The interventions lead to higher intake of certain micronutrients, except for folic acid from diet.

Doyle et al. sampled women in a hospital-based setting. Overall, the quality criteria were assessed as good resulting in a low risk of bias. The strength of evidence is II-2 [34,42] and I-a [39].

*Folic acid.* Thirty studies were identified reporting on the effectiveness of folic acid supplementation and fortification. Sixteen studies were individual-based programs of which 12 RCTs [13-22, 25-26], one cohort controlled trial [23], and three cohort studies [24, 27-28]; 14 cohort studies [43-56] were collective interventions: namely folic acid fortification or public campaigns.

Regarding individual-based programs, 16 studies [13-28] provided folic acid supplements. No studies restricted to only advising folic acid supplements.

From the 15 studies that provided supplements, there were three trials that provided folic acid supplements as well as counselling on folic acid: a significant beneficial effect on self-reported folic acid supplement use was showed [25-27]. Counselling varied from brief folic acid counselling to a computerized educational session. Only Morgan et al. succeeded in showing a significant increase in self-reported daily multivitamin intake. Morgan et al. and Schwarz et al. showed an increase of self-reported use up to six to ten months after the counselling and provision of supplements. Two trials, Watkins et al. and de Weerd et al. assessed the effectiveness of folic acid supplement provision and counselling with biomarkers in addition to self-reported outcomes. Watkins et al. did not show a significant increase in folic acid use based on self-reported outcomes and serum folate levels before and after the intervention. de Weerd et al. reported a significant increase of self-reported supplement use amongst women planning a pregnancy. An elevated red cell folate levels four months post intervention was found. All trials were conducted amongst women of childbearing age; pregnancy intention was not always specified. Susceptibility to bias was assessed as low; the strength of evidence is I-a [25,26] and II-2 [24, 27-28].



Besides the effect of individual folic acid interventions on behavior change, 11 studies reported on the effect on pregnancy outcome. No significant difference in miscarriage rates was shown in one study [13]. Nine studies showed associations with a lower risk for certain congenital anomalies (e.g. urinary tract anomalies, cardiovascular anomalies, limb deficiencies, oral facial clefts, and urinary tract defects, talipes, and hypospadias) [14-20, 22-23].

One study reported a lower incidence of low birth weight in the folic acid supplementation group; the trial did not show an effect on gestational birth weight or preterm birth [21]. Studies reporting on pregnancy outcomes varied in study quality. In MRC Vitamin Study Research Group et al. and Czeizel et al. 1992, 1993, 1993, 1994, 1998, and 2003 many quality items were not clarified. Therefore these studies were assessed as highly susceptible to bias. The strength of evidence is I-a [13-22] and II-2 [23].

Of 14 collective folic acid intervention studies, three cohort studies reported on the effectiveness of a folic acid campaign [43-45]. Chan et al. reported on behavior change and Myers et al. and Gindler et al. reported on pregnancy outcome.

Chan et al. investigated the effect of a folate campaign (information regarding the importance of folic acid in the reduction of NTDs, and pamphlets advertising available resources) targeted to interconceptional women of reproductive age as well as health care professionals. Self-reported consumption of folate rich food and folic acid tablet

use periconceptionally increased from 12% to 18.6% and from 10.1% to 26.7% one year after the campaign.

Myers et al. and Gindler et al. evaluated the effect of a public health campaign targeted to women attending a premarital examination. The intervention in both studies included the advice for women to take folic acid daily from the premarital examination until the end of the first trimester of pregnancy. In Myers et al. supplementation was associated with a risk reduction of 41% in imperforate anus of the child. The study of Gindler et al. showed a higher relative risk (RR) of miscarriages for women with folic acid use (RR 1.03; 95% CI 0.89-1.20). Susceptibility to bias was assessed as low; the strength of evidence is II-2 [43-45].

Regarding collective intervention, 11 large cohorts [46-56] were included reporting on the effectiveness of folic acid fortification. One study reported on behavior change assessed with biomarkers [55] and ten studies evaluated changes in prevalence rates of congenital anomalies [46-54, 56].

Liu et al. evaluated the effectiveness of folic acid food fortification amongst women of childbearing age and seniors over 65 years, recruited pre-fortification through a random telephone survey. Post-fortification the annual rate of NTDs was decreased by 78%, red blood cell folate was significantly increased, and the proportion of women taking a vitamin supplement containing folic acid was significantly increased from 17% to 28%. Susceptibility to bias was assessed as low; the strength of evidence is II-2 [55].

Eight large cohorts assessed the effectiveness of fortification in reduction of NTD prevalence rates [46-52, 54]. Cases were retrospectively selected from birth certificate information and registered databases. All studies showed a decline, ranging from 10% to 54%, in incidence of NTDs post-fortification. Not all studies included stillborn and terminated pregnancies in the time period assessed. Furthermore, subgroup analysis of spina bifida and anencephaly showed a decrease in prevalence varying between 16% and 60%. Susceptibility to bias was assessed as low; the strength of evidence is II-2 [46-52, 54].

Canfield et al. assessed prevalence rates of other congenital abnormalities besides NTDs post-fortification. A decrease in prevalence rates was noted for anencephaly, spina bifida, transposition of the great arteries, cleft palate, pyloric stenosis, upper limb reduction defects, omphalocele, and obstructive genitourinary defects. Susceptibility to bias was assessed as low; the strength of evidence is II-2 [53].

Yazdy et al. showed a significant decline of 6% in orofacial clefts following folic acid fortification in a subgroup of non-Hispanic whites. Susceptibility to bias was assessed as low; the strength of evidence is II-2 [56].

*Multiple risk factors.* Seven studies were identified reporting on the effectiveness of multiple risk factors. The majority of these studies were individual-based programs,

of which two were RCT's [30,31], two were cohort studies [32,37], and one was a cross-sectional study [33]; there were two group-based RCTs [40,41].

Williams et al. retrospectively assessed the effectiveness of receipt of PCC with regard to preconceptional health behaviors. PCC was defined as any form of contact with a health care worker to prepare for a healthy pregnancy. The population consisted of inter-conceptional women planning a pregnancy. Although the definition of PCC was broad, any receipt of PCC (content undefined) lead to higher self-reported intake of multivitamins one month before pregnancy and cessation of alcohol during the three months before pregnancy. Susceptibility to bias was assessed as low; the strength of evidence is II-2 [33]. Hammiche et al. assessed the effectiveness of a tailored lifestyle and dietary consultation in a hospital sampled sub-fertile population that was planning pregnancy. Couples that attended a second counselling session after three months reported higher intake of fruit and fish and reduction of their dietary risk score based on self-reported behaviors and biomarkers. However, only a selection of the sampled sub-fertile patients within a hospital-based setting attended the second consultation. Susceptibility of bias was assessed as low; the strength of evidence is II-2 [37]. Ockhuijsen et al. assessed the effectiveness of PCC consultation in smoking cessation and weight reduction amongst sub-fertile women. The outcome was self-reported smoking cessation and self-reported and weighed mean weight reduction. With consultations every four weeks during a follow-up period varying between three months and one year, 50% (15/30) of obese women lost weight (mean 6.1 kg; SD 3.6) and 30% (7/23) of women quit smoking. Because follow-up period varied amongst study participants there is a susceptibility to a detection bias, as the study results are only applicable to a hospital-based population of sub-fertile women. Overall susceptibility of bias was assessed as low; the strength of evidence is II-2 [32].

Two different multiple risk factor studies assessed effectiveness regarding pregnancy outcomes [30,31]. Lumley et al. assessed the effect of a home visit with pre-pregnancy information, advice and counselling given by midwives amongst low-income women in a community setting. The intervention was compared with a postpartum home visit in which peripartum experiences were discussed. Although birth weight was 97.4 grams lower in the intervention group there was no significant difference in the outcomes: preterm birth (<32 weeks); low birth weight (<2,500 grams) and small for gestational age (birth weight < $10^{th}$ percentile). Quantitative outcomes showed higher occurrence of preterm birth, low birth weight and perinatal deaths. Due to recruitment of women who were at high-risk for poor birth outcomes there is susceptibility for a selection bias. Overall the study was assessed as low susceptibility to bias; the strength of evidence is I-a [30].

Elsinga et al. investigated the effectiveness of systematic PCC risk detection and intervention compared with the standard care given by general practitioners amongst

women contemplating pregnancy. The study population mainly consisted of Dutch and high-educated women. The outcome was self-reported behavior change and adverse outcome of subsequent pregnancy. Systematic counselling and intervention lead to a significant higher intake of folic acid and lower alcohol consumption before pregnancy. Adverse pregnancy outcome (defined as premature birth (<37 weeks); low birth weight (<2,500 grams), small for gestational age (growth <p2,3) and congenital anomalies) was 16,2% in the intervention group vs. 20,2% in the control group. The OR for an adverse pregnancy outcome after preconception counselling was 0.77; 95%CI 0.48-1.22. Susceptibility to bias was assessed as low; strength of evidence is I-a [31].

Hillemeier et al. assessed the effectiveness of a preconceptional group-based intervention program regarding nutrition and physical activity amongst women 'capable of becoming pregnant.' The comparison group did not undergo any intervention. Women in the intervention group were more likely to read food labels, to use a daily multivitamin that contains folic-acid, and to meet recommended levels of physical activity. However, half of the study population did not attend the follow-up consultation and was excluded. Weisman et al. performed a follow-up study to assess the maintenance of the aforementioned behavior changes 12-months after the intervention. After 12 months women of the intervention group were more likely to use daily multivitamin containing folic acid and to have a lower BMI. Intervention effects on physical activity were not maintained, and effects on reading food labels for nutritional values diminished between the six and 12-month follow-up period.

Allocation concealment in Hillemeier et al. and Weisman et al. was unclear and patient sampling was unclear resulting in a potential selection bias. Overall susceptibility to bias was assessed as low; the strength of evidence is I-a [40,41].

*Physical activity and weight loss.* No studies reporting a specific intervention targeting physical activity and weight loss in a preconceptional population were found. Numerous studies did find that when preconceptional health was addressed this had a beneficial effect on physical activity in the short run [37,40] and weight loss [32].

## DISCUSSION

Regarding *alcohol* consumption only one single risk factor study was available. Women engaged in risky behaviors reduced their alcohol consumption to less risky levels following a relatively intensive intervention [36]. However, a multiple risk factor approach in which reduction of alcohol consumption was one of the targeted health behaviors in women contemplating pregnancy was shown to be effective among highly educated women [31]. The identified studies to assess the effectiveness in altering behavior re-

garding alcohol consumptions are only proven effective for a selective group and therefore more evidence is needed to justify that this intervention be embedded in routine care. No studies reported on the effectiveness regarding pregnancy outcome.

The effectiveness of PCC in reducing preconceptional *smoking* cessation is not clear. Hughes et al. only reported maintenance of smoking cessation, verified by a biomarker, on the long-term and only among a small sub-population. A 'stages of change' approach does not seem effective in terms of cessation in the short term but could be considered to achieve maintenance of smoking cessation (38). Results from other studies using a biomarker showed contradictory results: a decrease in initial smokers [29] versus no smoking cessation [35]. However, a large proportion reduced smoking [35]. No studies reported on the effectiveness regarding pregnancy outcome.



*Nutritional* interventions seemed to be effective in changing dietary health behavior. However, alterations were only assessed among a selective group of women, e.g. women living on food stamps with prior adverse pregnancy outcomes [39,42]. Regarding the effect on pregnancy outcome, long-term nutritional support was associated with a positive effect on birth weight [34]. The interventions provided in the available studies are only proven effective for a selective group and therefore more evidence is needed to justify that they be embedded in routine care for the general public contemplating pregnancy.

*Folic acid* interventions were differentiated in individual advice and/or provision of folic acid supplements, and in collective interventions such as public campaigns and food fortification studies. Folic acid interventions proved to be effective in achieving self-reported intake of folic acid when folic acid supplements were provided [25-27]. The studies that assessed effectiveness of provision of folic acid with serum folate as a biomarker were conflicting. However in one of these studies the self-reported outcomes did not support folic acid provision either [24]. The other study did show a slight increase in self-reported folic acid use and maintenance of levels biologically shown by erythrocyte folic acid four months post-intervention [28]. Based on interventions provided in the available studies, it remains unclear whether sole advice to take folic acid supplementation is sufficient to achieve folic acid supplementation compared to the provision of folic acid supplements. To compare effectiveness of sole advice versus advice including provision of folic acid supplements a RCT would need to be conducted, preferably using biomarkers. 11 RCTs reported on the effect of individual folic acid advice, mostly including provision on pregnancy outcomes. Based on one study (with non-significant outcomes) there does not appear to be an effect on the miscarriage rate [13]. Nine studies showed associations with a lower risk for certain congenital anomalies

[14-20, 22-23]. One study showed a lower incidence of low birth weight [21]. Study quality items were unclear in a majority of these studies; it is unclear to what extent results are applicable for the general public. Because folic acid is widely proven to be effective in reduction of the risk for NTDs, this evidence should be considered as further support for interventions to achieve folic acid supplementation preconceptionally.

The findings of the effectiveness of collective approaches regarding folic acid are in line with findings from the individual interventions, described above, regarding the behavior outcomes and effect on pregnancy outcomes. Increase of folic acid intake due to food fortification was further supported by the finding that folate biomarkers increased amongst women post-fortification [55]. Furthermore, a folate campaign was also effective in increasing self-reported consumption of folate rich food and folic acid supplementation [43].

Similar to the individual folic acid studies, the campaigns and fortification studies showed reduced occurrence of congenital anomalies, mainly NTDs [44, 46-54, 56].

Studies on *multiple risk factors* in reducing risky health behaviors all seemed to be effective in one or more targeted risk behaviors, e.g. weight loss, reduction of the number of cigarettes smoked, a higher daily consumption of fruit, fish, and multivitamins and cessation of drinking [31-32, 37, 40]. However, the contents of the interventions were often not specified. One trial succeeded in showing the effectiveness of a multiple risk factor approach on adverse pregnancy outcomes amongst a higher educated group of women in the Netherlands [31]. Further evidence is necessary regarding the beneficial effects of a multiple risk factor approach for PCC above single intervention studies.

### Strengths and limitations

As the studies identified in the review contained clinically heterogeneous data and therefore could not be pooled. Clinical heterogeneity was a result of differences in interventions applied to different (sub) populations in different settings. Tailoring interventions seems to be very important in order to meet demands of different populations; however it does not allow meta-analysis regarding this topic. The timeframe of the intervention within the pregnancy planning scheme was often undefined or classified differently. The duration, method of follow-up and reported outcomes were reported differently by studies. For the aforementioned reasons, this review is descriptive of nature.

The evidence from the studies included in this review is likely to be at some risk of bias. While studies made efforts to reduce bias by aspects of study design such as accounting for loss to follow-up and reporting predefined outcomes, risk associated with unclear patient sampling and unclear allocation concealment could not easily be addressed.

Follow-up was insufficient in a number of studies to measure change in health behavior. Missing data are a particular problem in studies where women are followed over

time, but they are mostly excluded from the analysis. Possible outcomes become difficult to interpret and apply only for a subset of the study population. Findings for those women which are followed up at all data collection points may not be applicable to those women with missing data. For instance, missing data could reflect the fact that an intervention was not feasible for all participants. As a result of missing data, overestimation of the effect could be measured, because the subset of the study population is not representative of the wider population.

Ten [25-27, 31, 33, 36, 39, 41-43] of the nineteen studies relied on only self-report for information on behavior change post-intervention. Self-reported outcomes may not be reliable [57]. In this review the more recent studies introduced the use of biomarkers to assess behavior change. This seems a very welcome introduction, which should be integrated in further research in this topic. A drawback with biomarkers is the diagnostic value regarding the degree to which behaviors have changed. Furthermore not all studies elaborated on the cut-off levels they applied in the interpretation of biomarkers [29, 38, 40, 55]. As the majority of studies did not include follow-up of subsequent pregnancies after the preconceptional intervention or maintenance of health behavior change, the effect on pregnancy outcome could often not be assessed. Because some studies were conducted in specific populations (e.g. hospital-based with sub-fertile women, women at higher risk for adverse pregnancy outcomes, and low income women) it is not clear how easy it would be to transfer interventions to other settings or the general population. Regarding adequate implementation of interventions, it should also be noted that many studies do not describe the details of the intervention thoroughly. More information is necessary, such as who delivered the intervention and how the intervention was exactly implemented to ensure adequate implementation of interventions in the future.

Study populations often compromised of women of childbearing age, without further elaboration of pregnancy intention. It may be that the period with pregnancy intention is a window of opportunity to change risky health behaviors [36]. Women are potentially more motivated to change their behavior in order to have a healthy child. This motivation could be very crucial in the effect of the intervention in achieving and maintaining behavior change.

Besides population and intervention characteristics, as stated above, organizational factors in the setting are of great importance. These organizational factors are largely dependent on the nation's health-care infrastructure, insurance system, and socio-economic factors (1). Articles in this field often lack these details or lack reflection on the relation of these factors with the reported findings. Transfer of this knowledge seems very valuable.

## CONCLUSION

As evidence for preconceptional risk factors associated with adverse pregnancy outcomes is large, there is a need for effective interventions to reduce these risk factors and improve pregnancy outcomes. However, overall, based on the available evidence, there is a relatively short list of core interventions for which there is substantial evidence of effectiveness when applied in the preconception period. Regarding alcohol, evidence is lacking for interventions in the preconceptional period. Regarding nutrition, preconceptional interventions are effective in terms of dietary change and birth weight. Smoking interventions are effective in achieving smoking reduction in the preconception period. Regarding folic acid, individual interventions and collective interventions to increase folic acid use are effective in terms of behavior change and improvement of pregnancy outcomes. The additional benefits of a programmatic approach above a single intervention approach remain difficult to assess; there were no comparative studies. Integration of single interventions into care is a challenging discussion for which implementation studies are necessary. Naturally, despite the relatively short list of core interventions, health care providers should continue with information provision about the consequences and risks of risky behavior to couples wishing to conceive.

Recommendations for future research are: 1) include follow-up of pregnancy outcomes, (2) confirmation of self-reported outcomes, for instance with biomarkers, (3) description of determinants (such as contemplation of pregnancy) that are associated with effective or ineffective treatment outcomes to supply information on the generalizability of findings, and (4) provision of specific information regarding the content of interventions and the setting to guide implementation of interventions.

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## APPENDIX 1: SEARCH STRATEGY

PubMed: (preconception*[tw] OR pre-conception*[tw] OR prepregnan*[tw] OR pre-pregnan*[tw] OR pregestation*[tw] OR pre-gestation*[tw] OR periconception*[tw] OR peri-conception*[tw] OR interconception*[tw] OR inter-conception*[tw] OR interpregnan*[tw] OR inter-pregnan*[tw] OR intergestation*[tw] OR inter-gestation*[tw] OR internatal*[tw] OR inter-natal*[tw]) AND (education*[tw] OR promotion*[tw] OR care[tw] OR cares[tw] OR caring*[tw] OR healthcar*[tw] OR campaign*[tw] OR counsel*[tw] OR wellness*[tw] OR intervent*[tw]) AND (matern*[tw] OR mother*[tw] OR paternal*[tw] OR father*[tw] OR parent*[tw] OR man[tw] OR men[tw] OR woman[tw] OR women[tw] OR couple*[tw]) AND (eng[la] OR dut[la] OR ger[la] OR fre[la] OR spa[la]) NOT (animals[mesh] NOT humans[mesh])

Embase: ((preconception* OR prepregnan* OR pregestation* OR periconception* OR interconception* OR interpregnan* OR internatal* OR intergestation* OR pre-conception OR pre-conceptional OR pre-pregnancy OR pre-pregnant OR pre-gestation OR pre-gestational OR peri-conception OR peri-conceptional OR inter-conception OR inter-conceptional OR inter-pregnancy OR inter-pregnant OR inter-gestation OR inter-gestational OR inter-natal) NEXT/2 (education* OR promotion* OR care OR cares OR caring* OR healthcar* OR campaign* OR counsel* OR wellness* OR intervent*)):ti,ab,de AND (matern* OR mother* OR paternal* OR father* OR parent* OR man OR men OR woman OR women OR couple*):ti,ab,de AND ([english]/lim OR [dutch]/lim OR [german]/lim OR [french]/lim OR [spanish]/lim) NOT ([animals]/lim NOT [humans]/lim)

Web of Science: ((preconception* OR prepregnan* OR pregestation* OR periconception* OR interconception* OR interpregnan* OR internatal* OR intergestation* OR pre-conception OR pre-conceptional OR pre-pregnancy OR pre-pregnant OR pre-gestation OR pre-gestational OR peri-conception OR peri-conceptional OR inter-conception OR inter-conceptional OR inter-pregnancy OR inter-pregnant OR inter-gestation OR inter-gestational OR inter-natal) NEAR/2 (education* OR promotion* OR care OR cares OR caring* OR healthcar* OR campaign* OR counsel* OR wellness* OR intervent*)) AND (matern* OR mother* OR paternal* OR father* OR parent* OR man OR men OR woman OR women OR couple*) NOT (animal* NOT [human*]) AND ([english]/lim OR [dutch]/lim OR [german]/lim OR [french]/lim OR [spanish]/lim)

## APPENDIX 2: QUALITY ASSESSMENT CRITERIA AND ASSESSMENT OF STRENGTH OF EVIDENCE

**Quality assessment criteria: adapted from (10, 58)**

| *Domain* | *Criteria* |
|---|---|
| I Methods for selecting study participants | The source population was appropriate AND in- or exclusion criteria were defined. |
| II Methods for measuring exposure and outcome variables | Methodology was adequate to detect stated outcomes |
| III Design specific sources of bias | a) randomized controlled trials: allocation was concealed<br>b) selection bias: patient selection and sampling (and in case of a case-control or cross sectional study case selection or when applicable matching) was adequate<br>c) detection bias: the length of follow-up was adequate to detect outcome and equally applied amongst all groups<br>d) attrition bias: loss to follow-up/ drops outs were reported and handled appropriately in analysis<br>e) reporting bias: outcomes were pre-specified and there was no selective report on outcomes |
| IV Statistical methods | Statistical procedures were described adequately and if applicable adjustment for confounding factors was reported |
| V Conflicts of interest | Source of funding or conflicts of interests were reported |

**Classification of strength of evidence adapted from the Canadian Task Force for Preventive Medicine (11)**

I-a: at least 1 properly conducted randomized controlled trial BEFORE pregnancy
I-b: at least 1 properly conducted randomized controlled trial not necessarily before pregnancy
II-1: well-designed controlled trials without randomization
II-2: cohort or case-control studies
II-3: multiple time series with or without intervention or dramatic results in uncontrolled experiments

# PART II

## General Preconception Care: Ready for a Baby

# Chapter 5

## Determinants of the intention of preconception care use: lessons from a multi- ethnic urban population in the Netherlands

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## ABSTRACT

**Objectives** To investigate the determinants of the intention of preconception care use of women in a multi-ethnic urban population.

**Methods** The ASE-model –a health behaviour model- was used as an explanatory framework. A representative sample was taken from the municipal population registers of two districts in Rotterdam, the Netherlands, 2009-2010. 3,225 women (aged 15-60 years) received a questionnaire, which was returned by 631: 133 Dutch, 157 Turkish and Moroccan, and 341 Surinamese and Antillean. Descriptive, univariate and multivariate analyses were performed.

**Results** The multiple logistic analyses showed that intention to attend preconception care was significantly higher in women with a Turkish and Moroccan background (β 1.02, p=0.006), a higher maternal age (β 0.04, p=0.008) and a positive attitude (β 0.50, p<0.001). Having no relationship (β -1.16, p=0.004), multiparity with previous adverse perinatal outcome (β -1.32, p=0.001), a high educational level (β -1.23, p=0.03), having paid work (β -0.72, p=0.01) and experienced barriers level (β -0.15, p=0.003) were associated with less intention to use preconception care.

**Conclusions** Modifiable determinants as attitude and barriers can be addressed to enhance preconception care attendance.

## INTRODUCTION

Despite major advances in medical care and the relatively high level of prosperity, poor perinatal outcomes continue to be a problem in the Netherlands [1]. Adverse outcome comprises perinatal mortality and morbidity. For many adverse conditions, antenatal care is often too late [2]. Evidence accumulates on the periconceptional period as the critical stage of exposure to subsequent perinatal risks [3,4]. Therefore, to the extent that risks are modifiable and effective interventions are available, interventions should start before conception. The main goals of preconception care (PCC) are health promotion, risk assessment, counselling and interventions to eliminate risk factors or to reduce their impact. E.g. there is ample evidence on specific components such as the importance of periconceptional folic-acid supplementation [5-8]. Despite significant prospective benefits of PCC the number of consultations are very low [9-11]. Insight in the determinants that encourage or discourage use of PCC is essential to design tailored interventions.



So far, information about determinants of the intention of PCC use among the general population and high risk groups, such as immigrants, is absent or limited to one or two subgroups [9-11].

The aim of the present study was to investigate the determinants of the intention of PCC use in women of a large urban multi-ethnic population, with the social-psychological Attitude–Social Influence–Self Efficacy (ASE) model as point of departure [12].

## METHODS

### Theoretical framework

The ASE-model [13,14] (see Figure 1) postulates that intention to behaviour predicts subsequent behaviour and that intention to behaviour is primarily determined by *attitudes*, *social influences, and self-efficacy* expectations. The ASE-model has been successfully applied in several studies to explain various aspects of health behaviour, such as smoking cessation [15,16] fruit and vegetable consumption [17,18] and fat intake [19]. A person's *attitude* towards a specific behaviour (e.g. PCC use) is the result of the consequences that a person expects from performing that behaviour (e.g. "PCC will enhance a healthier pregnancy"). *Social influences* are the processes whereby people directly or indirectly influence thoughts, feelings and actions of others (e.g. husbands of women considering pregnancy). *Self-efficacy* expectations pertain to a person's belief in his or her own ability to perform the behaviour successfully and relates to one's skill-level. The model additionally emphasizes the importance of minimizing barriers for an intention to be transformed into behaviour. *Barriers* to attend PCC include e.g. being afraid of blood withdrawal. Parallel to it, a person needs to have the appropriate skills for practis-

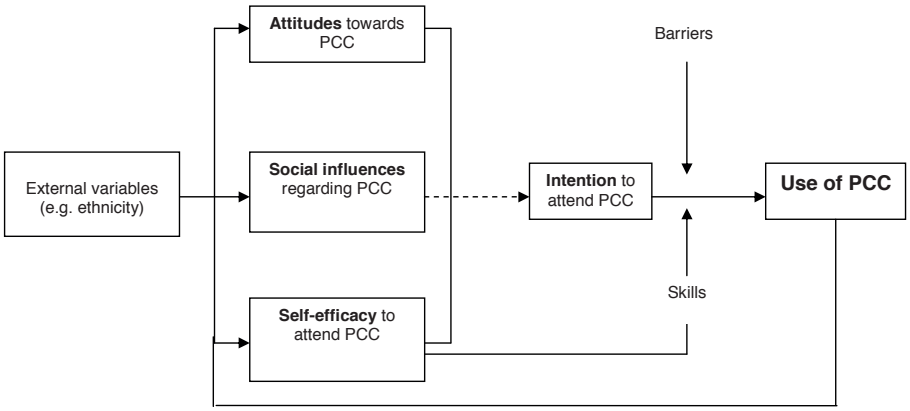


**Figure 1.** Determinants of the intention of preconception care (PCC) use according to the Attitude, Social influences, Self- efficacy model

ing the specified behaviour. *Skills* include both a sufficient educational level and other abilities, e.g. knowledge of risk factors and Dutch language proficiency. Age, gender and ethnicity are considered *external variables* influencing both ASE-determinants and the desired behaviour.

### Development of the questionnaire

A team of experts (psychologist, gynaecologist, epidemiologist, statistician, specialist in health education) took part in the process of the questionnaire development. The literature was searched for validated questionnaires [20-23] to compose the questions in the concepts of the ASE-model. An initial 123-item questionnaire was developed. The feasibility of the pilot version of the questionnaire was tested in six multi-ethnic subjects with a various level of education (mean age: 37 years; range 29-48 years). Subjects were questioned regarding their impressions of the questionnaire; the clarity of the instructions, items and response choices; and their interpretations and opinions of the relevance of each question. Individuals were also asked to provide suggestions on how to reword the instructions, questions and response options. Overall, subjects were positive regarding the questionnaire. Based on their suggestions minor wording changes were made to the instructions and questions. One question was split into two questions, yielding 124 questions.

### Measurements

*Ethnicity* was based on the country of birth of the individual registered in the civil administration. We categorised respondents living in a deprived *neighbourhood* based on the postal code, which can be converted appropriately by the published Dutch index of

deprivation 2007. *Multiparity* was measured by asking if the woman had living children. *Adverse perinatal health outcomes* were assessed by asking for the presence of at least five indicators of perinatal morbidities: preterm birth (<37 weeks of gestation); low birth weight (<2500 grams); congenital anomalies; low Apgar (<7, 5 minutes after birth); admission to NICU.

**ASE-determinants**

Cronbach's α was used to test the internal consistency of the ASE-determinants questions with an increasing Cronbach's α indicating a higher intercorrelation among the questions.

Women's *attitude* towards PCC was measured by whether they rated each of the following statements as strongly disagree, disagree, neither agree nor disagree, agree, strongly agree: (1) PCC before pregnancy is unnecessary, (2) PCC should be free of charge for everyone planning to conceive, and (3) if you visit PCC, you know how to become pregnant in a healthy manner. High scores indicate a positive attitude towards PCC (Cronbach's α in this sample=0.31).

Women's *social-influences* regarding seeking advice for attending a visit of PCC was assessed whether they rated each of the following statements as strongly disagree, disagree, neither agree nor disagree, agree, strongly agree: (1) My husbands opinion is important to me, (2) My family's opinion is important to me, (3) My friends' opinion are important to me, (4) My neighbours' opinion are important to me, and (5) I am afraid of negative reactions if I have a baby with problems. High scores indicate a high degree of perceived social influences (Cronbach's α in this sample =0.86).

Women's expectations toward their own belief in the ability to perform the demanded behaviour successfully before pregnancy -*self-efficacy*- was measured by asking them to rate the following statements as very difficult, a bit difficult, easy, very easy, and I'm not overweight or don't smoke/drink/use drugs: (1) If you have overweight, how difficult is it to lose weight?, (2) If you smoke, how difficult is it to quit?, (3) If you drink alcohol, how difficult is it to quit?, (4) If you use (soft) drugs, how difficult is it to stop using?, (5) How difficult is it to take folic-acid daily?, and (6) How difficult is it to attend PCC regularly (e.g. once per month) to seek advice or get information? High scores indicate positive expectations of women to realise the desired behaviour (Cronbach's α in this sample =0.58).

**Skills**

*Educational* and *household income* levels were used as indicators of socio-economic position indicating high/low level of skills. *Educational level* was defined as the highest completed education (no education/primary education, lower secondary education,

higher secondary education, and higher vocational college/university) and classified into three categories: 1) low; 2) moderate; and 3) high. *Household income* was recorded on a scale from 0 to >2500 euro on which respondents could mark the net household income. The marked amount was divided into 3 categories (<1000 euro; 1000-2500 euro; and 2500 euro and more) with standardization by household size.

*Dutch language proficiency* was measured by asking: When someone talks to you in Dutch, are you able to understand? yes often/always, yes sometimes, no. A summated score was calculated which was subsequently recoded in low, moderate or high mastery of Dutch language.

*Women's knowledge of risk factors* for a healthy pregnancy was measured by whether they rated each of the following statements as true: (1) pregnancies close behind each other are good for baby's health, (2) smoking adversely affects fertility, (3) being underweight or overweight adversely affects fertility, (4) sexually transmitted disease must be treated before pregnancy, (5) all medications from drugstores are safe and can be used during pregnancy, and (6) the best moment to start with folic-acid supplementation is when you got pregnant. High scores indicate a high knowledge of perinatal risk factors (Cronbach's α in this sample =0.59).

### Barriers

Perceived *barriers* were measured by asking respondents to rate the following statements as: strongly disagree, disagree, neither agree nor disagree, agree, strongly agree: (1) I am afraid to attend PCC if blood is withdrawn, (2) PCC takes too much time and effort, (3) I am reluctant regarding PCC, (4) PCC is useless, (5) if I attend PCC I feel pressured to have a perfect baby, (6) I'm afraid of negative reactions from my husband or family when I attend PCC, and (7) Religion forbids attendance of PCC. High sum-scores indicate that women perceive more barriers (Cronbach's α in this sample =0.69).

### Intention to attend

*Intention* to attend PCC was assessed by asking to rate the following statements as: strongly disagree, disagree, neither agree nor disagree, agree, strongly agree: (1) If I have access to free PCC counselling before pregnancy, I would definitely go, (2) If I have access to PCC counselling before pregnancy and it costs 15 Euro, I would definitely go, (3) If I have to quit smoking and/or drinking before pregnancy, I would definitely quit (4) If I have access to PCC every month before pregnancy for advice and a free test, I would definitely go, and (5) If I have to take daily folic-acid before pregnancy, I would definitely do it. High scores indicate a high intention to incline for PCC (Cronbach's α in this sample =0.83).

## Participants and data collection

We included a northern and southern district in the city of Rotterdam consisting of 120,000 inhabitants of whom 60% is of immigrant origin and 30% lives below welfare standard with mean perinatal mortality rates of 8.9 per 1000 births (north) and 11.3 per 1000 births (south). Perinatal morbidity comprised of preterm birth, intrauterine growth restriction, congenital anomalies and low Apgar (<7, 5 minutes after birth) exists in 17.4% and in 18.1% of all births in the northern and southern district respectively [24]. In Rotterdam perinatal mortality rates range from 2 to 37 per 1000 births in neighbourhoods [25].

To obtain a representative sample, we predefined 15 strata consisting of three age categories (15- ≤30, 30- ≤45, 45- ≤60 years) and five ethnic groups (the four largest immigrant groups: Turkish, Moroccan, Surinamese and Antillean, and a Dutch reference group). The oldest (and partially non-fertile) age categories were also included as it seemed interesting considering the importance of social influence of older persons/ family members on behaviour of the fertile age group [26]. For each stratum, 75 women were drawn from the municipal population registers.

Between January 2009 and October 2010, 3,225 women received a questionnaire in Dutch accompanied by an English or Turkish translation depending on the respondent's ethnic background. In general Surinamese and Antilleans speak fluently Dutch whereas



**Table 1.** Characteristics of the population in the northern and the southern district of Rotterdam.

| | *Northern district (n=50321)* | *Southern district (n=70422)* |
|---|---|---|
| **Ethnicity, %** | | |
| Dutch | 49 | 34 |
| Turkish and Moroccan | 19 | 29 |
| Surinamese and Antillean | 10 | 15 |
| **Age, %** | | |
| 0-14 yrs | 14 | 19 |
| 15-64 yrs | 76 | 70 |
| > 65 yrs | 10 | 11 |
| **Type of relationship, %** | | |
| Married | 24 | 31 |
| Relationship/unmarried | 1 | 1 |
| No relationship | 63 | 53 |
| **Educational level, %** | | |
| Low | 29 | 17 |
| Moderate | 51 | 33 |
| High | 20 | 50 |
| **Income level, %** | | |
| Low | 55 | 60 |
| Moderate | 33 | 31 |
| High | 12 | 9 |

Rotterdam, the Netherlands, 2010.

Turks and Moroccans who were born abroad do not always master the Dutch language. Arab translations were not used since most Moroccans in the Netherlands speak Berber-Moroccan, which is an oral language. After two weeks, respondents received a reminder. In case of insufficient response trained interviewers contacted non-responders for oral interviews by home visits. The characteristics of the non-responders are comparable with the characteristics of the population in the two districts of Rotterdam (Table 1).

### Statistical analyses

First we compared baseline characteristics according to ethnic background using the Chi-Square or Fisher's Exact tests for categorical variables and the Mann-Whitney U Test for age. Measured by statements, we compared ASE-determinants regarding intention to attend PCC using the Mann-Whitney U Test and the Chi-square test for social influences and barriers. The skewed variables ('knowledge of risk factors', 'attitude', 'self-efficacy' and 'intention') were stated in a median.

The regression model was built choosing the dependent (external variables, ASE, skills, and barriers) and independent (intention of attending PCC) variables using the 'enter' method. To avoid selection due to missing values, we included the category 'not reported' as separate category for the independent variables 'educational level' and 'Dutch language proficiency'. All tests were two-sided, and *p* values of 0.05 were considered statistically significant. The analysis was performed with the SPSS software for Windows, version 15.0.

## RESULTS

Questionnaires were filled out by 631 women (overall response rate 20%: Dutch 21%, Turkish and Moroccan 25%, and Surinamese and Antillean 54%) of which 42 women (6.7%) completed the questionnaire by oral administration.

Of all ethnic groups, Turkish and Moroccan were the oldest ($p=0.004$), more often married ($p<0.001$) and more frequently living in deprived neighbourhoods ($p<0.001$). More immigrant women had at least one child ($p<0.001$) and had more frequently experienced an adverse perinatal outcome ($p<0.001$) in a previous pregnancy when compared to Dutch women. Turkish and Moroccan women were more often low to moderately educated ($p<0.001$). Dutch, Surinamese and Antillean women more frequently had a low to moderate income level ($p<0.001$) and more frequently paid work ($p<0.001$). The Dutch language proficiency of Turkish and Moroccan women differed from the other groups, they reported more often a moderate language proficiency ($p<0.001$) (Table 2).

**Table 2.** Baseline characteristics of the participants by ethnic background (n=631)

| | *Dutch (n=133)* | *Turkish and Moroccan (n=157)* | *Surinamese and Antillean (n=341)* | *P* |
|---|---|---|---|---|
| ***External variables*** | | | | |
| **District, n (%)** | | | | *<0.001* |
| Northern | 70 (53) | 54 (34) | 186 (55) | |
| Southern | 63 (47) | 103 (66) | 155 (45) | |
| **Median age (years, range)** | 37 [18-62] | 42 [21-62] | 41 [16-62] | *0.004* |
| **Type of relationship, n (%)** | | | | *<0.001* |
| Married | 45 (34) | 102 (65) | 76 (22) | |
| Relationship/unmarried | 47 (35) | 12 (8) | 106 (31) | |
| No relationship | 41 (31) | 43 (27) | 158 (47) | |
| **Neighbourhood, n (%)** | | | | *<0.001* |
| Deprived | 59 (44) | 110 (70) | 214 (63) | |
| **Parity, n (%)** | | | | *<0.001* |
| 1 or more | 56 (42) | 114 (73) | 227 (68) | |
| **Adverse outcome, n (%)** | 33 (25) | 58 (37) | 187 (55) | *<0.001* |
| ***Skills*** | | | | |
| **Educational level, n (%)** | | | | *<0.001* |
| Low | 12 (9) | 72 (50) | 47 (15) | |
| | 48 (37) | 60 (41) | 193 (60) | |
| Moderate | 70 (54) | 13 (9) | 84 (26) | |
| High | | | | |
| **Income level, n (%)** | | | | *<0.001* |
| Low | 57 (43) | 119 (76) | 148 (43) | |
| Moderate | 53 (40) | 33 (21) | 177 (52) | |
| High | 23 (17) | 5 (3) | 16 (5) | |
| **Paid work, n (%)** | 99 (77) | 52 (35) | 231 (72) | *<0.001* |
| **Dutch language proficiency, n (%)** | | | | *<0.001* |
| Low | 0 | 17 (11) | 2 (1) | |
| Moderate | 7 (5) | 63 (40) | 20 (6) | |
| High | 124 (95) | 75 (49) | 315 (93) | |

Rotterdam, the Netherlands, 2009 and 2010.
Chi-Square test or Fisher's exact test was performed.
Differences in age were tested with Mann-Whitney U Test.

About half of the women had little knowledge of the adverse effect of smoking (Dutch 58%, Turkish and Moroccan 54% and Surinamese and Antillean 45%;p=0.04) and over-underweight (Dutch 60%, Turkish and Moroccan 44% and Surinamese and Antillean 60%;p=0.003) on fertility (Fig. 2). Adequate knowledge of folic-acid use was especially low for immigrant women (Dutch 76%, Turkish and Moroccan 62% and Surinamese and Antillean 57%;p<0.001). Furthermore, knowledge levels differed across ethnic groups. Turkish and Moroccan women overall had the lowest knowledge levels while the Dutch women had high knowledge levels. The Surinamese and Antillean group took an intermediate position.

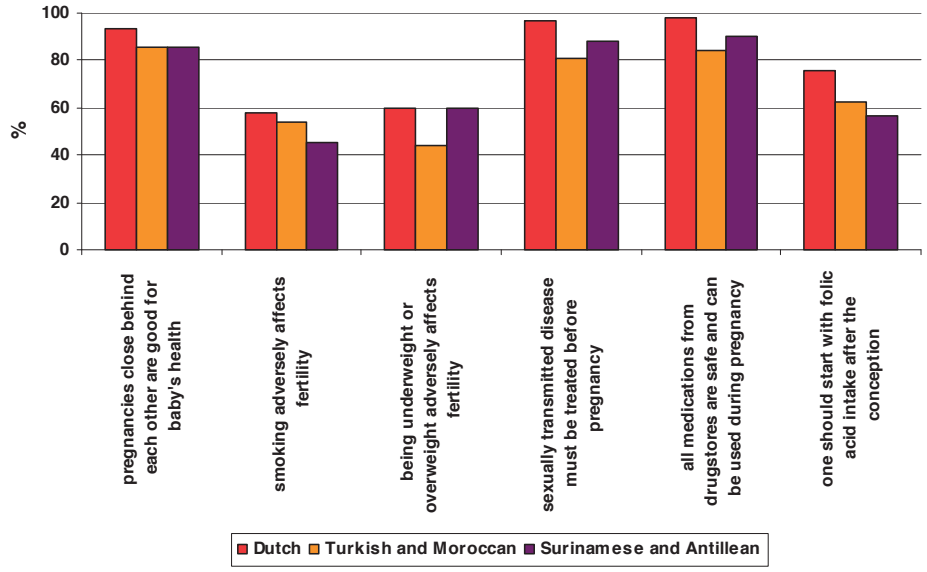


**Figure 2.** Knowledge of risk factors (% of correct answers, n=631)
Rotterdam, the Netherlands, 2009 and 2010.

Women reported their husband (p=0.21) as the most important social influence; the ethnic groups did not differ in this respect. Significant ethnic differences however exist in the influence of family (p<0.001), friends (p=0.01) and neighbours (p<0.001), these are playing a more influential role for Turkish and Moroccan women. In accordance with Figure 2, knowledge about risk factors was significantly (p<0.001) higher for Dutch women (Table 3); the immigrant groups did not differ in this aspect. Often reported barriers were time and effort (p=0.35) and, to lesser extent blood withdrawal (p=0.06) and ethnic groups did not differ in this respect. Moreover, about 50% of Dutch women regarded PCC as useless, a significantly higher proportion compared to the immigrant groups (p<0.001). Turkish and Moroccan women reported a significantly higher proportion of feeling pressured to have a perfect baby (p=0.05). Significant ethnic differences existed in the intention to attend PCC, immigrant women being more positive (Dutch 6.33; Turkish and Moroccan 8.0, and Surinamese and Antillean 7.33;p<0.001).

**Table 3.** Attitudes, social influences, self-efficacy, knowledge of risk factors, barriers regarding PCC and intention to use PCC (n=631)

| | *Dutch (n=133)* | *Turkish and Moroccan (n=157)* | *Surinamese and Antillean (n=341)* | *P* |
|---|---|---|---|---|
| **Attitude towards PCC (median;range 0-10)** | 7.5 [0-10] | 7.4 [2.5-10] | 7.5 [0-10] | 0.29 |
| **Social influences regarding PCC, n (%)** | | | | |
| Husband is important | 82 (67.8) | 98 (77.8) | 236 (73.6) | 0.21 |
| Family is important | 36 (29.8) | 68 (54.8) | 121 (38.8) | *<0.001* |
| Friends are important | 23 (19.0) | 42 (35.0) | 72 (23.2) | *0.01* |
| Neighbours are important | 2 (1.7) | 23 (19.2) | 16 (5.2) | *<0.001* |
| Being afraid for negative reactions | 10 (8.3) | 15 (12.2) | 46 (14.6) | 0.21 |
| **Self-efficacy to attend PCC* (median;range 6-27)** | 11 [6-20] | 11 [6-22] | 11 [6-27] | 0.92 |
| **Knowledge of risk factors for a healthy pregnancy (skills) (median;range 0-10)** | 8.6 [0-10] | 7.1 [0-10] | 7.1 [0-10] | *<0.001* |
| **Barriers regarding PCC**, n (%)** | | | | |
| Fear for blood withdrawal | 5 (7.4) | 12 (22.2) | 25 (14.1) | 0.06 |
| Time and effort | 23 (33.8) | 12 (22.2) | 48 (27.1) | 0.35 |
| Reluctance to PCC | 4 (5.9) | 4 (7.5) | 17 (9.7) | 0.62 |
| Preconception care is useless | 31 (45.6) | 7 (13.2) | 35 (20.1) | *<0.001* |
| Feeling pressured to have a perfect baby | 7 (10.3) | 12 (22.6) | 18 (10.3) | *0.05* |
| Being afraid of negative reactions | 2 (2.9) | 5 (9.4) | 13 (7.5) | 0.32 |
| Forbidden by religion | 0 (0) | 3 (5.7) | 4 (2.3) | 0.13 |
| **Intention to use PCC (median;range 0-10)** | 6.33 [0-10] | 8.0 [0-10] | 7.33 [0-10] | *<0.001* |

Rotterdam, the Netherlands, 2009 and 2010.
PCC=preconception care.
* A higher score represents larger degree of self-efficacy.
** A higher score represents more barriers.

The multivariate regression analyses showed that Turkish and Moroccan background, higher age and a positive attitude were significantly associated with higher intention to attend PCC (Table 4). Variables contributing to a significantly lower intention to attend PCC were: having no relationship, multiparity with previous adverse outcome, high educational level, having paid work and experienced barriers level.

**Table 4.** Results of the multiple linear regression analysis of the intention to attend PCC (n=631)

| | *β* | *95% CI* | *P* |
|---|---|---|---|
| ***External variables*** | | | |
| **Ethnicity (reference: Dutch)** | | | |
| - Turkish and Moroccan | 1.02 | 0.30 to 1.73 | *0.006* |
| - Surinamese and Antillean | 0.70 | -0.20 to 1.60 | 0.13 |
| **Higher maternal age (every increase of age in years)** | 0.04 | 0.01 to 0.07 | *0.008* |
| **Type of relationship (reference: married)** | | | |
| - relationship/unmarried | -0.58 | -1.43 to 0.28 | 0.19 |
| - no relationship | -1.16 | -1.95 to -0.37 | *0.004* |
| **Neighbourhood (reference: non-deprived)** | | | |
| - deprived | 0.19 | -0.37 to 0.74 | 0.50 |
| **Multiparity with or without previous adverse perinatal outcome (reference: nulliparity)** | | | |
| - multiparity with adverse outcome | -1.32 | -2.09 to -0.55 | *0.001* |
| - multiparity without adverse outcome | -0.30 | -1.62 to 1.02 | 0.65 |
| ***ASE-determinants*** | | | |
| **Attitude level towards desired behavior (range 0-10)** | 0.50 | 0.36 to 0.65 | *<0.001* |
| **Social influences towards desired behavior (importance)** | 0.06 | -0.20 to 0.31 | 0.67 |
| - husband | 0.08 | -0.25 to 0.40 | 0.64 |
| - family | 0.19 | -0.21 to 0.58 | 0.35 |
| - friends | -0.34 | -0.80 to 0.11 | 0.14 |
| - neighbours | 0.04 | -0.31 to 0.40 | 0.81 |
| - being afraid for negative reactions | | | |
| **Self-efficacy level towards desired behavior (range 6-27)** | -0.02 | -0.09 to 0.06 | 0.68 |
| ***Skills*** | | | |
| **Educational level (reference: low)** | | | |
| - moderate | -0.98 | -1.95 to 0.004 | 0.05 |
| - high | -1.23 | -2.31 to -0.15 | *0.03* |
| - 'not reported' | -2.38 | -4.61 to -0.16 | *0.04* |
| **Income level (reference: low)** | | | |
| - moderate | 0.11 | -0.63 to 0.84 | 0.77 |
| - high | 0.51 | -0.67 to 1.69 | 0.39 |
| **Paid work (yes)** | -0.72 | -1.29 to -0.15 | *0.01* |
| **Dutch language proficiency (reference: low)** | | | |
| - moderate | 2.40 | -0.31 to 5.11 | 0.08 |
| - high | 1.87 | -0.84 to 4.58 | 0.17 |
| - 'not reported' | 1.75 | -1.54 to 5.04 | 0.30 |
| **Knowledge level of perinatal risk factors (range 0-10)** | 0.09 | -0.05 to 0.23 | 0.19 |
| ***Barriers*** | | | |
| **Barriers level (range 7-22)** | -0.15 | -0.25 to -0.05 | *0.003* |

Rotterdam, the Netherlands, 2009 and 2010.
PCC= preconception care.
CI= Confidence Interval.
Adjusted R square 0.46.

### Analysis of interaction between variables

Investigation of the correlation between variables included in the multiple linear regression model was performed using Spearman correlation. As expected, strong positive association was found between the variables of social influences: family-friends (r=0.80), family-neighbours (r=0.74), neighbours-friends (r=0.84), and friends-negative reactions (r=0.73). Further, adverse outcome was correlated with parity (r=0.87); these variables were converted to an interaction variable multiparity with/without adverse outcome.'

## DISCUSSION



This study is one of the first population-based studies investigating determinants of the intention of PCC use. First, Turkish and Moroccan background, higher age and a positive attitude are related to a *higher* intention to attend PCC and secondly having no relationship, multiparity with adverse outcome, high educational level, having paid work and a high barrier experience are related to a *lower* intention. These results give insight into the determinants of the intention of PCC use and they provide information about how women can be stimulated and reached to attend PCC. E.g. multiparous women with adverse outcome in the past could be proactively referred by doctors in the Centre for Youth and Family to interconception care. Highly educated women could be addressed on schools, education programs and campaigns on the importance of PCC. Evening consultation hours could be introduced by health care professionals to make PCC more accessible for working women.

Before discussing the results we review possible limitations of our study. Although possible response bias should be taken into account, we don't believe any response bias has been introduced. The non-responders were not a selective group; no significant differences in characteristics (gender, age, neighbourhood, education) between responders and non-responders were found. The most frequent reason for non-response was returned incomplete or not filled out questionnaires, due to removal, wrong address in the registry or death. Compared to the immigrant women, Dutch women were less represented; 21% in our study vs. 55% in the population of Rotterdam. The representativeness of Turkish and Moroccan women (25% in our study vs. 12% in the population of Rotterdam) and Surinamese and Antillean women (54% in our study vs. 12% in the population of Rotterdam) was relatively higher in our sample. However, we do not expect that this had affected our results. There is a study on the effect of selective ethnicity-related non-response. The ABCD-study on ethnicity related perinatal health [27] was able to pursue an empirical approach of non-response effects: data on non-respondents (outcomes and determinants) could be retrieved anonymously from national registries.

It was observed that the prevalence of outcomes and determinants (like e.g. education) were affected due to selective participation. However, associations and results from regression analysis for a number of known perinatal relations of social and medical determinants with perinatal health were not affected to any relevant degree. Although, the outcome of our study is a different outcome than the ABCD-study we assume that the relation studied is not affected by differential non-response selection bias.

Retrospective data, e.g. adverse clinical outcomes in our questionnaire, are often subjected to recall bias and could lead to a potential for over- or underestimation. Pregnancy and delivery are very important for most women and not easily to forget. However, there can be very well difference of interpretation of an outcome between doctor and the mother. This could have an effect on the estimation of adverse outcomes in our (sub) study group. The Generation R study showed that among Antilleans and Surinamese a lower prevalence of SGA [28] and a higher prevalence of preterm deliveries [29] exist.

Our results are comparable to a recent study [30] exploring the *intentions* of Turkish female immigrants to participate in preconception carrier screening for haemoglobinopathies. The wish to reduce uncertainty induced the intention to participate in preconception carrier screening [31]. Secondly, we found that increasing age is associated with higher intention to attend PCC. Possibly because of a higher awareness of perinatal risk factors prior to pregnancy and higher health literacy compared to young adults. Women with a low level of health literacy have higher disease outcomes [32] and have less knowledge of preventive health practices [33], and are less motivated in preventive activities. Additional research has to explore the relation between risk-perception, knowledge and intention of PCC use. Thirdly, women without a relationship - as expected - had less intention to attend PCC, possibly because they feel it is not their concern yet. Nonetheless, women without a relationship can become pregnant too and therefore should be informed about preconceptional health. Fourthly, multiparous women with a previous adverse perinatal outcome are less inclined to attend PCC. In a study [34] identifying factors that are predictive of late initiation of antenatal care, a high obstetric risk was significantly associated with late initiation of antenatal care by primiparous women. One might reason that less intention to attend PCC is the result of negative experience of the adverse outcome. This might be due to the negative experience with health professionals or the expectation that PCC can not influence outcome in a positive way.

Furthermore, the vast majority of women reported a positive attitude regarding PCC. As in our study, in two other studies [35,36], a great willingness on the part of women to optimise their health in preparation for pregnancy was reported.

Higher educated women were *less* intended to attend PCC. This finding is consistent with a qualitative study [37] exploring why women did not respond to an invitation to attend for PCC. These women perceived themselves as having sufficient knowledge

of PCC and/or not being at risk. In two other studies [9,11] evaluating knowledge and beliefs of women about PCC demonstrated that a majority of women do understand the importance of optimising their health prior to conception. These aforementioned studied populations demonstrated deficiencies in knowledge of risk factors that impact maternal and fetal health. Although, in our study the level of knowledge of risk factors appeared low, it was not a determinant of intention of PCC use.

We expected a relationship between Dutch language proficiency as a *skill* and intention of PCC use. We, however, found no such relationship in contrast to a previous Dutch study on folic acid knowledge and use in a multi-ethnic pregnancy cohort [38]. In our study the majority of Turkish and Moroccan women considered their Dutch language proficiency as good which is in accordance with the annual national survey of the Social and Cultural Planning [39], 45-50% of both Turkish and Moroccan reported no difficulty with the Dutch language. We calculated the correlation between Dutch language proficiency and intention to attend PCC and the highest association was found for moderate language proficiency. We don't believe low literacy was a barrier, because questionnaires were accompanied with a translation and non-responders were visited at home for oral administration by interviewers in their own language.



Although we found clear ethnic differences in the influence of family in the decision of women to attend PCC, it had insufficient explanatory power of intention of PCC use. Lakeman et al. [20] explored the determinants of participation in preconceptional ancestry-based carrier couple screening for cystic fibrosis and haemoglobinopathies. Similar with our findings a higher social influence for participants of non-Western origin was found.

Furthermore, *self-efficacy* is an important independent predictor for other behaviours such as smoking cessation [15,16], but we found no independent influence on the intention to attend PCC. Apparently, women consider themselves capable enough to visit a GP or a midwife, which is of course quite different then smoking cessation or losing weight.

Finally, we found a clear relationship between experienced *barrier* and intention of PCC use. Working women were less inclined to visit a PCC consult, maybe because work complicates visiting PCC during office hours. This result is an important signal to health care professionals who should facilitate access to PCC services. Health professionals could introduce evening consultation hours to facilitate access to PCC.

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# Chapter 6

## Knowledge on preconceptional folic acid supplementation and intention to seek for preconception care among men and women in an urban city: a population-based cross-sectional study

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## ABSTRACT

**Background** To study the knowledge of a large city population on preconception folic acid supplementation and intention to seek for preconception care within an urban perinatal health program.

**Methods** Cross-sectional surveys run in Rotterdam, the Netherlands, in 2007 and annually from 2009-2014. A random sample of residents aged between 16-85 years was taken each year from the municipal population register. Bivariate analysis, interaction analysis, trend analysis and logistic regression were performed.

**Results** Knowledge on preconceptional folic acid supplementation significantly improved (+20%) between 2007 and 2009, and the intention to consult a GP or midwife in the preconception period significantly increased (+53%) from 2007 to 2012. Logistic regression analyses showed that low socio-economic status was significantly associated with low preconceptional folic acid knowledge, but with higher intention to seek out preconception care. An interaction effect was found between educational level and ethnicity, showing that the higher the educational level the lower the gap of level of knowledge between the different ethnic groups.

**Conclusion** Despite campaigns about folic acid supplementation knowledge on this supplement remains low. The intention amongst men and women to seek out preconception care is still insufficient. Structural interventions to increase and maintain awareness on folic acid supplementation, especially among high-risk groups, are needed.

## BACKGROUND

Preconception care (PCC) is an essential component of maternal and child healthcare. PCC is defined as the set of preventive interventions targeted at women of reproductive age and their partners to improve pregnancy outcomes. A wide range of preconception risk factors are found to be associated with adverse foetal outcomes, and many of these risk factors are amenable to prevention [1, 2]. For selected outcomes (e.g. neural tube defects (NTDs)), prevention through PCC have shown to be effective [3].

A population study showed that 98% of couples hoping to have a child exhibit at least one risk factor amenable for intervention, thus justifying individual counselling [4]. Despite the seemingly straightforward positive benefits of PCC and the high percentage (80%) of planned pregnancies (among the native Dutch population) fit for the application of PCC [5], the observed number of individual PCC consultations is negligible [6]. Lack of knowledge about common preconception risk factors seems to be one of the critical factors hindering the widespread application of PCC: in a population study in Rotterdam half of the non-pregnant study population (n=631) were unaware of the adverse effect of smoking and being overweight on fertility [7]. Although, this outcome is in contrast with other results [8], specific preconception health knowledge, e.g. folic acid (FA) use, was also scarce [7].



Since appropriate FA use before and during early pregnancy has been shown to protect against NTDs and other congenital anomalies [9, 10], public awareness campaigns have been launched to raise FA supplementation [11]. In the Netherlands, the last government-sponsored mass-media campaign was in 1995. In absence of continued reinforcement of this message, the use of FA supplementation has lowered. The initiative of local pharmacies in 2004 to inform women using oral contraceptives of the benefits of preconceptional FA supplementation seemed to have had little effect on FA use, with supplementation levels remaining at 36% [12].

In 2009, the Rotterdam municipality and the Erasmus University Medical Centre, supported by health scientists, launched the Ready for a Baby program [13] aimed at improving perinatal health. The PCC sub-study was the first chain in this comprehensive urban program, including PCC pilot projects in selected North (2008-2010) and South (2010-2012) districts of the city of Rotterdam. Beyond interventions to raise awareness for preconceptional FA use and PCC utilization, the program aimed at reaching vulnerable population groups, such as migrants and those with low socio-economic status (Figure 1).

The aim of the present study was to investigate knowledge of preconception FA supplementation and intention to seek for PCC in the city of Rotterdam.

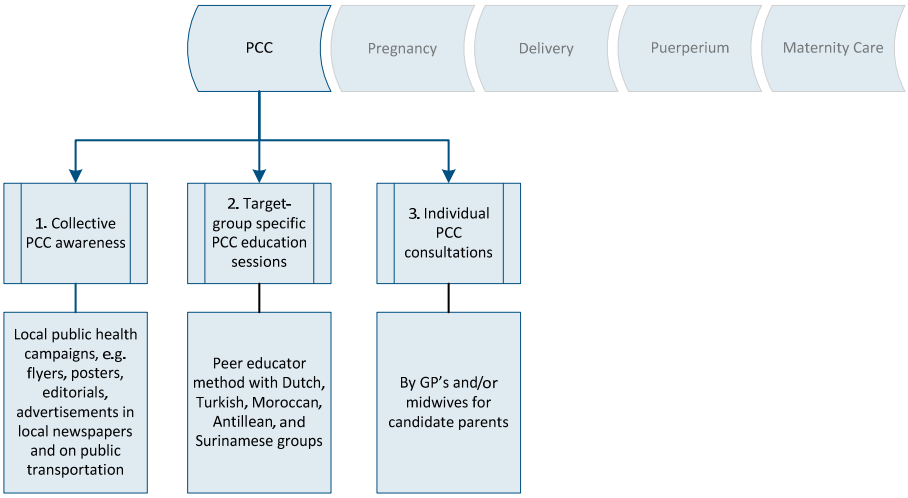


**Figure 1.** Obstetrical chain of care within the Ready for a Baby program

The PCC sub-study was the first chain in this comprehensive perinatal health program. The objective of the PCC sub-study was to develop and organize standardized general PCC. For this purpose three approaches were combined in two pilot districts of Rotterdam: (1) collective PCC awareness through local public health campaigns, (2) target group-specific PCC education sessions through the 'peer educator' method, and (3) individual PCC consultations by GP's and midwives.

## METHODS

### Study design

Within the PCC sub-study three pillars (Figure 1) were combined to have maximum reach and impact: 1) the aim of the public campaign was to raise awareness and attention about the provision and the content of PCC, and to provide information about activities in the PCC pilot projects. 2) The aim of the target groups-specific PCC sessions was to transfer knowledge and awareness about PCC and to motivate the target group to make use of individual PCC. Three types of education were developed and executed by six women and one men from different ethnic origin given in their native language through their existing network in the neighbourhoods and places where people met each other, e.g. mosques and schools. The course centered around information provision about the importance of a good preparation of a pregnancy, the timely intake of FA supplementation, prenatal screening, and the prevalence of genetic disorders among some migrant groups, such as sickle cell disease and Thalassemia with several materials to make the sessions interactive. On the side note other health promotion approaches were also involved like enhancing autonomy and empowerment, but the effects of these other approaches on the results were not measured in this study. In the final session, the group of women accompanied by the peer educator visited a midwifery practice in

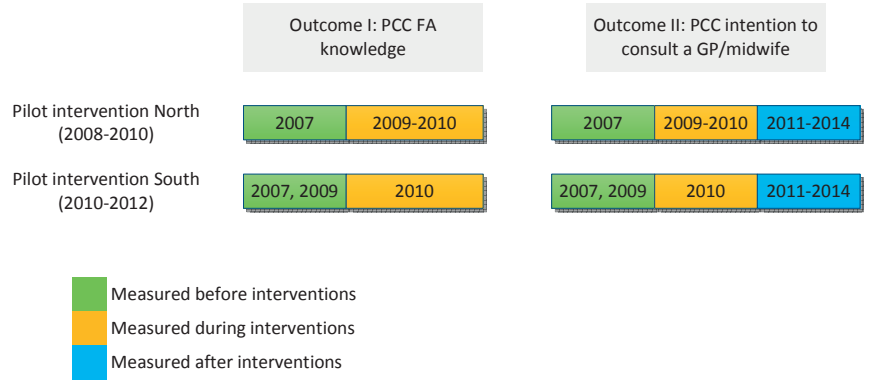


**Figure 2.** Outcomes within the Omnibus Survey per pilot intervention district and measured study years correlating with the pilot interventions



the neighbourhood. The men's session was compromised to a single session. 3) General individual PCC was provided by GP's and midwives using www.ZwangerWijzer.nl; an evidence-and practice-based web application that for candidate parents allows to make an individual risk assessment [14].

In this population-based study we used seven citywide cross-sectional surveys (2007, 2009-2014) which measured citywide, and two districts knowledge on preconception FA supplementation and intention to seek out PCC at different times. Using these seven cross-sectional surveys we performed a trend-analysis to observe changes in PCC knowledge. See figure 2 for a scheme of the study design.

## Outcomes

The primary outcome was preconception FA knowledge measured over three years (2007, 2009, and 2010). This outcome reflected the affirmative response to the question 'A woman who wishes to become pregnant should take FA supplementation before she tries to become pregnant', with three non-ordered response levels (no, that is not necessary; yes, she certainly should; and don't know/ not relevant). After 2010 this outcome was not included in the survey due to different policy prioritization.

The secondary outcome was the response to the question regarding the intention to seek out PCC, measured over seven consecutive years (2007, 2009-2014). This outcome reflected the response to the question 'A woman who wishes to become pregnant should consult a GP or midwife before she tries to become pregnant', with four non-ordered response levels (no, that is not necessary; only in case of problems; yes, she certainly should; and don't know/ not relevant). In 2008 both outcomes were not included in the survey.

In terms of medical adequacy (first outcome) and given that every couple could benefit from PCC (second outcome), '*yes, she certainly should*' was regarded as the only correct response. Response levels on both outcomes were recoded into a two-level outcome ('other' vs. 'yes') in order to perform logistic regression analysis.

### Population

Rotterdam is the second largest city in the Netherlands (610,412 inhabitants: 48% non-Dutch origin) with the highest number of deprived neighbourhoods (seven) and large socio-economic inequalities [15]. The four major immigrant groups are: Surinamese 8,5%; Turkish 7,8%; Moroccan 6,7%; and Antillean 3,8% [16]. Although the ethnic minorities and the age category <45 years are underrepresented in the Omnibus Survey, the response rate is still representative for the whole city, and large enough to make statements and search for changes in trends [17]. The age category over 45 years was included in the analysis as knowledge of elderly family members about PCC can influence the behaviour of younger people within their family [18]. Although the existing of cultural and socio-economic differences relating to responsibility and family planning, men were also included. Their role in PCC is important: family planning is a shared responsibility and some risk factors, such as smoking and sexually transmitted diseases, are joint [19]. Moreover, literature on gender differences in PCC utilization is scarce.

### Data collection

Study-specific survey items were added to the *Omnibus Survey*, a paper survey run annually using a random sample of 3,500 Rotterdam citizens aged between 16-85 years. The study-specific items were previously tested and included in a survey which was used to study the determinants of the intention of PCC use [7]. In case of insufficient response among the immigrant groups, trained male and female interviewers administered the Dutch questionnaire face-to-face in order to achieve representativeness. The percentage of these face-to-face interviews fluctuated between 2,2% and 8,6% of the total study sample per year. The response rate (including additional face-to-face interviews) between 2007 and 2014 gradually decreased from 42% (n= 1,329) to 29% (n=897) (Table 1). Explanations for this decrease could be that Dutch language proficiency acts as a barrier to fill out the written survey and/or big city's population are less receptive to forms of social participation, such as participating in a municipal survey.

**Table 1.** Study size and response rate per study year in the Omnibus Survey

| *Study year* | *[a] PCC FA knowledge* | | *[b] PCC intention to consult a GP/ midwife* | |
|---|---|---|---|---|
| | *Response size, n* | *Response rate, %* | *Response size, n* | *Response rate, %* |
| 2007 | 1,314 | 38 | 1,329 | 42 |
| 2009 | 1,240 | 35 | 1,250 | 40 |
| 2010 | 1,212 | 35 | 1,225 | 38 |
| 2011 | NA | NA | 1,194 | 38 |
| 2012 | NA | NA | 1,105 | 37 |
| 2013 | NA | NA | 1,080 | 35 |
| 2014 | NA | NA | 897 | 29 |

[a] Preconceptional folic acid knowledge based on: "A woman who wishes to become pregnant should take folic acid supplementation before she tries to become pregnant". Rotterdam, the Netherlands, 2007, 2009 and 2010

[b] Preconceptional intention to consult a GP or midwife based on: "A woman who wishes to become pregnant should consult a GP or midwife before she tries to become pregnant". Rotterdam, the Netherlands, 2007, 2009-2014

[c] NA= Not Accounted

[d] Response size represents the number of returned and filled out surveys

[e] Each study year the study sample covered 3,500 participants aged 16-85 drawn from the municipal register



## Independent variables

*Time in years* corresponding with before, during and after the pilot campaigns. *Ethnicity* was based on the country of birth of the individual and his/her parents as registered in the civil administration. The different ethnicities were subsequently recoded into three categories: (1) non-Western immigrants (e.g. Moroccan, Turkish, Antillean, Surinamese, Cape Verdean, Aruban, Asian, and African); (2) Western immigrants (e.g. European and American); and (3) Dutch.

*Educational level*, *household income*, *employment status,* and *neighbourhood* were used as indicators of socio-economic status. *Educational level* was determined on the basis of the highest completed education (no education/primary education, lower secondary education, higher secondary education, and higher vocational college/university) and classified into two categories: 1) low and; 2) moderate and high. *Household income* reflected monthly income and was divided into 6 categories (<950 euro, 950-1300 euro, 1300-1900 euro, 1900-3150 euro, 3150-3500 euro, and 3500 euro and more) being consecutively adjusted for the number of persons in the household and classified into 1) minimum; 2) minimum-moderate; 3) moderate-2x moderate; and 4) >2x moderate. To determine *employment status* respondents were asked whether they had paid work and their responses were recoded into: 1) unemployed and; 2) employed. Respondents were

categorized as residing in or outside a deprived *neighbourhood* on the basis of the postal code of their place of living derived from the Government Decision of May 2007 [20].

The variable *children living in the household* was measured by asking how the household was composed (alone, two adults with no children in household, (married) couple with children in household, and one parent with children in household) and was classified into 1) no and 2) yes.

*Religion* was measured by asking the respondents whether they considered themselves as belonging to a religion; answers were recoded into: 1) no and; 2) yes.

### Data analysis

A Chi-Square test ($X^2$-statistics) was used for bivariate analysis of correct preconceptional FA knowledge and correct knowledge regarding intention to seek out PCC (p-values <0.05 were regarded statistically significant). Using Spearman's rank correlation, no coefficient association ($r > 0.60$) was found between both outcomes. Trend analysis for changes in knowledge of preconception FA supplementation and PCC consultation was performed for both pilot districts separately as well as citywide (including the two pilot districts). The logistic regression analysis was performed in a two- and three-stage approach: in model I the study years were entered, in model II socio-demographics, socio-economic status and other variables were included, and in model III the observed interaction between ethnicity and educational level was included. Results are reported as (adjusted) odds ratios (OR), with 95% Confidence Intervals (CI).

### Details of ethical approval

The research proposal has been reviewed by the Medical Ethics Review Committee of the Erasmus Medical Center. As a result of this, the Committee informed us that the rules laid down in the Medical Research Involving Human Subjects Act (also known by its Dutch abbreviation WMO), do not apply to this study as data collection was anonymous and no invasive treatments were performed. It was therefore not necessary to obtain informed consent.

## RESULTS

Characteristics of the study population and percentages of correct answers for both outcomes are shown in Table 2. Significantly more correct answers for the preconception FA questions were given by those in the following respondent categories: females, those aged between 25-44 years old, Dutch respondents, individuals with a moderate and high educational level, those with income more than two times the moderate household income, employed respondents, respondents living in households with children,

**Table 2.** Characteristics of the study population in the Omnibus Survey

| | [a] PCC FA knowledge (n= 3,766) | Correct answer (%) | [c] p-value | [b] PCC intention to consult a GP/ midwife (n=8,080) | Correct answer (%) | [c] p-value |
|---|---|---|---|---|---|---|
| ***Socio-demographics*** | | | | | | |
| **Gender, %** | | | *<0.001* | | | *<0.001* |
| Men | 45 | 26 | | 45 | 21 | |
| Women | 55 | 43 | | 55 | 18 | |
| **Age in years, %** | | | *<0.001* | | | 0.18 |
| 16-24 | 11 | 24 | | 11 | 22 | |
| 25-44 | 33 | 51 | | 33 | 19 | |
| ≥45 | 56 | 27 | | 56 | 19 | |
| **Ethnicity, %** | | | *<0.001* | | | *<0.001* |
| Non-Western immigrants | 24 | 29 | | 23 | 26 | |
| Western immigrants | 9 | 35 | | 9 | 21 | |
| Dutch | 67 | 37 | | 68 | 17 | |
| ***Socio-economic status*** | | | | | | |
| **Educational level, %** | | | *<0.001* | | | *0.02* |
| Low | 42 | 27 | | 40 | 21 | |
| Moderate and high | 55 | 41 | | 60 | 19 | |
| **Household income, %** | | | *<0.001* | | | *<0.001* |
| Minimum | 22 | 25 | | 24 | 25 | |
| Minimum-moderate | 22 | 29 | | 22 | 22 | |
| Moderate-2x moderate | 28 | 37 | | 31 | 16 | |
| > 2x moderate | 22 | 47 | | 23 | 16 | |
| **Employment status, %** | | | *<0.001* | | | *<0.001* |
| Unemployed | 49 | 27 | | 46 | 21 | |
| Employed | 51 | 42 | | 54 | 18 | |
| **Neighbourhood, %** | | | 0.22 | | | *<0.001* |
| Non-deprived | 67 | 36 | | 66 | 18 | |
| Deprived | 33 | 34 | | 34 | 22 | |
| ***Other variables*** | | | | | | |
| **Children living in the household, %** | | | *<0.001* | | | *0.02* |
| No | 60 | 29 | | 63 | 20 | |
| Yes | 40 | 43 | | 37 | 18 | |
| **Religion** | | | *0.003* | NA | | NA |
| No | 52 | 37 | | | | |
| Yes | 48 | 32 | | | | |

[a] Preconceptional folic acid knowledge based on: "A woman who wishes to become pregnant should take folic acid supplementation before she tries to become pregnant". Rotterdam, the Netherlands, 2007, 2009 and 2010

[b] Preconceptional intention to consult a GP or midwife based on: "A woman who wishes to become pregnant should consult a GP or midwife before she tries to become pregnant". Rotterdam, the Netherlands, 2007, 2009-2014

[c] p-value for differences between correct answers

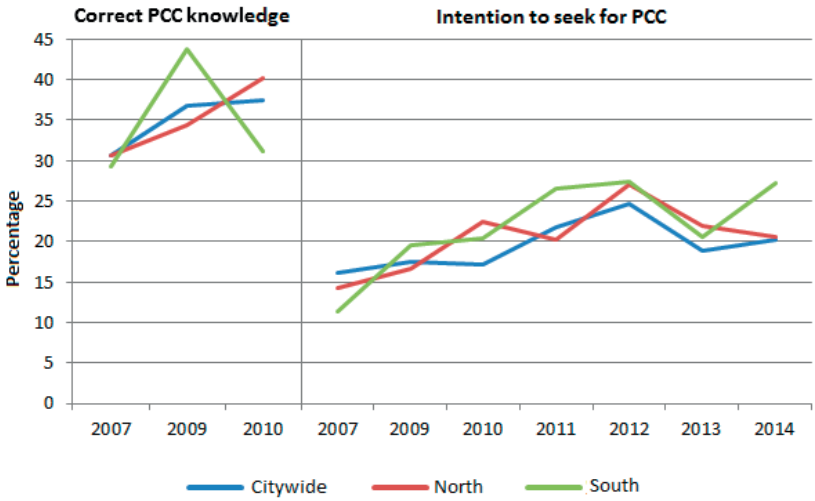


**Figure 3.** Trend analysis for correct PCC knowledge and intention to seek for PCC for the city of Rotterdam and focusing on the pilot districts North and South (2007, 2009-2014)

and non-religious respondents. Significantly more correct answers for the intention to seek out PCC were given by the following respondent categories: males, non-Western respondents, individuals with a low educational level, those with a minimum household income, unemployed respondents, respondents living in deprived neighbourhoods, and those living in households with children.

Trend analysis (Figure 3) showed that the overall correct knowledge of preconceptional FA supplementation significantly increased from 30,7% in 2007 to 36,8% in 2009 ($p=0.001$), with no further increase in 2010. For district North (n=298; response rate 36,9%) a non-significant increase of 31% was found between 2007 (30,6%) and 2010 (40,2%). For district South (n=103; response rate 9,8%) a fluctuating pattern was found, with a non-significant increase from 29,3% in 2007 to 43,7% in 2009, followed by a non-significant decrease to 31,2% in 2010.

The overall intention to seek out PCC significantly increased from 16,1% in 2007 to 24,6% in 2012 ($p<0.001$), with a temporary decrease to 18,8% in 2013 and an increase to 20,3% in 2014. For district North (n=694; response rate 34,8%) a non-significant increase was observed between 2007 (14,3%) and 2010 (22,4%), with a fluctuating pattern afterwards. For district South (n=711; response rat 28,6%) a significant increase was observed between 2007 (11,3%) and 2012 (27,4%), with a fluctuating pattern exhibiting decreases and increases after 2012.

**Table 3.** Results from logistic regression analysis for preconceptional folic acid knowledge and preconceptional intention to seek for care with "yes, she certainly should" as reference category

| | *Preconceptional folic acid knowledge* | | | *Preconceptional intention to seek for care* | |
|---|---|---|---|---|---|
| | I | II | III | I | II |
| **Study years** | | | | | |
| 2007 | 0.74 (0.63-0.87)** | 0.73 (0.61-0.88)** | 0.73 (0.61-0.88)** | 0.53 (0.40-0.69)** | 0.51 (0.39-0.68)** |
| 2009 | 0.97 (0.82-1.14) | 1.00 (0.83-1.19) | 0.99 (0.83-1.19) | 0.61 (0.47-0.81)** | 0.61 (0.46-0.81)** |
| 2010 | reference | reference | reference | 0.58 (0.44-0.77)** | 0.61 (0.46-0.81)** |
| 2011 | NA | NA | NA | 1.14 (0.86-1.51) | 1.19 (0.89-1.59) |
| 2012 | NA | NA | NA | 1.42 (1.07-1.90)* | 1.54 (1.14-2.07)* |
| 2013 | NA | NA | NA | 1.00 (0.75-1.34) | 1.01 (0.75-1.37) |
| 2014 | NA | NA | NA | reference | reference |
| ***Socio-demographics*** | | | | | |
| **Gender (reference: women)** | | | | | |
| Men | | 0.42 (0.36-0.49)** | 0.42 (0.36-0.49)** | | 1.41 (1.22-1.64)** |
| **Age in years (reference: 25-44)** | | | | | |
| 16-24 | | 0.31 (0.24-0.40)** | 0.30 (0.23-0.39)** | | 1.38 (1.07-1.79)* |
| 45 and older | | 0.40 (0.34-0.48)** | 0.40 (0.33-0.47)** | | 1.09 (0.91-1.30) |
| **Ethnicity (reference: Dutch)** | | | | | |
| Non-Western immigrants | | 0.57 (0.46-0.71)** | 0.45 (0.33-0.62)** | | 1.94 (1.59-2.35)** |
| Western immigrants | | 0.69 (0.53-0.91)* | 0.74 (0.44-1.26) | | 1.59 (1.23-2.05)** |
| ***Socio-economic status*** | | | | | |
| **Educational level (scale)** | | 1.31 (1.10-1.55)* | 1.20 (0.98-1.47) | | 1.13 (0.94-1.35) |
| **Household income (reference: >2x moderate)** | | 0.59 (0.46-0.77)** | 0.60 (0.46-0.77)** | | 1.56 (1.22-2.01)** |
| Minimum | | 0.66 (0.53-0.83)** | 0.66 (0.52-0.82)** | | 1.60 (1.26-2.02)** |
| Minimum-moderate | | 0.79 (0.65-0.96)* | 0.78 (0.64-0.95)* | | 1.07 (0.87-1.31) |
| Moderate-2x moderate | | | | | |
| **Employment status (reference: employed)** | | 0.93 (0.78-1.10) | 0.92 (0.78-1.10) | | 1.18 (1.00-1.40) |
| Unemployed | | | | | |

**Table 3.** Results from logistic regression analysis for preconceptional folic acid knowledge and preconceptional intention to seek for care with "yes, she certainly should" as reference category (continued)

| | *Preconceptional folic acid knowledge* | | | *Preconceptional intention to seek for care* | |
|---|---|---|---|---|---|
| | I | II | III | I | II |
| **Neighbourhood (reference: deprived)** | | | | | |
| Non-deprived | | | | | 0.97 (0.83-1.15) |
| ***Other variables*** | | | | | |
| **Children living in the household (reference: yes)** | | | | | |
| No | | 0.60 (0.51-0.71)** | 0.60 (0.51-0.70)** | | 1.60 (1.36-1.88)** |
| **Religion (reference: yes)** | | | | | |
| No | | 1.03 (0.88-1.21) | 1.03 (0.87-1.20) | | NA |
| ***Interaction*** | | | | | |
| **Ethnicity*educational level (ref: Dutch* educational level)** | | | | | |
| | | | 1.46 (1.01-2.11)* | | |
| Non-Western* educational level | | | 0.92 (0.50-1.70) | | |
| Western* educational level | | | | | |

[a] Preconceptional folic acid knowledge among respondents answering 'other' vs. 'yes' on: "A woman who wishes to become pregnant should take folic acid supplementation before she tries to become pregnant". N=3,766; Rotterdam, the Netherlands, 2007, 2009 and 2010

[b] Preconceptional intention to consult a GP or midwife among respondents answering 'no' vs. 'yes' on: "A woman who wishes to become pregnant should consult a GP or midwife before she tries to become pregnant". N=2,771; Rotterdam, the Netherlands, 2007, 2009-2014

[c] In model I the study years were entered, in model II socio-demographics, socio-economic status and other variables were included, and in model III the observed interaction between ethnicity and educational level was included

[d] Data are in OR, odds ratio (95% confidence interval). OR= exp (β), where β is the coefficient in the logistic model

[e] * $p \leq 0.05$; ** $p \leq 0.001$

[f] NA= Not Accounted

[g] Nagelkerke for preconceptional folic acid knowledge: step I $R^2$ =0.006, step II $R^2$=0.181, step III $R^2$=0.181 and for preconceptional intention to seek for care: step I $R^2$ =0.042, step II $R^2$=0.

Results from the logistic regression analysis for both outcomes with 'yes, she certainly should' as reference category are shown in Table 3. Knowledge of preconception FA supplementation was significantly lower in: the study year 2007, in men, in persons aged between 16-24 years or 45 years and older, in persons with a non-Western immigrant background, in minimum and minimum-moderate income households, and in households without children. The intention to seek out PCC was significantly lower in the study years 2007, 2009, and 2010. Significantly higher PCC intention was found in: the study year 2012, in men, in persons aged between 16-24 years, in persons with an immigrant background, in minimum and minimum-moderate income households, and in households without children.

### Analysis of interaction between determinants

Regarding the outcome preconceptional knowledge of FA supplementation, one interaction was found between ethnicity and educational level. The knowledge gap between non-Western immigrants and the Dutch was significantly larger amongst individuals with low levels of education. This gap was not apparent among individuals with high levels of education. No significant interactions were observed between gender and the variables: age, educational level, employment status, neighbourhood, having children in the household, and religion.



## DISCUSSION

The present study demonstrates that correct knowledge concerning both FA supplementation (30,7% in 2007 vs. 36,8% in 2009) and the need for PCC consultation before pregnancy (16,1% in 2007 vs. 24,6% in 2012) significantly increased citywide during the study years. . Non-significant changes in districts North and South where the interventions took place were observed. With a public health approach via the Ready for a Baby program in the North and South districts of Rotterdam interventions were set up to raise awareness for preconceptional FA use and PCC utilization. These interventions may have influenced knowledge in the two intervention districts. Although, representativeness of the study sample is good enough for generalizability and validity, still it remains difficult to measure effects citywide from interventions executed in a part of the city. Moreover, measuring intervention effects was not the objective of this study.

First, we will discuss results related to preconceptional FA knowledge. The inclusion of both men and women in our study enabled the evaluation of gender differences in knowledge. As expected, men had less correct knowledge about the need for preconceptional FA supplements. Corresponding results were found in another study conducted in a random sample of men and women in the US [21].

With regard to age differences, preconceptional FA knowledge was lower among the younger respondents (16-24 years) and the non-fertile age group (45 years and older) [22, 23]. For the younger age category, similar results have been found in other studies [24-26]. The number of teenage (<20 years) births is less than a half percent of all births in the Netherlands. However, the youngest age groups comprise of future parents and teenage mothers are still common among Surinamese and Antillean girls [27].

As expected, our results showed that individuals aged between 25-44 years showed the highest level of correct knowledge concerning preconception FA supplementation.

Respondents aged over 45 years were included in our study, because their knowledge and beliefs can influence behaviour of younger people. Studies showed that social influences (e.g. knowledge and habits) plays an important role in the development of behavior [28]. Approaches with social network and social influences have been successfully used for a range of health behaviors, including HIV risk practices, smoking, exercises, dieting, family planning, and mental health [29]. In addition, cultural diversity in social influences exists and is a variable that merits attention in health programs. We also found that preconception FA knowledge was lower amongst non-Western women. This may suggest that language proficiency within the host country has consequences for knowledge of preconception FA supplements [30, 31]. As expected and supported by other studies, irrespective of ethnic background, individuals with higher levels of education more often showed correct knowledge of preconception FA use [12, 26, 32]. Whether this also leads to actually behaviour change (e.g. preconception FA use) is unknown from our study. However, a recent study found a positive association between level of education and both knowledge and preconceptional FA supplementation [33]. This finding is in line with other studies revealing a gap with respect to FA use due to a difference in knowledge between women of different educational levels [34, 35].

Also in our study, the knowledge gap between non-Western immigrants and Dutch was significantly larger amongst individuals with lower levels of education. No apparent difference in knowledge was found among highly educated individuals. Different health and peer education programs have been conducted in the Netherlands to promote healthy behaviors amongst less educated non-Western immigrants [13, 36, 37]. One of the intentions in Ready for a Baby was to increase the low reproductive health (care) literacy of non-Western ethnic minority groups using targeted and customized peer education sessions [38]. These sessions were successful in reaching and educating non-Western ethnic minorities about reproductive behaviour e.g. utilization of FA supplements, and antenatal and postnatal care [38]. Besides knowledge transfer by educational sessions, nudging is a promising method which has generated great interest among policymakers [39]. Nudging suggests an approach to behaviour change that focuses on altering environmental cues to prompt healthier behaviour, e.g. making non-smoking

more visible through mass-media campaigns, instead of regulating, e.g. ban smoking in public places.

In households without children, less correct knowledge about preconceptional FA use was observed. We expect that persons with children are more informed about FA use because of their previous contact with a GP, midwife or gynaecologist. In contrast with our results, other studies conducted in the Netherlands indicated that a previous pregnancy influenced FA knowledge and use of women in a negative way [12, 34].

Secondly, we will discuss the intention to seek out PCC. For this outcome a significant citywide increase was found from 16,1% in 2007 to 24,6% in 2012, followed by a temporary significant decrease. Within the two pilot districts a similar pattern was found. We assume that the intention to seek out PCC increased as a result of the interventions during the Ready for a Baby program (2008-2012), and decreased when the interventions stopped. This would support the hypothesis that one-time campaigns seem insufficient for structural (preconceptional) behaviour change and continuous attention is needed.

The results showed a clear SES gradient: correct preconception FA knowledge was low amongst the low SES group, while low SES showed higher levels of intention to consult a GP or midwife preconceptionally. We believe that these low SES respondents have less internal resources (e.g. education, health literacy, and language proficiency) to rely on their own abilities, which results in higher utilization of health care services (e.g. higher intentions to seek for PCC).



Our study has some limitations. First, our results may have been affected by non-response rates. Relative to the Dutch population, immigrants were less represented over the eight study years. However, we do not expect this to have affected our results for the following reason. The Amsterdam Born Children and their Development-study on ethnicity related perinatal health [40] examined the effect of selective ethnicity-related non-response. The study was able to pursue an empirical approach of non-response effects: data on non-respondents (outcomes and determinants) could be retrieved anonymously from national registries. It was observed that the prevalence of outcomes and determinants (like e.g. education) were affected due to selective participation. However, associations and results from regression analysis were not affected to any relevant degree. Second, although a questionnaire is a method for collecting information, misclassification or bias through language proficiency should always be considered.

Our study has several strengths. Firstly, it had large numbers of participants, including different ethnic and socio-economic groups, allowing us to evaluate a large number of covariates. Secondly, the study was not limited only to women of childbearing age and/or women who wish to fall pregnant, but was based on the general population in a large city in the Netherlands. This enhances the external validity of the findings. Finally, as it was not limited to women, we were able to evaluate gender differences.

## CONCLUSION

This study shows that knowledge on preconceptional FA supplementation is still too low, especially among low SES respondents. For the intention to seek for PCC a vice versa effect was found; namely the lower the SES, the higher the PCC intention. An one-time national public campaign with FA recommendations [34] did not manage to attain a permanent change in (preconceptional) behaviour and/or knowledge. Preconception health should be considered as a critical stage in the continuum pregnancy related care. We recommend a continuous approach to increase PCC knowledge among the general population. This approach has to go far beyond one-time campaigns or interventions including integration with other preventive health care maximizing demand for and uptake of preconception interventions, especially by adolescents and low socio-economic status groups. This could be realized through activities at school (e.g. integrating PCC in sexual health education at high schools), general health-education programs at school, or in health care center. Peer education seems to be a promising health promotion approach, which can be employed with regard to many subgroups that are now difficult to reach for the regular health care [38]. Finally, involvement of men in preconception health and health care use could be an opportunity to increase PCC uptake.

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# Chapter 7

## Process evaluation of a community-based multi-level preconception health intervention: Ready for a Baby

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Submitted

## ABSTRACT

**Objective** To evaluate the development and implementation of a community-based and multi-level preconception health intervention in two districts of a multi-ethnic city in the Netherlands.

**Methods** Using Saunders' Guidelines for Process Evaluation, we went through seven steps to analyze and report results of a three pillar preconception health intervention study. We developed a comprehensive implementation and monitoring plan based on the specific setting, context, and the program framework. Moreover, we used multiple data sources to examine evidence for organizational implementation at various levels, including project managers, involved primary health caregivers, and peer educators.

**Results** One of the two districts met the criteria for implementation of the three pillars. Peer education sessions successfully reached a large and diverse target group. At the same time, there were several barriers to implementation, including logistical problems for health professionals in the implementation of preconception care.

**Conclusion** To our knowledge, this is the first study evaluating the development and implementation of general preconception care in which optimal linkage was sought with organizations beyond those of the medical domain, e.g. migrant institutes. This evaluation may help to contribute in the development of effective strategies to implement PCC for the general population.

## INTRODUCTION

In the Netherlands, there is incomplete outreach of preconception care (PCC) programs [1] while pregnancy outcomes are relatively unfavourable compared to other European countries [2]. Therefore, the Erasmus University Medical Centre and the Rotterdam municipality initiated a community-based and multi-level intervention to increase preconception health. This intervention was part of the *Ready for a Baby* program [3] and consisted of various interventions in the obstetrical chain of care (preconception care, antenatal care, delivery care, maternity care, and youth and family care) as well as social welfare services (figure 1).


**Figure 1.** Obstetrical chain of care within the Ready for a Baby program
The preconception health intervention study was the first chain in this comprehensive perinatal health program.



PCC seeks to improve prospective parents' health and health behaviours prior to conception in order to improve pregnancy outcomes [4]. General PCC is typically provided by general practitioners (GPs) or community midwives, who try to reduce the medical and behavioural risks for prospective parents, e.g. by switching from potentially harmful medication to safer alternatives. Components of PCC have been shown to be cost-effective, as it can prevent many adverse pregnancy outcomes - and also long-term adverse health outcomes [5].

While PCC is effective at improving pregnancy outcomes, the uptake and structural implementation of this preventive form of care is still rather low. While 80% of pregnancies among Western women are planned in the Netherlands [6], prospective parents with a wish to conceive commonly do not make use of PCC. Even with a targeted invite for PCC, only 27% of low-risk women contemplating pregnancy actually attended such a consultation with their GP [1]. Low rates of PCC uptake are also common in other Western countries [7]. Research has suggested that this is because of people's unfamiliarity with the availability and potential benefits of PCC [8, 9] and because women assume that they are healthy enough and sufficiently informed [10, 11]. Uptake amongst ethnic minorities and people with a low socio-economic status is particularly low [12, 13]. Studies have suggested that their lower uptake is partially due to a lack of fit between PCC approaches and their needs, e.g. multilingual and adapted to their culture and norms

[14, 15]. Furthermore, as the components of PCC vary internationally – in terms of the target population, interventions and the setting - there is currently no consensus about the best way to deliver PCC for the general population. A key challenge is therefore identifying how PCC can best be implemented and delivered at a population level.

This article provides a process evaluation of the preconception health intervention mentioned above. The objective was to develop and implement a community-based and multi-level preconception health intervention in two districts of the multi-ethnic city of Rotterdam. The intervention consisted of three pillars, spanning mass media campaigns, peer education and PCC consultations (figure 1). We chose to implement campaigns and peer education as previous studies indicate that they are an effective strategy for improving health behaviours and for improving PCC uptake [16, 17]. PCC consultations were offered by GPs and midwives. This is helpful as the majority of the population in the Netherlands are in contact with these professionals - 80% of them consult their GP annually [18].

PCC interventions have been evaluated in variety of settings, e.g. primary care, hospital-based, PCC clinics, and inter-conception care [19]. To our knowledge, this is the first evaluation of a multi-level and community-based preconception health intervention. Although such an approach is more labour- and resource intensive, it has the potential to reach the more marginalised populations by reducing their barriers to accessing healthcare. [20]. While various studies have advocated such a community-based and multi-level approach to increase health outcomes, very few of such interventions seem to exist in public health [21, 22].

## METHODS

We evaluated the preconception health intervention study using Saunders' Guidelines [23] for Process Evaluation in seven steps (figure 2). We describe the steps we took in the Methods (Steps 1-5) and Results (Steps 6 and 7) sections.

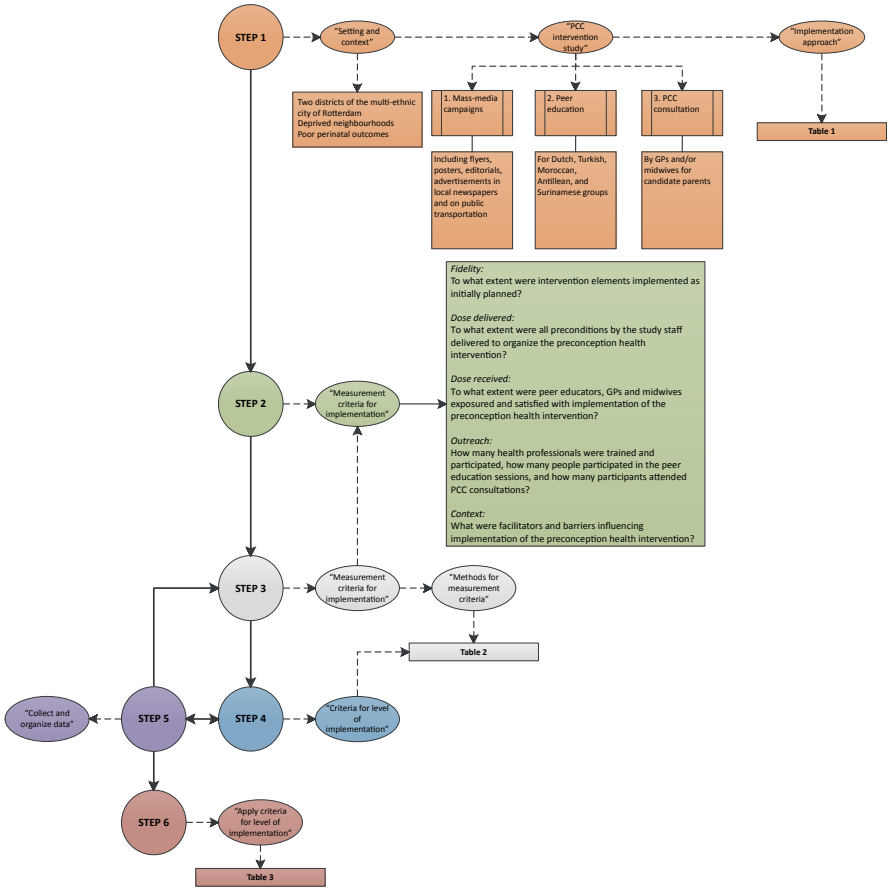


**Figure 2.** Seven steps in the process evaluation
The steps presented incorporate a detailed understanding of the program and the purposes of the process evaluation. Steps 3-5 considered iteratively.

## Step 1: Setting, Context, and Intervention

*Setting and context*. The preconception health intervention was implemented in the districts North and Feijenoord in the city of Rotterdam.

The city of Rotterdam has the highest number of deprived neighbourhoods and the most prominent socio-economic and health inequalities in the Netherlands [24]. In 2012, both districts were inhabited by a total of 120,000 people, composed of 60% of non-Dutch origin and 30% living below welfare standard. These two districts showed particularly adverse pregnancy outcomes: mean perinatal mortality rates ranged from

8.9 to 11.3 per 1,000 births [25]. Preterm birth (< 37 weeks), small for gestational age (birth weight < p10th percentile for gestational age), congenital disorders and / or a suboptimal start after birth (Apgar score < 7 after 5 minutes) ranges between 17.4% and in 18.1% of all births [25]. In other words, about every fifth baby born in these districts has an unhealthy start in life, entailing substantial short-term and long-term emotional, economic and societal costs [26]. Studies suggest these adverse outcomes are partially due to lower performance of hospital care in these areas. It is not clear if this is due to lower performing PCC services [24].

Before implementation of the preconception health intervention, we assessed the knowledge of PCC risk factors and the determinants of PCC use among the population living in the two districts [27]. About half of the surveyed women (n=631) had no knowledge of the adverse effect of smoking and over- or underweight on fertility. Adequate knowledge of folic acid use was especially low (57-62%) amongst non-Western ethnic minority women. Significant ethnic differences existed in the intention to attend PCC: non-Western ethnic minority women had stronger intentions than Dutch women (on a 10-point scale: 8 vs 6.33).

*The preconception health intervention*. Our intervention strategy is multi-level, as it targets changing *social norms* in selected neighbourhoods via mass-media campaigns, educating *individuals* via peer education, and improving *health care services* to provide better PCC. Figure 2 outlines the three pillars of the studied intervention. Below we briefly outline the aims of each pillar:

*I. The aim of the mass media campaign* was to raise awareness about availability and necessity of PCC as well as healthy preconception behaviours. The campaign started in district North ran from the summer of 2008 until end 2010, and the campaign in district Feijenoord started in the summer of 2010 and continued until spring 2012. More than 10,000 flyers, 400 posters, advertisements in local newspapers, publicity on public transportation, editorials and websites were distributed.

*II. The aim of the peer education sessions* was to increase preconception-related health literacy and to increase motivation to attend PCC consultation, especially amongst underserved populations. Six women representing the prominent ethnic origins across the two districts (two Turkish, one Moroccan, one Hindustani-Surinamese, one Antillean and one Cape Verdean) and one Turkish male were trained as peer educators. In turn, these peer educators then recruited participants for the peer education sessions through their existing network and community meeting places, e.g. mosques and schools.

The peer health educational sessions were developed by the Dutch National Genetic Resource and Information Centre, which promotes healthy behaviours and healthy environments by developing programs [3]. These were interactive sessions, often done in various languages to include a wide range of non-Dutch participants, addressing preconception health and the importance of PCC. The meetings for a group of female participants consisted of four different sessions, and were either delivered in schools or community places, or – using the Tupperware method – at the home of a woman in the community. In the latter case, the hostess also helped recruit participants. Both approaches included a visit to a midwifery practice, or a visit from a midwife to the session. The sessions led by the male peer educator took place in common meeting places for men, for example a coffee house or a mosque, and consisted of a shortened single-meeting session.

*III. The aim of the PCC activities* was to increase the availability and quality of PCC consultation in the two districts. GPs and midwives were trained to use a web-based PCC archive system, called PreconceptieWijzer.nl, to help them enter data from their clients. This application is complementary and linked to the self-administered ZwangerWijzer.nl [28] questionnaire for couples designed to be filled in prior to conception. This latter questionnaire helped save time during the consultations. During these trainings, GPs and midwives also received additional training on how to adequately screen for risks and to treat clients. As PCC consultations by GPs and midwives were not yet covered by universal health care insurance, the Erasmus University Medical Centre and Achmea Health Insurance successfully applied for additional funds to subsidize PCC consultation at the Dutch Healthcare Authority.



*Implementation approach*

Next to being multi-level, we also opted for a community-based approach. The intervention is community-based as it involves a range of different stakeholders – including policy makers, politicians, healthcare providers, researchers and of course prospective parents. To achieve high-level political and financial support, as well as agreement from local change agents (described below), we facilitated meetings with members of the municipal health authority, health professionals, and peer educators, in which we emphasized the need and urgency for this program and asked for feedback and input. We also involved important community leaders such as migrant and religious institutions to help us tailor our program to the needs of the target group, e.g. PCC peer education sessions in different languages and outreach of ethnic minorities.

The program team consisted of two project managers - one appointed by the municipal health care services and one by the Erasmus University Medical Centre- and a number of

program advisers and a communication team. The program team led the development of materials for the public health campaign (e.g. flyers, posters, and editorials) and peer health education. We offered training, technical assistance, and support to local policy makers and health care providers so that they could facilitate the implementation of the preconception health intervention within their respective organizations [29].

We use the logic model (table 1) to describe the purpose, strategies, and expected impacts and organizational outcomes of the intervention [23, 30]. The logic model describes the relationships between the resources and activities (inputs), the outputs and impacts, and the outcomes of a program. As such, it also serves as the basis for the evaluation and monitoring of a program.

**Step 2: Fidelity, Dose, Outreach and Barriers**

Recommended elements to evaluate the completeness and acceptability of a program include fidelity, dose delivered, dose received, and outreach [31]. Figure 2 outlines the measurement criteria for the implementation of the preconception health intervention.

**Step 3: Evaluation criteria, methods and sources**

The development of implementation monitoring methods involved two elements: (1) developing detailed measurement criteria as described in step 2; and (2) determining methods for measurement criteria: data sources, instruments, and data collection procedures [31]. Implementation monitoring in primary health caregiver practices was essential to study possible facilitators and barriers. However, it was not feasible to conduct extensive observation within the organizations. Frequent interviews with GPs and midwives would have been disruptive to the primary mission of carrying and providing healthcare service. Therefore, we tapped into multiple data sources on various organizational levels (administration, involved primary health care professionals, peer educators, project managers) using a variety of data collection tools (e.g. documentation, interviews, and written surveys) and data collection procedures (e.g. phone and in-person interviews). This enabled us to triangulate information from multiple levels and points of view that may result in a more holistic understanding of the project activities.

All measurements were performed by using a predefined rating scale and were completed by the investigators at the end of the preconception health intervention study. We subdivided the evaluation of the preconception health intervention into three pillars. The measurement criteria, data sources, instruments, number of items (see Supplement 1), rating scales, and implementation criteria variables are presented in table 2.

**Table 1.** Ready for a Baby PCC Logic Model (chain of events) and Overview of Measurement and Data Sources

| | *Inputs* | *Immediate impact* | *Short-term impact* | *Organizational outcome* |
|---|---|---|---|---|
| Logic Model – the chain of events leading to implementation of the preconception health intervention | • Developing effective working relationships with:<br>- Local district municipalities (North and Feijenoord district);<br>- Municipal health authority;<br>- Recruited GPs and midwives;<br>- Peer educators<br>• Developing the Ready for a Baby program team and discussing the program methods with the municipal leader, the district managers and policy makers in the districts<br>• Developing materials for the public health campaign and peer health education<br>• Training of GPs and midwives to deliver PCC consultation<br>• Training of peer health educators to deliver peer health education sessions<br>• Facilitating logistic support for the delivery of PCC consultation with tools (online questionnaire www.Zwangerwijzer.nl, and flowcharts for referral between GPs and midwives)<br>• Organizing (temporary) reimbursement for PCC consultation by the Dutch Healthcare Authority | • Established working relationships between local district managers, municipal health authority, GPs and midwives, and peer educators<br>• Peer health educators are skilled in delivering peer health education sessions<br>• GPs and midwives are skilled in delivering PCC consultation | • (1) Mass-media campaign<br>(2) Peer education sessions by peer educators<br>(3) PCC consultation by GPs and/or midwives | Strengthening implementation of the preconception health intervention |

**Table 1.** Ready for a Baby PCC Logic Model (chain of events) and Overview of Measurement and Data Sources (continued)

| | *Inputs* | *Immediate impact* | *Short-term impact* | *Organizational outcome* |
|---|---|---|---|---|
| Measurement criteria: how we assessed these chain of events | *Process: Dose delivered (completeness)* | *Process: Dose received (exposure and/or satisfaction)* | *Process: Fidelity (quality)* | *Outcome: Organizational change* |
| | Assess to which extent preconditions to organize the three pillars were delivered by the Ready for a Baby program staff:<br>• Formation of a team with local district municipalities, municipal health authority, peer educators, GPs and midwives<br>• Organizing project meetings to discuss the content of the program<br>• Organizing PCC training for peer educators, GPs and midwives<br>• Supporting logistic support, e.g. use of tools<br>• Providing reimbursement fee | Assess PCC functioning, skills and confidence:<br>• Use of PCC tools by peer educators, GPs and midwives<br>• Satisfaction among peer educators, GPs and midwives | • Assess the extent to which the mass media campaign, peer education, and PCC consultation were implemented as initially planned | • Assess the facilitators and barriers influencing the implementation of the preconception health intervention |

Legend: In this table we describe our logic model (i.e. the chain of events that will eventually lead to the goal of the intervention, i.e. implementation of the preconception health intervention). Moreover, the table also indicates the measurement criteria we applied to trace whether these events occurred.

**Table 2:** Measurement Criteria, Data Sources, Instruments, Rating Scale, and Implementation Criteria used to Assess General PCC Implementation

| Measurement criteria | Data Sources and instruments | No. of Items | Rating Scale | Implementation Criteria |
|---|---|---|---|---|
| *PUBLIC HEALTH CAMPAIGN*<br>Development of materials in organized meetings | Public campaign observation (investigator) | 4 | 3 = excellent; 2 = moderate; 1 = needs improvement | Rated ≥ 2.5 |
| How GPs and midwives rated the materials of the public campaign for PCC awareness | Satisfaction survey (caregivers) | 4 | 3 = excellent; 2 = moderate; 1 = needs improvement | Rated ≥ 2.5 |
| Completeness of implementation, e.g. appropriate use | End-of-intervention survey part 1 (caregivers) | 5 | 3 = excellent; 2 = moderate; 1 = needs improvement | Rated ≥ 2.5 |
| *PEER EDUCATION*<br>Development of the content and materials for the peer education sessions | Study logbook (investigator) | 3 | 3 = excellent; 2 = moderate; 1 = needs improvement | Rated ≥ 2.5 |
| How peer educators rated the peer education sessions for PCC awareness | Satisfaction survey (peer educators) | 3 | 3 = excellent; 2 = moderate; 1 = needs improvement | Rated ≥ 2.5 |
| Completeness of implementation, e.g. number of attended participants | End-of-intervention survey part 2 (caregivers) | 7 | 3 = excellent; 2 = moderate; 1 = needs improvement | Rated ≥ 2.5 |
| *PCC CONSULTATION*<br>Development of the PCC consultation | Observation (investigator) | 4 | 3 = excellent; 2 = moderate; 1 = needs improvement | Rated ≥ 2 |
| How GPs and midwives rated the PCC consultation | Satisfaction survey (caregivers) | 2 | 3 = excellent; 2 = moderate; 1 = needs improvement | Rated ≥ 2 |
| Completeness of implementation, e.g. embedding in daily practice | End-of-intervention survey part 3 (caregivers) | 6 | 3 = excellent; 2 = moderate; 1 = needs improvement | Rated ≥ 2 |

Legend: In this table we show the measurement criteria for the assessment of the three pillars. Moreover, the table also shows which sources of data we used to verify this. The number of items are attached as a Supplement. The implementation criteria indicates a cut-off of the rating scale showing that implementation was met in case of higher implementation criteria rates.

**Table 3:** General Development and Organization of Preconception Health Intervention Across City Districts

| | **Assessment of the three pillars** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *Public health campaign* | | | *Peer education* | | | *PCC consultation* | | | |
| *District* | Observation | Satisfaction survey | End-of-intervention | Study logbook | Satisfaction survey | End-of-intervention | Observation | Satisfaction survey | End-of-intervention | Sum |
| North | 3 | 2 | 2 | 3 | 3 | 3 | 2 | 1 | 1 | 5/9 |
| Feijenoord | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 1 | 8/9 |
| Implementation Criteria | Rated $\geq$ 2.5 | Rated $\geq$ 2.5 | Rated $\geq$ 2.5 | Rated $\geq$ 2.5 | Rated $\geq$ 2.5 | Rated $\geq$ 2.5 | Rated $\geq$ 2 | Rated $\geq$ 2 | Rated $\geq$ 2 | 6, 7, 8 or 9/9 |

Legend: This table shows the data sources and their implementation criteria for the two districts. The shaded portions indicate that they met criteria for implementation.

### Step 4: Develop Criteria for Level of Implementation

We set criteria for each data collection tool and for all data sources to determine the level of implementation. Criteria for level of implementation, as presented in table 2, are specific to each pillar and depend on the response scale, the range of responses, and the cut-off determined by the program staff. We adopted the cut-offs for levels of implementation as used by Saunders et al. [23]. Criteria for implementation were met if at least 6 of 9 data sources for the three pillars were included, as indicated in the *Implementation Criteria* row in table 3. These criteria are consistent with results from a review by Durlak and DuPre on implementation work, indicating that 60% implementation produces positive results and that implementation above 80% is rare [32].

### Step 5: Collect and Organize Data

The investigator, peer educators, GPs and midwives collected data according to the description outlined in step 3. We conducted interim evaluations with district leaders, peer educators, and primary caregivers. Additionally, we performed in-person interviews with attendants of peer education sessions and primary caregivers. We entered data into software programs or Excel spreadsheets. Finally, we distributed end-of-intervention reports to all stakeholders (e.g. district municipalities, health authority, and health professionals).



## RESULTS

Results for the application of criteria for implementation is described in step 6 and 7.

### Step 6: Apply Criteria for Level of Implementation

The rating scale assessed with multiple data sources for each pillar and district is presented in table 3. A highlighted rating score indicates evidence for implementation based on the criteria for each data source. The summary column shows the number of data sources meeting the criteria over the total number of data sources used to assess implementation.

*Fidelity.* District Feijenoord met the implementation criteria for the three pillars.

### Step 7: Use of Implementation Data

*Dose delivered.* Despite the provided reimbursement fee, the motivation fluctuated during the project period among midwives, and especially among GPs. The peer educators, which were educated for peer health education sessions, were highly motivated. Periodic project meetings were used to exchange experiences, elaborate on the contents of

the program, and monitoring of possible barriers and/or questions from the field (e.g. support in the use of web applications).

*Dose received.* In general, all health professionals contributed to the mass media campaign (e.g. distributing flyers and posters in their practices) and five of them provided PCC consultations, where they worked with one or two e-health tools: ZwangerWijzer.nl and Preconceptiewijzer.nl. During interviews the first author conducted with GPs and midwives, we found that midwives considered PCC to be their primary responsibility, which explains their higher motivation compared to GPs. Both professional groups experienced barriers to implementing PCC, see *Context* below.

*Reach.* Six persons were trained to provide peer education [3]. A total of 450 women and 300 men attended a full peer education course. 86 men and 219 women filled out a questionnaire for evaluation purposes (n=325). The majority of the respondents were aged between 30-45 years and lived in deprived neighbourhoods, and showed the following prevalence of preconceptional risk factors: smoking (1-43%), BMI > 25 kg/$m^2$ (36-50%), and use of prescribed medicines (32-38%). Reasons for participation among women was having a child wish, recurrent miscarriages, and information provision, and, among men was information provision and interest in influencing factors on fertility. Respondents mentioned folic acid use, contraceptive use, fertility cycle and influencing factors, hereditary diseases, cultural taboos, and unknown obstetric system in the Netherlands as knowledge gaps which require attention and information provision. Moreover, 30 GPs and five midwives learned how to conduct a systematic PCC consultation. Based on reports from primary health caregivers and insurance declarations, we found that 43 PCC consultations took place between July 2009 and March 2012.

*Context.* To examine factors that could influence level of PCC implementation in daily practice we conducted in-person interviews with the participating GPs and midwives (total n=12). They provided the following explanations for the low number of PCC consultations: 1) GPs (n=6) reported low fee for PCC consultation (€55 for GPs versus €105 for midwives); (2) required extra administration (n=6); (3) difficulties in working with the tool www.PreconceptieWijzer.nl (n=6); (4) existing logistic problems, e.g. missing rooms for couples to fill in ZwangerWijzer.nl at the GP practice prior to PCC consultation (n=4); (5) insufficient collaboration between midwives who do not see (m)any couples contemplating pregnancy and GPs which see these couples but show fluctuating motivation for providing PCC (n=7); (6) women not actively seeking for PCC consultation in the case of unplanned pregnancies (n=8); and (7) difficulties in filling in the Dutch questionnaire (www.ZwangerWijzer.nl) at home by women and men prior to the PCC consultations, mainly due to language barriers (n=8).

To better understand the lack of uptake of PCC consultations, we organized focus group meetings with peer education participants who had not attended these consultations (n=33 of which five had a child wish). Participants reported the following main reasons: (1) not having time and interest in PCC consultation, (2) lack of knowledge about the existence and content of PCC, (3) and planning a pregnancy as going against their cultural norms.

Participants reported to visit their GP first to obtain preconceptional information in case of a child wish. However, the Antillean and Surinamese group (n=17) mentioned to seek for care abroad because of the limited confidence in the Dutch healthcare system. These latter groups, however, highlighted the importance of the provision of sexual and preconceptional information at schools because of the high rates of teenage pregnancies. Some of the participants (n=5) had no health insurance and reported also financial barriers.

## DISCUSSION



The preconception health intervention had multi-level targets: changing *social norms* in selected neighbourhoods via mass-media campaigns, educating *individuals* via peer education, and improving *health care services* to provide better PCC. In order to implement the preconception health intervention, we chose for a community-based strategy that engaged local community stakeholders, policy makers and health care providers, supported by high-level political and financial support. The process of introducing the three pillars and training and engaging community stakeholders was time consuming; however, it resulted in a shared understanding of the project goal and approach amongst stakeholders. Strong collaboration between the program office and the stakeholders from the field was essential which formed the basis for the implementation This strategy seemed to have payoff: district Feijenoord met the criteria for implementation for the three pillars.

The mass-media campaign continued throughout the study period and all GPs and midwives successfully engaged in the distribution of especially multi-lingual posters and leaflets at their daily practice.

The target-group specific education sessions were successful in reaching the target group (over 700 participants). As a result of the interest found in the peer education sessions during our intervention, Perinatal Health Educators were later educated In Rotterdam and more than 2,000 women and men were subsequently reached at mosques, migrant organizations and educational institutes for PCC education sessions [33].

Health professionals mentioned logistical and financial barriers in the implementation and provision of PCC, and members of the target group indicated that they were not aware of the existence and/or relevance of PCC. These barriers are in line with other studies [19, 34].

Although women and men were interested in PCC during the peer education sessions, as also found in an earlier study [35], the number of PCC consultations remained low.

Implementation monitoring revealed less-than-complete implementation for district North, which is consistent with the literature [32]. Variability in implementation could be partially related to variability in organizational characteristics, resources, and complexity (populations served and services provided), as well as the need for more time for organizational uptake of new policies and practices [36].

Based on the findings of our process evaluation, we come to the following recommendations for implementing this preconception health intervention in other settings:

- Seek for collaboration with local government, public health and health caregivers to ensure high-level but also local political and financial support
- Connect community projects as closely as possible with the unique needs of target groups (e.g. ethnic groups)
- Involve migrant and religious institutions to tailor the program to the needs of the target group
- Emphasize more strongly the importance of PCC consultations during peer education sessions
- Invest in training of multilingual peer educators
- Integrate a fee for the declaration of PCC consultations by GPs and midwives
- Train GPs further on the importance and benefits of PCC

Additional research, now in progress (the Healthy Pregnancy 4 All project [34]), is examining how PCC consultation could be implemented as a standard approach for prospective parents.

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# Part III

# Chapter 8

## General discussion

## AIM OF THIS THESIS

The aim of this thesis was to increase our understanding of an optimal design of a general PCC program as well as its implementation. I addressed this aim in two parts.

In part I, firstly I gave an overview of the concept of PCC with the benefits, the situation in the Netherlands and worldwide, and several potential approaches and challenges. Secondly, I reported about the results of the consultations that we did with experts during a consensus meeting about the optimal design and content of general PCC. Thirdly, I reported about the results of a systematic review that we conducted about effective lifestyle interventions amongst preconceptional women- in terms of behavioural change and pregnancy outcome.

In part II, I reported about the three studies that we performed in the context of the Ready for a Baby program. I first investigated the general populations' knowledge about preconceptional risk factors, followed by their attitude regarding the use of individual PCC, and finally evaluated the process of the development and the implementation of the general preconception health intervention.

## PRINCIPAL FINDINGS

### Part I: Point of departure

We argued that governments carry a responsibility for organizing PCC to guarantee that all women have an equal opportunity to receive adequate PCC, taking into account the situation in their countries (**chapter 2**). Two characteristics of PCC in particular favour a top-down approach initiated by governments, in addition to the bottom-up initiatives organized by caregivers. First, general PCC is a rather new concept, requiring a new mind-set, for which governments should create awareness. Second, PCC is multifaceted. It should be part of an interlinked chain that creates connections in the course of life- from PCC through prenatal, neonatal, child, and youth care. And it entails the need for many healthcare disciplines to cooperate –GPs, midwives, obstetricians, clinical geneticist, and other maternal and child health professionals. To avoid barriers and to guarantee a continuum of optimal care, these links are crucial. These characteristics may complicate and slow down the bottom-up organization of PCC because many disciplines must reach consensus.

The optimal design of a general PCC program was investigated during a consensus meeting by assessing the experts' view. Consensus was achieved on the majority of the discussed key elements of PCC, including the definition, the categorization, institutes and health care professionals, which should play a role in reaching target groups, the

content and delivery, and the need for development of evidence-based risk assessment instruments (**chapter 3**). Experts stated that the line between the different categories of PCC (general individual PCC and specialized PCC) is not always very evident. A lack of consensus existed about which health care professional should have a core responsibility in which category of PCC. However, as PCC has a very broad content, experts agreed that it is merely impossible for one caregiver to address all risk factors. Besides consensus on a national level among PCC experts, consensus on a city or even district level is tremendously important for the uniform delivery of PCC. As the possible content of PCC is growing [1], there is a need for prioritization in the interventions for a woman's specific risk profile. This should be based on the impact of risk factors and the effectiveness of interventions. The available studies regarding effectiveness of lifestyle interventions prior to pregnancy for women was summarized in a systematic review in **chapter 4.** This showed a relative short list of effective preconceptional interventions for folic acid supplementation, smoking reduction, and healthy nutrition in terms of behavioural change and/or pregnancy outcome.

**Part II: Ready for a Baby program**

In the studies conducted in Part II, we investigated the general populations' knowledge about preconceptional risk factors and their attitude regarding the use of individual PCC. Furthermore, we evaluated the process of the development and the implementation of a general PCC health intervention study within the Ready for a Baby program.

One of the determinants influencing and predicting health behaviour is the intention that women have to actually perform the desired behaviour, in this case visiting a GP and/or midwife for PCC consultation (**chapter 5**). We explored this by using the Attitude- Social influences- Self-Efficacy (ASE-) model among women living in the two pilot districts - North and South. We demonstrated higher intention to attend PCC consultation for women with a Turkish and Moroccan background, for women with a higher maternal age and a positive attitude.

We demonstrated a low level of knowledge for preconceptional risk factors, e.g. folic acid use. We found differences between ethnic groups: non- Western women had the lowest knowledge level, while the Dutch women had high knowledge levels (**chapters 5 and 6**). As expected, when the educational level was higher in both groups the differences in knowledge was lower.

For the optimal implementation of general PCC we combined three pillars for maximum impact: (1) collective public health campaigns using different methods (multi-lingual posters and leaflets, advertisements in local newspapers, and columns in the local media), (2) a PCC education program tailored to specific target groups (short courses for women and men about healthy pregnancy and the importance of PCC), and (3)

individual PCC counselling by GPs and/or midwives for prospective parents. With our process evaluation study we showed that one of the two pilot districts met criteria for the implementation of the three pillars (**chapter 7**). In general, GPs and midwives successfully distributed the posters and leaflets at their practices. All ethnic minority women and Turkish men were well reached by the peer education sessions and the 'Tupperware' method turned out to be a success. The high outreach with the peer education sessions and respondents' positive attitude regarding individual PCC consultation, and their intention to make use of the consultation did not automatically lead to a higher number of consultations. We demonstrated practical and motivational barriers in the provision and implementation of individual PCC consultation in daily practice of GPs and midwives. In addition, parents-to-be as well as primary caregivers remain insufficiently aware of pregnancy-related risk factors, possibilities for prevention, and of the role of properly timed, specific risk-reducing behaviour [2].

The principal findings related to this thesis are summarized in figure 1.

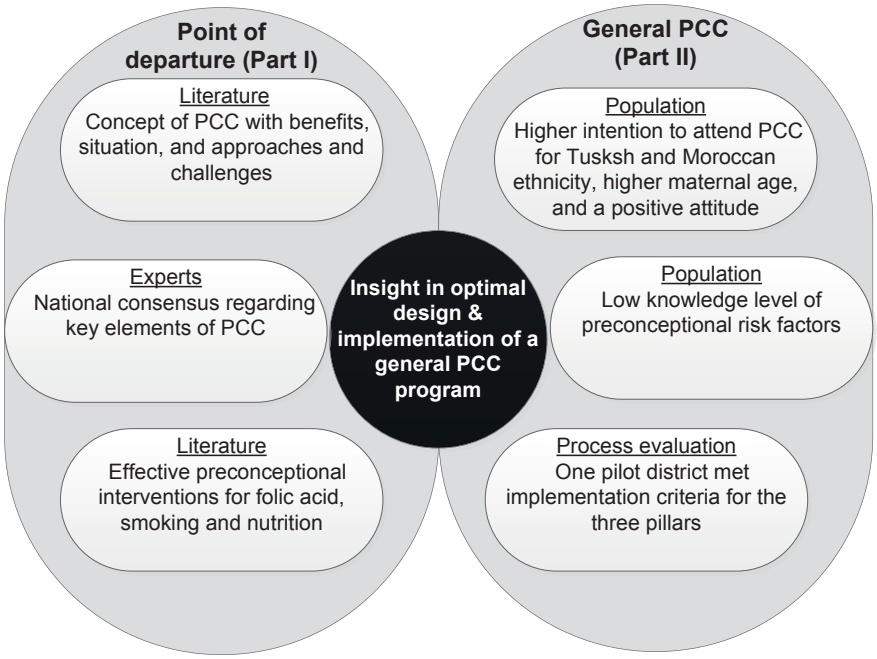


**Figure 1.** Principal findings related to this thesis

## DISCUSSION OF THE FINDINGS

### Preconceptional folic acid knowledge

As stated above, low knowledge level of preconceptional risk factors existed in our study population with differences between ethnic groups. Since appropriate folic acid supplementation before and during early pregnancy has been shown to protect against neural tube defects and other congenital anomalies [3], preconceptional folic acid use is an important part of PCC.

Therefore, more should be done to raise women's awareness of the benefits of timely use of this supplement. Women of childbearing age should find it normal and natural to optimize their health in preparation for pregnancy by taking for example folic acid supplementation. This might require not just a mass-media campaign about the benefits of preconceptional folic acid supplementation, but also information about PCC as part of the regular school curriculum on sexual education. Integrating the concept of PCC at education might influence knowledge in preconceptional risk factors. Also, most physicians are insufficiently aware of the high prevalence of risk factors among the general population and of the importance of the first trimester. Making risk-assessment tools up-to-date and available (e.g. multilingual), such as ZwangerWijzer.nl, would increase awareness among providers and consumers. The increased awareness of lifestyle and nutritional issues brought about by PCC might also persist after pregnancy, resulting in a healthier overall lifestyle [4].



### Peer education

Non-Western (e.g. Turkish and Moroccan) ethnic minority populations are usually difficult to reach. In our study 'active' recruitment strategies (e.g. verbal recruitments by peers and/or organizations) appeared to be more effective in reaching this target group than passive methods (e.g. mails and/or posters), as also shown in a previous study [5]. Recent studies suggest that peer education is an effective strategy for reaching participants that are from deprived neigbourhoods and typically underserved by health services [5, 6]. Suggested explanations for the broad reach among these groups include the presence of close-knit social communities and organizations with social influences within their cultures. These close-knit communities and organizations are mainly absent in deprived neighbourhoods for Western women. During the peer education sessions Western women and men were not targeted, however differential effects of social deprivation on Western and non-Western women in the city of Rotterdam were demonstrated [7]. Better neighbourhood social quality was clearly associated with better perinatal outcomes for Western women. We believe that also Western women would benefit from these peer education sessions and should be targeted.

Through the peer education sessions we got some unexpected information. An example is the thought of women that folic acid has to be something harmful, because the word includes 'acid', so how could it be a vitamin. Another eye-opener was the fact that some women were getting pregnant despite their use of contraceptive. The problem was that they were using their multi-phase contraceptive pill clockwise as opposed to counter clockwise, because they interpreted that it was similar to reading Arabic. The findings indicate that we should invest more time and effort in explorative studies amongst the target groups. There is still more to learn when it comes to the barriers and the needs of people to perform a desired behaviour, in this context healthy preconceptional behaviour.

**Individual PCC consultation**

Because PCC may improve the health of future children as well as the prospective parents' informed decision-making, it is important that couples wishing to conceive seek consultation.

A study which examined women's intention to seek preconception counselling after filling out a web-based risk assessment questionnaire (ZwangerWijzer.nl) showed that 30% of women (n=767) reported that they would seek for preconception counselling after general information provision based on their risk profile. This percentage is lower than 57% found by another study which hypothetically asked women whether they were interested in preconception counselling 'should they decide to have children' [2]. Intended behaviour in a hypothetical context differs from intended behaviour when actual decisions have to be taken, which in turn differs from actual behavior. This was also concluded from a pilot study in 2007 on general PCC using the web-based risk assessment ZwangerWijzer.nl in Rotterdam. Parents-to-be were encouraged by a public campaign to fill out the risk assessment, and send the risk profile to a caregiver to seek preconception consultation. While the use of the website increased during the campaign, the actual number of preconception consultations did not [8, 9]. The road between need for information and attending PCC consultation seems long and not straightforward at all. Even if women's attitude towards PCC was positive, as demonstrated in our study, they seemed to be hesitant to attend PCC consultation. In addition, when women were invited for PCC consultation by their own GP, 72-75% accepted this offer and attended a consultation [10]. An interview study showed that women do not consider themselves as part of the target group for PCC. Three reasons were found for this: 1) they think they do not run a risk, 2) they misunderstood the aim of PCC, and 3) they think they know enough [11, 12]. In our complementary focus groups interviews with attendees of peer education sessions, these aforementioned three reasons were also mentioned for not attending individual PCC. Preconception counselling requires that couples contemplating pregnancy recognize the impact of risks on the future's baby health. When they do not

recognize this, they will not be an easy target for preconception counselling. Weisman et al. found that the more risk factors were identified, the less likely it was that women have a high internal locus of control and therefore that it would be less likely they would seek preconception counselling [13]. These findings suggest that use of PCC may be promoted by creating awareness of the benefits of PCC (e.g. mass-media campaigns, leaflets in practices of GPs and midwives, and peer education) and/or by strengthening women's internal locus of control (e.g. improving skills by altering level of knowledge by couples and caregivers and/or increasing motivation to attend preconception counselling to make it a standard form of care).

**Caregivers**

Traditionally, in the Netherlands community midwifes provide PCC consultations. However, we found out that the general population finds the GP the appropriate caregiver in relation to PCC. This seems to provide a window of opportunity since the majority (80%) of women in the reproductive age visit their GP annually, providing GPs the opportunity to inform these women about the benefits of timely utilization of PCC. However, in contrast with earlier studies [14, 15], GPs appeared to be less motivated than midwives to provide individual PCC consultation in daily practice. Since 2012, PCC is integrated in the Dutch College of General Practitioners' practice guidelines (NHG), which gives the GPs guidelines for assisting couples to be well informed about the best possible health before conception. As it appears, this relies heavily on the motivation and expertise of the GP to provide preconception information [10].



We investigated why GPs are less inclined to implement PCC in daily practice. In depth interviews with GPs revealed practical, motivational and financial barriers. A reimbursement fee of €55 per PCC consultation appeared to be too low for GPs and therefore not worthwhile to invest in new knowledge and skills. Previous research found that GPs did not offer PCC to a sufficient degree, probably because they are unaware of individual women's desire to conceive, and because they do not usually discuss potential risk factors on a speculative basis- i.e. just in case the woman conceives [16, 17]. In practice, GPs receive few spontaneous requests for preconceptional advice. Given that women have an insufficient knowledge of risk factors or of the necessity to address risk factors before becoming pregnant, this is not surprising. This is not out of lack of interest, as women certainly seek information on risk factors. The problem is that they do so only after they get pregnant. The emphasis of the Dutch prenatal system on the second and third trimesters is likely to have contributed to this behaviour.

The community midwives were motivated and assigned to offer PCC to women, which is in line with another study [14]. Compared to the GPs, midwives only see women during pregnancy and during a short period after delivery, which gives them less opportunity

to address PCC. Some midwives specialize in PCC and offer special office hours for PCC, which has a low uptake of consultations, as reported from the field. Probably this is due to the fact that midwives do not reach most couples before conception, which is also mentioned as the great barrier in our study. Further, difficulties in working with the tool www. PreconceptieWijzer.nl and required extra administration were reported.

Community midwives and GPs situated in neighbourhood practices provide primary care, while obstetric caregivers in hospitals provide secondary and tertiary care. These professionals work autonomously. Nevertheless, they need to coordinate activities to support women during their pregnancy and labor/birth, as well as the period before conception. As, the current public debate in the Netherlands emphasizes the need for improved coordination in midwifery and obstetrics, especially between primary and secondary care [18, 19], little collaboration also occurred at primary care level, between midwives and GPs in the two pilot districts. In order to achieve success in the referral of couples contemplating pregnancy by GPs to the nearest midwife, we organized (evaluation) meetings with the primary caregivers and designed flowcharts with referral information. However, the collaboration between GPs and midwives was not sought and no referrals were made. An initiative for uniform delivery of PCC has been taken by the national College Perinatal Care, which is developing a Preconception Indicator List (PIL). This list gives - on basis of preconceptional risk factors - caregivers guidelines for the right care and referral to other (medical) disciplines and/or organizations within obstetrical care.

## METHODOLOGICAL CONSIDERATIONS

The studies described in this thesis have been conducted as the first chain within the Ready for a Baby program. The Ready for a Baby program is a community-based study, which covers the entire perinatal health care chain.

One of the strengths of this study is that we designed and evaluated general PCC in a primary care setting with joint collaboration of government, municipal health service, university and stakeholders from the field. Although this approach was time-consuming, it is unique in the Netherlands. A few methodological considerations will be discussed in the next paragraphs.

### Information bias

One of the strengths of the PCC program is that we collected information of both women and men beyond their fertile ages. This is unique as most studies obtained retrospective information in women only [20, 21]. We used self-reported questionnaires, which could

have led to information bias from measurement error. There are two types of information bias, namely recall bias and misclassification. Recall bias could have occurred as data regarding prior pregnancy outcome was collected retrospectively. Pregnancy and delivery are very important for most women and not easily forgotten. Differences of interpretation of an outcome between parents and professionals can result in an over- or underestimation of adverse outcomes in the (sub) study group. The Generation R study showed almost similar percentages of adverse outcomes for the (sub)groups [22] when compared to our results. Some of the variables of interest, including educational level, smoking, attitude regarding PCC, and folic acid supplementation knowledge were gathered through self-reported questionnaires. Therefore, socially desirable answers could have been given and misclassification may have occurred. However, this was assumed to be equal in all studied (sub) groups.

**Selection bias**

Selection bias can occur when an association between a determinant and outcome is different for participants and for non-participants who were eligible for the study. This can be the result from non-response at baseline or loss to follow-up. Loss to follow-up is not an issue in our study, as we had no prospective follow-up. In the Omnibus survey used for the study to investigate in preconceptional folic acid knowledge and intention to make use of individual PCC consultation, non-Western respondents and respondents in the age category younger than 45 years were relatively less represented. However, the response rate was still representative for the whole city, and large enough to draw conclusions with regard to changes in trends.

We used and distributed posters, flyers and questionnaires in different languages (e.g. Papiamento, Arabic, and Turkish) within our interventions. The Dutch questionnaires could have led to selection bias due to a language barrier. However in our study, 45-50% of both Turkish and Moroccan women reported no difficulty with the Dutch language. Further, we translated the Dutch questionnaires to English and Turkish and conducted face-to-face interviews in case of underreporting in order to optimize response rates and overcome non-response. Peer educators assisted the men and women with less Dutch proficiency to fill out evaluation questionnaires. We don't believe that language led to bias because our interventions and questionnaires were multilingual and tailored to our target group.

**Health behaviour model**

We used the 'Attitude- Social influences- Self- efficacy' (ASE-) [23] model to predict subsequent behaviour, e.g. intention to attend PCC consultation. This model has been successfully applied in several studies to explain various aspects of health behaviour, such as smoking cessation [24], fruit and vegetable consumption [25], and fat intake

[26]. The ASE-model is based on a reflective, goal-oriented system driven by our own values and intentions. We found that the ASE-model insufficiently predicted intention to attend PCC consultation, as only 'attitude' had sufficient explanatory power. This puts forward the question whether the ASE-model is an appropriate model in predicting subsequent behaviour. Therefore, new experiments with other health behaviour models in the field of PCC are needed. New insights from the behavioural sciences could be helpful to explore of new routes to intervention design that could present an effective strategy for the effective use of PCC. For example, interventions using nudges are increasingly popular and are expected to more effectively address (un)healthy behaviours [27, 28]. In addition, these interventions promise a similar impact on participants independent of their socio-economic status due to their appeal to universal human behavioural traits. Nudging is driven by immediate feelings and triggered by our environments. It alters people's behaviour in a predictable way without forbidding any options or significantly changing their economic incentives. Suggestions could be providing information through mass-media campaigns about what other women are doing ('the majority of women with a child wish to use folic acid supplementation') or changing the layout of supermarkets and/or pharmacies to make folic acid supplementation more visible.

## RECOMMENDATIONS

In order to implement and provide general PCC, the outcome of this study points at the following recommendations for policymakers, caregivers, and researchers.

### Recommendations for policymakers

- It is important that local and national governments promote PCC by integrating components of preconception health into existing local public health and related programs;
- Policymakers should facilitate insurance companies to financially cover preconception visits;
- In raising awareness, high schools may be a useful entry for educating all, and especially ethnic minorities, about the importance of preconception health and about the use of timely seeking PCC;
- Special effort is required to get to the hard to reach groups, such as those of low socio-economic status. This may call for the involvement of migrant and religious institutions and use of non-conventional methods, like engaging social peer group networks and community social workers as a means of connecting to existing situation and needs of specific groups;

- Interconception care and care coordination models for women at high social and medical risk should be developed and evaluated, e.g. by using existing services for women in the postpartum period to provide or link to interventions (e.g. youth and family care).

**Recommendations for caregivers**

- Disciplines involved in PCC should organize biannual meetings to enlarge the shared responsibility amongst stakeholders and to upgrade the scale at which PCC is delivered;
- Models for integrating components of PCC should be developed and evaluated to facilitate delivery of individual PCC consultation in primary care practices;
- Primary caregivers awareness regarding the importance of addressing preconception health among all women and men of fertile age should be increased through the use of educational programs in trainings and/or related professional organizations, e.g. the Dutch College of General Practitioners' practice guidelines (NHG);
- Caregivers should include information on fertility and on the menstrual cycle and fertile days, as men and women appeared to be interested in these themes;
- Evening consultation hours could be introduced to make PCC more accessible for working couples;
- Men should also be included and targeted for PCC; having a child is a shared responsibility. Besides offering an opportunity for disease prevention and health promotion in men, PCC is important for improving family planning and pregnancy outcomes, enhancing the reproductive health and health behaviours of women, and preparing men for fatherhood.



**Recommendations for researchers**

- PCC consultations should be carefully monitored; including the study of the effects of preconception interventions on pregnancy outcome and behaviour change, and process evaluations should be performed regularly. Additional research, the PCC sub-study within the Dutch national Healthy Pregnancy 4 All project, evaluated effectiveness of recruitment strategies for PCC consultation and effectiveness of PCC consultation regarding behaviour change;
- New routes to intervention design, e.g. nudging should be explored;
- New evidence-based standardised risk assessment instruments should be developed and existing instruments should be tailored and optimized, e.g. multilingual for different ethnic groups;
- To justify generalizability and embedding in daily practice, PCC intervention studies should be performed in the general population. We found from the systematic

review that PCC intervention studies mostly were performed in selected populations and thus eligible for selected populations.

## GENERAL CONCLUSION

The studies described in this thesis highlighted the barriers and facilitators for the implementation of a general PCC program. The thesis emphasizes the importance to integrate preconception interventions across various levels of care and areas of expertise. Without community support and designs that truly represents the needs of the communities, programs will be ineffective. To summarize, there are still barriers which merit careful consideration and adaption of mindset, practice, and policy.

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# Chapter 9

## English Summary

## Nederlandse samenvatting

## ENGLISH SUMMARY

In this thesis, the aim was to gain more insight in the optimal design and implementation of a general PCC program. Our results were presented and summarized in two parts.

## PART I: POINT OF DEPARTURE

In **chapter 1** we introduce the topic and objectives of this thesis.

In **chapter 2** we argued that governments carry a responsibility for organizing PCC to guarantee that all women have an equal opportunity to receive adequate PCC, taking into account the situation in their countries. Two characteristics of PCC in particular favour a top-down approach initiated by governments, in addition to the bottom-up initiatives organized by caregivers. First, general PCC is a rather new concept, requiring a new mind-set, for which governments should create awareness. Second, PCC is multifaceted. It should be part of an interlinked chain that creates connections in the course of life- from PCC through prenatal, neonatal, child, and youth care. And it entails the need for many healthcare disciplines to cooperate –GPs, midwives, obstetricians, clinical geneticist, and other maternal and child health professionals. To avoid barriers and to guarantee a continuum of optimal care, these links are crucial. These characteristics may complicate and slow down the bottom-up organization of PCC because many disciplines must reach consensus.

The optimal design of a general PCC program was investigated during a consensus meeting by assessing the experts' view. Consensus was achieved on the majority of the discussed key elements of PCC, including the definition, the categorization, institutes and health care professionals, which should play a role in reaching target groups, the content and delivery, and the need for development of evidence-based risk assessment instruments (**chapter 3**). Experts stated that the line between the different categories of PCC (general individual PCC and specialized PCC) is not always very evident. A lack of consensus existed about which health care professional should have a core responsibility in which category of PCC. However, as PCC has a very broad content, experts agreed that it is merely impossible for one caregiver to address all risk factors. Besides consensus on a national level among PCC experts, consensus on a city or even district level is tremendously important for the uniform delivery of PCC. As the possible content of PCC is growing, there is a need for prioritization in the interventions for a woman's specific risk profile. This should be based on the impact of risk factors and the effectiveness of interventions. The available studies regarding effectiveness of lifestyle interventions prior to pregnancy for women was summarized in a systematic review in **chapter 4.**

This showed a relative short list of effective preconceptional interventions for folic acid supplementation, smoking reduction, and healthy nutrition in terms of behavioural change and/or pregnancy outcome.

## PART II: READY FOR A BABY PROGRAM

In the studies conducted in Part II, we investigated the general populations' knowledge about preconceptional risk factors and their attitude regarding the use of individual PCC. Furthermore, we evaluated the process of the development and the implementation of a general PCC health intervention study within the Ready for a Baby program.

One of the determinants influencing and predicting health behaviour is the intention that women have to actually perform the desired behaviour, in this case visiting a GP and/or midwife for PCC consultation (**chapter 5**). We explored this by using the Attitude- Social influences- Self-Efficacy (ASE-) model among women living in the two pilot districts - North and South. We demonstrated higher intention to attend PCC consultation for women with a Turkish and Moroccan background, for women with a higher maternal age and a positive attitude.

We demonstrated a low level of knowledge for preconceptional risk factors, e.g. folic acid use. We found differences between ethnic groups: non- Western women had the lowest knowledge level, while the Dutch women had high knowledge levels (**chapters 5 and 6**). As expected, when the educational level was higher in both groups the differences in knowledge was lower.



For the optimal implementation of general PCC we combined three pillars for maximum impact: (1) collective public health campaigns using different methods (multi-lingual posters and leaflets, advertisements in local newspapers, and columns in the local media), (2) a PCC education program tailored to specific target groups (short courses for women and men about healthy pregnancy and the importance of PCC), and (3) individual PCC counselling by GPs and/or midwives for prospective parents. With our process evaluation study we showed that one of the two pilot districts met criteria for the implementation of the three pillars (**chapter 7**). In general, GPs and midwives successfully distributed the posters and leaflets at their practices. All ethnic minority women and Turkish men were well reached by the peer education sessions and the 'Tupperware' method turned out to be a success. The high outreach with the peer education sessions and respondents' positive attitude regarding individual PCC consultation, and their intention to make use of the consultation did not automatically lead to a higher number of consultations. We demonstrated practical and motivational barriers in the provision and implementation of individual PCC consultation in daily practice of GPs and midwives.

In addition, parents-to-be as well as primary caregivers remain insufficiently aware of pregnancy-related risk factors, possibilities for prevention, and of the role of properly timed, specific risk-reducing behaviour.

Finally, in **chapter 8**, we summarize and discuss the main findings of this thesis, we present the methodological considerations, and we provide recommendations for future research.

The studies in this thesis have shown that for the fulfillment of conditions for the implementation of general PCC an agreement and in-close collaboration with authorities and professionals is crucial. Given that knowledge regarding preconceptional risk factors is scarce among the general population, continuous based mass-media campaigns adapted to the needs of target groups and through (preconception) health education at schools are needed. Our study results imply an approach as close as to the target group and the needs of these groups, such as multilingual meetings. We showed that hard to reach groups such as ethnic minorities are well reached with the peer education approach. This approach should be included in recruitment strategies to reach the hard to reach groups. Key recommendations for the delivery and implementation of PCC in primary care could be training of GPs for PCC, higher financial fee, and better collaboration between GPs and midwives. Additional research after the Ready for a Baby program, the Healthy Pregnancy 4 All program, is investigating in the effectiveness of different recruitment methods and effectiveness of individual PCC consultation regarding behavioural change. Effectiveness of individual PCC consultation regarding pregnancy outcomes remains a priority and an important recommendation for future research.

## NEDERLANDSE SAMENVATTING

In 2000, 20004 en opnieuw in 2010 bleek de positie van Nederland in Europa wat betreft perinatale sterfte (doodgeborenen van 22 zwangerschapsweken tot 7 dagen na de geboorte) ongunstig. In 85% van de gevallen werd perinatale sterfte voorafgegaan door perinatale morbiditeit (Big 4aangeboren afwijkingen, geboorte <37 weken zwangerschap, geboortegewicht <p10, en een Apgar score <7 vijf minuten na de geboorte; 'Big4'). De meest nadelige uitkomsten werden in achterstandswijken en in Rotterdam aangetoond. In deze stad heeft één op de zes kinderen een suboptimale start na de geboorte met een groter risico op ontwikkelings- en gedragsproblemen op de lange termijn.

Deze ongunstige uitkomsten in Rotterdam hebben geleid tot bijeenkomsten met experts waarin risicofactoren en mogelijke oplossingen voor dit probleem werden aangedragen en geanalyseerd. Op basis hiervan werd het 'Klaar voor een Kind' programma ontwikkeld, geïnitieerd door de GGD Rotterdam Rijnmond en het Erasmus MC. Het doel van dit 10-jarige programma was het bevorderen van de perinatale gezondheid en het terugdringen van het perinatale sterftecijfer binnen Rotterdam tot het landelijk gemiddelde.

Het 'Klaar voor een Kind' programma volgt de obstetrische keten met Preconceptiezorg (PCZ) als eerste schakel. Het doel binnen deze schakel was het ontwikkelen, uitvoeren en evalueren van een preconceptionele gezondheidsinterventie in twee deelgemeenten van Rotterdam. Drie benaderingsmethoden, welke individuele en collectieve PCZ combineren, werden uitgevoerd.

De tweede schakel had als doel de kwaliteit van prenatale zorg te verbeteren door het ontwikkelen, uitvoeren en evalueren van een risicoscreeningsinstrument de zogenoemde 'R4U' (Rotterdam Reproductive Risk Reduction scorekaart), inclusief psychosociale en sociaaleconomische risicofactoren en zorgpaden.

Net als in de prenatale fase werd in de derde schakel ingezet op de verbetering van de zorg via de 'R4U' en zorgpaden. De vierde schakel had als doel het introduceren van kraamzorg in nieuwe instellingen (bv. het geboortecentrum) en aan populaties die met deze vorm van zorg onbekend zijn. Het doel in de vijfde schakel was om de kloof tussen bevalling en kraamzorg te overbruggen. Ontwikkelingen in de stad werden gevolgd en projectmatige evaluaties werden uitgevoerd. In dit proefschrift richten wij ons op de PCZ schakel.

Algemene PCZ is gericht op alle koppels met een kinderwens en vindt hoofdzakelijk plaats in de eerste lijn (huisarts en/of verloskundige). De Nederlandse Gezondheidsraad

adviseerde in 2007 om algemene PCZ te integreren in het gezondheidssysteem. Tot op heden vindt dit nog op kleine schaal plaats. Het hoofddoel van het proefschrift is dan ook om meer inzicht te krijgen in de optimale ontwikkeling en implementatie van een algemeen PCZ programma. De resultaten van het proefschrift worden in twee delen gepresenteerd.

## DEEL I

In **hoofdstuk 1** presenteren we het onderwerp en de doelstellingen van dit proefschrift.

**Hoofdstuk 2** introduceert het concept van PCZ. We bespreken de voordelen van PCZ, de ontwikkelingen in Nederland en wereldwijd, en de uitdagingen voor de implementatie van PCZ. We bespreken hoe PCZ kan bijdragen aan de verbetering van de reproductieve gezondheid. De reproductieve gezondheid is in de laatste decennia nauwelijks verbeterd. Het uitblijven van verbeteringen, ondanks verbeterde kwaliteit en verbeterde toegang tot prenatale zorg, suggereert dat prenatale zorg alleen niet voldoende is. PCZ verbindt verschillende fasen in de levensloop van het toekomstige kind, van preconceptioneel via prenataal naar de kindertijd, en legt verbindingen tussen verschillende zorgdisciplines. We beargumenteren dat een top-down beleid nodig is om een bottum-up aanpak succesvol te maken.

In **hoofdstuk 3** presenteren we de uitkomsten van bijeenkomsten met PCZ experts waarin is getracht nationaal consensus te bereiken over de onderdelen en de vorm van PCZ. Vijf onderdelen van PCZ zijn bediscussieerd en de (on)bereikte consensus en de kennishiaten hebben we beschreven. Als uitgangspunt is een uitgebreid literatuuronderzoek uitgevoerd om in beeld te brengen wat 1) de definitie van PCZ is, 2) de categorieën van PCZ zijn, 3) de relevante doelgroepen en de methoden voor bereik zijn, 4) de risicofactoren die moeten worden opgenomen in PCZ zijn met hun effectieve interventies, en 5) de bestaande risicoscreenings instrumenten zijn. Er werd consensus bereikt over een nieuwe definitie van PCZ: 'PCZ bestaat uit een set van interventies of een programma met als doel het identificeren van risicofactoren om toekomstige ouders in staat te stellen geïnformeerde keuzes te maken en/of biomedische, (psycho) sociale en leefstijlfactoren te modificeren voor hun toekomstige kind, door middel van counseling, preventie en management.' Los van de definitie is de potentie van PCZ om perinatale mortaliteit en morbiditeit te verminderen opgenomen als voetnoot. Verder was er consensus om de indeling van PCZ in collectieve en individuele PCZ, zoals geclassificeerd door de Nederlandse Gezondheidsraad, te handhaven. Er was consensus ten aanzien van de verantwoordelijke zorgprofessional binnen deze indeling. Deskundigen noemden de scheiding tussen algemene en specialistische PCZ vaag wat impliceerde

dat meerdere zorgverleners in aanmerking zouden kunnen komen om zowel algemene als specialistische PCZ uit te voeren. Vanwege de uitgebreide inhoud van PCZ, leek het behandelen van risicofactoren een onmogelijke taak voor één zorgverlener en zouden hulpverleners een prioritering moeten maken voor wat betreft de interventies. Het voorstel was deze prioritering te baseren op de impact van risicofactoren en op de bewezen effectiviteit van interventies. Verder werden er instellingen en beroepsbeoefenaars geïdentificeerd en vastgesteld die als sleutelfiguren een rol zouden moeten spelen in het bereiken van de doelgroepen. Tenslotte, werd de noodzaak tot het ontwikkelen en leveren van evidence-based risicoscreenings instrumenten nogmaals onderstreept.

In **hoofdstuk 4** voerden we een literatuur studie uit om effectieve preconceptionele interventies te identificeren die zouden kunnen leiden tot gedragsverandering en/of effecten op zwangerschapsuitkomsten onder vrouwen in de algemene bevolking. Op basis van meerdere selectiecriteria vonden we bewijs voor preconceptionele interventies gericht op voeding (gedragsverandering en toename geboortegewicht van de pasgeborenen), roken (afname in aantal gerookte sigaretten en in aantal rokers) en foliumzuur (gedragsverandering en verbetering van zwangerschapsuitkomsten). Dit waren veelal studies met interventies gericht op één risicofactor en in selecte populaties. Ondanks de relatief korte lijst van effectieve preconceptionele interventies, pleitten we ervoor dat hulpverleners moeten doorgaan met het informeren van toekomstige ouders over de nadelige effecten van bijv. roken of alcohol drinken in de preconceptionele periode. Het is onomstreden bewezen dat deze en andere risicofactoren in de preconceptionele periode geassocieerd zijn met nadelige zwangerschapsuitkomsten.



## DEEL II

De **hoofdstukken 5, 6 en 7** richten zich op de studies in de twee deelgemeenten van Rotterdam, uitgevoerd in het kader van het Klaar voor een Kind programma.

Voorafgaand aan de interventies is in de twee deelgemeenten een nulmeting met behulp van vragenlijsten uitgezet om de determinanten van intentie tot gebruik van PCZ te onderzoeken onder vrouwen tussen de 15 en 60 jaar (**hoofdstuk 5**). Het Attitude-Sociale Invloeden- Zelfredzaamheid model, een gezondheidsgedrag model, hebben we als verklarend model gebruikt. Hieruit bleek een hogere intentie om een PCZ consult bij te wonen als vrouwen een Turkse of Marokkaanse achtergrond hebben, een hoger maternale leeftijd hebben en een positieve attitude hebben. Een lagere intentie om een PCZ consult bij te wonen hing samen met het ontbreken van een relatie, multipariteit met een negatieve zwangerschapsuitkomst in de voorgeschiedenis, een hoog opleidingsniveau, betaald werk, en ervaren barrières (zoals tijdgebrek onder werkende

vrouwen). We beargumenteerden dat deze determinanten informatie geven over hoe vrouwen kunnen worden gestimuleerd en bereikt om PCZ bij te wonen.

In **hoofdstuk 6** tonen wij de resultaten van het kennisniveau van mannen en vrouwen ten aanzien van preconceptioneel foliumzuur inname en het preconceptioneel consulteren van een huisarts/verloskundige. Hiervoor hebben we de gemeentelijke Omnibus enquête geanalyseerd (2007, 2009-2014). Dit is een vragenlijst welke jaarlijks wordt afgenomen onder een steekproef van de Rotterdamse bevolking, wat zich goed leent om trends te observeren. Voor Rotterdam werd er tussen 2007 en 2009 een 20% significante toename in kennis van preconceptioneel foliumzuur inname gevonden. Tussen 2007 en 2012 vonden we een significante toename van 53% van het kennisniveau om preconceptioneel wel of geen huisarts/verloskundige te raadplegen. In de twee deelgemeenten werd een niet-significante toename in kennis over de studiejaren voor beide uitkomsten gevonden. Mogelijk was er een relatie tussen de PCZ interventies in het Klaar voor een Kind programma en de uitkomsten van de Omnibus enquête in de twee pilot deelgemeenten. Het doel van deze studie was niet om effecten van interventies te onderzoeken. Het is verder niet mogelijk om de uitkomsten van de interventies die zijn uitgevoerd op deelgemeente niveau te generaliseren op stadniveau.

**Hoofdstuk 7** beschrijft in zeven stappen het evaluatie proces van de ontwikkeling en implementatie van het preconceptionele gezondheidsinterventie in het Klaar voor een Kind programma. Drie benaderingsmethoden, welke bestaan uit 1) massa mediale PCZ campagne, 2) peer education, en 3) PCZ consulten, werden afzonderlijk geëvalueerd binnen de twee deelgemeenten. Een van de twee deelgemeenten voldeed aan de implementatie criteria van de drie benaderingsmethoden. We hebben laten zien dat intensieve samenwerking met verschillende partijen van belang is voor een gezamenlijk doel en inzet. Alhoewel de doelgroep goed werd bereikt met de peer education methode en er financiering was voor de PCZ consulten gegeven door huisartsen/verloskundigen, bleef het aantal PCZ consulten laag. Uit focusgroep interviews met participerende huisartsen en verloskundigen werden er barrières geïdentificeerd om vrouwen en mannen met een kinderwens te bereiken. Tevens speelden logistieke en facilitaire problemen in de dagelijkse praktijken een rol bij het implementeren van PCZ.

**Hoofdstuk 8** presenteert een samenvatting en discussie van de hoofdbevindingen en conclusies van dit proefschrift, bespreken we een aantal methodologische punten en geven we aanbevelingen voor toekomstig onderzoek.

De studies in dit proefschrift hebben aangetoond dat de voorwaarden om algemene PCZ te implementeren om consensus vragen. Een nauwe samenwerking met instanties en hulpverleners bleek uitermate belangrijk om draagvlak te creëren. Er bestond veel on-

wetendheid over preconceptionele risicofactoren (zoals foliumzuur inname) en over het concept van PCZ onder de algemene bevolking. Verbetering van het kennisniveau zou bewerkstelligd kunnen worden door grootschalige continue massa-mediale campagnes aangepast aan behoeften van doelgroepen en (preconceptionele) gezondheidsonderwijs op scholen. Onze studieresultaten impliceren een benaderingsmethode wat zo dicht mogelijk bij de doelgroep staat, zoals meertalige voorlichtingsbijeenkomsten. We hebben laten zien dat lastig te bereiken groepen zoals allochtone groeperingen het best bereikt worden met de peer education methode. Deze peer education methode zou geïntegreerd moeten worden in wervingsmethoden om deze doelgroep te bereiken. Belangrijke aanbevelingen voor het bevorderen van de implementatie en aanbieden van PCZ in de eerste lijn zouden zijn: (na)scholing van huisartsen, hogere financiële tegemoetkoming en betere samenwerking tussen verloskundigen en huisartsen. Op een vervolg op het Klaar voor een Kind programma, het HP4ALL programma, wordt verder onderzoek verricht naar de effectiviteit van verschillende wervingsmethoden en van individuele PCZ consulten in het kader van gedragsverandering. Het onderzoeken van de effectiviteit van individuele PCZ consulten ten aanzien van zwangerschapsuitkomsten blijft een prioriteit en een belangrijke aanbeveling voor toekomstig onderzoek.

# Chapter 10

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Manuscripts

PhD portfolio

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*Brian W. Jack*

## MANUSCRIPTS

**Temel S**, Erdem Ö, Voorham AJJ, Bonsel GJ, Steegers EAP, Denktaş S. Knowledge on preconceptional folic acid supplementation and intention to seek for preconception care among men and women in an urban city: a population-based cross-sectional study. BMC Pregnancy Childbirth. 2015 Dec 18;15(1):340.

**Temel S**, Van Voorst SF, De Jong-Potjer LC, Waelput AJ, Cornel MC, Rombout- de Weerd S, Denktaş S, Steegers EA. The Dutch national summit on preconception care: a summary of definitions, evidence and recommendations. J Community Genet. 2015;6(1):107-15.

**Temel S**, Van Voorst SF, Jack BW, Denktaş S, Steegers EA. Evidence-based preconceptional lifestyle interventions. Epidemiol Rev. 2014;36:19-30.

**Temel S**, Birnie E, Sonneveld HM, Voorham AJJ, Bonsel GJ, Steegers EAP, Denktaş S. Determinants of the intention of preconception care use: lessons from a multi-ethnic urban population. Int J Public Health. 2013;58(2):295-304.

**Temel S**, Schölmerich VL, Steegers EAP, Denktaş S. Process evaluation of general preconception care in a municipal perinatal health program: Ready for a Baby. Submitted.

Van der Zee B, De Beaufort I, **Temel S**, De Wert G, Denktaş S, Steegers E. Preconception care: An essential preventive strategy to improve children's and women's health. J Public Health Pol. 2011;32:367-79.

**Other**

Van Voorst SF, **Temel S**, Aalhuizen IM, Denktaş S, Steegers EAP. 'Preconceptiezorg' Preconception care. Handboek vrouwspecifieke geneeskunde. 2013. Chapter 22:249-63. (Chapter of a Dutch book)

Denktaş S, Jong-Potjer LC, Waelput AJM, **Temel S**, Voorst van SF, Vos AA, Schölmerich VLN, Bonsel GJ, Kooy van der J, Quispel C, Poeran VJJ, Peters IA, Vujkovic M, Bakker R, Steegers EAP. Preconception care: a review of the literature. Erasmus MC, Rotterdam, the Netherlands, 2012. (Literature study which is discussed with the WHO)

**Temel S**, Steegers EAP, Van der Weg-Kroeze E, Voorham AJJ, Bonsel GJ, Birnie E, Denktaş S. 'Eerste jaar project preconceptiezorg Deelgemeente Feijenoord-Rotterdam' First year preconception care in district South, Erasmus MC en GGD Rotterdam-Rijnmond, 2011. (Report for Rotterdam's district South council)

**Temel S**, Laven JS, Steegers-Theunissen RPM. Lifestyle and conception. Textbook of Periconceptional Medicine, 2009. Chapter 2:13-22. (Chapter of a English book)

Hammiche F, **Temel S**, Laven JS, Verhagen-van den Graaf IM, Steegers EAP, Steegers- Theunissen RPM. 'Vruchtbare adviezen' Fertile advices. Medisch Contact, 2008;63(41);1672-75. (Article in a Dutch scientific journal)

# PHD PORTFOLIO

## Summary of PhD training and activities

| | |
|---|---|
| **Name PhD student:** | Sevilay Temel |
| **Erasmus MC Department:** | Obstetrics & Gynaecology- Division of Obstetrics and Prenatal Medicine |
| **Research School:** | Netherlands Institute for Health Sciences (NIHES) |
| **PhD period:** | February 2010- May 2013 |
| **Promotor:** | Prof. dr. E.A.P. Steegers |
| **Co-promotor:** | Dr. S. Denktaş |

| | Year | Workload (ECTS) |
|---|---|---|
| **1. PHD TRAINING** | | |
| **General and specific courses** | | |
| Biomedical English Writing and Communication Course | 2011 | 4.0 |
| SPSS introduction course | 2011 | 2.0 |
| NIHES: Regression Analysis (ESP09) | 2011 | 1.9 |
| NIHES: Study Design (CC01) | 2011 | 4.3 |
| NIHES: Public Health Research (Hs02abc) | 2011 | 5.7 |
| **International Conferences** | | |
| SGI 60th Annual Scientific Meeting, Orlando, Florida, United States: **poster presentation** | 2013 | 1.0 |
| SGI 59th Annual Scientific Meeting, San Diego, California, Unites States: **poster presentation** | 2012 | 1.0 |
| 2nd European Congress of Preconception Care and Preconception Health, Rotterdam, the Netherlands: **oral presentation** | 2012 | 1.5 |
| 1st European Congress of Preconception Care and Preconception Health, Brussels, Belgium: **oral presentation** | 2010 | 1.5 |
| **National conferences** | | |
| Ready for a Baby congress, Rotterdam, the Netherlands: **oral presentation** | 2013 | 1.0 |
| NCVGZ, Dutch Annual Public Health Conference (in Dutch: 'Nationaal Congres Volksgezondheid'), Amsterdam, the Netherlands: **oral presentation** | 2011 | 1.0 |
| Symposium 'Urban Perinatal Health' (in Dutch: 'Grootstedelijk Perinatale Gezondheid'), Rotterdam, the Netherlands: **oral presentation** | 2011 | 1.0 |
| Dutch Congress of Preconception Care (in Dutch: 'Nederlands Congres Preconceptiezorg', Nieuwegein, the Netherlands: **poster and oral presentation** | 2011 | 1.5 |
| **Seminars, workshops, and (research) meetings** | | |
| Attending weekly and quarterly research meetings of the Department of Obstetrics and Gynaecology (and Urology) with **one oral presentation**, Rotterdam, the Netherlands | 2010-2013 | 4 |
| Attending the annual meetings of the Collaboration of Rotterdam Regional Gynaecologists' Teaching Hospitals (in Dutch: RGOC) and 'Wladimiroff symposium' with **two oral presentations**, Rotterdam, the Netherlands | 2010-2013 | 3 |
| Attending weekly research meetings of the Ready for a Baby program with multiple **oral presentations**, Rotterdam, the Netherlands | 2010-2013 | 4 |

| | | |
|---|---|---|
| Interim and end of study meetings with district North and South leaders, Rotterdam, the Netherlands: **two oral presentations** | 2011-2013 | 2 |
| Attending the monthly meetings of the Ready for a Baby program for participating partners ('Café Bebe') with **one oral presentation**, Rotterdam, the Netherlands | 2011-2012 | 2 |
| District South Council Meeting, Rotterdam, the Netherlands: **oral presentation** | 2012 | 0.5 |
| Attending the symposium on behalf of the 2.5 year anniversary of the 'Sophia Birth Centre', Rotterdam, the Netherlands | 2012 | 0.2 |
| Visit from professor Lucilla Poston and staff from the King's College, London, United Kingdom, to Rotterdam, the Netherlands: **oral presentation** | 2012 | 0.5 |
| Attending the Expert meeting on Preconception care, the Hague, the Netherlands | 2012 | 0.2 |
| Researchers Network Culture and Diversity (in Dutch: 'Onderzoekersnetwerk Cultuur en Diversiteit') of 'Zon Mw', the Hague, the Netherlands: **oral presentation** | 2011 | 0.5 |
| Regional Obstetric Collaboration Meeting (in Dutch: 'VSV'), Almelo, the Netherlands: **oral presentation** | 2011 | 1.0 |
| Attending the NCVGZ, Dutch Annual Public Health Conference (in Dutch: 'Nationaal Congres Volksgezondheid'), Rotterdam, the Netherlands | 2010 | 0.2 |
| Regional Midwifery Academy Meeting (in Dutch: 'Kringsymposium Verloskunde Academie), Rotterdam, the Netherlands: **oral presentation** | 2010 | 0.5 |
| **Other: Grant proposal assistance** | | |
| Assisted in the writing of a grant proposal for 'Zon Mw' the Netherlands Organization for health Research and Development | 2012 | 2 |
| **Other: Writing of municipal and other reports** | | |
| Assisted in the writing of 'Preconception Care: a review of the literature', for the World Health Organization | 2012 | 3 |
| Writing 'Report of the baseline measurement within the preconception care study for district South' (in Dutch: 'Rapportage nulmeting Schakel preconceptiezorg in deelgemeente Feijenoord') | 2012 | 3 |
| Writing the chapter of 'Preconception Care' for Perinatal Health Educators teaching module | 2011 | 4 |
| Writing 'Preconception Care: an Overview of the Evidence' for the 'dr Slager congress' | 2011 | 2 |
| **2. TEACHING ACTIVITIES** | | |
| **Lecturing** | | |
| Lectures on 'Preconception Care and the Ready for a Baby program' for NIHES Master's candidates; course 'Urban Perinatal health and Health Care' | 2011-2012 | 2 |
| Lecture and practicals on 'Preconception Care' for medical student; minor 'Circle of Life' | 2011 | 2 |
| Lectures and practicals on 'Preconception Care' for Perinatal Health Educators | 2011 | 2 |
| Lectures on 'Preconception Care' for first year and third year midwifery students | 2010 | 2 |
| Lecture on 'Preconception Care' for midwives aspiring to obtain a Master's Degree | 2010 | 1 |
| **Tutoring** | | |
| Tutoring midwives and GPs in the practical use of tools for PCC consultation | 2010-2013 | 4 |
| **Supervising theses** | | |
| 'Projectmatig en Multidisciplinair werken aan Grootstedelijke Vraagstukken' report of eight students from the High School of Rotterdam ('HRO) | 2011 | 4 |
| Two students from the Midwifery Academy | 2011 | 2 |

**Other activities**

| | | |
|---|---|---|
| Attending peer education meetings, practices of midwives and GPs, migrant institutes | 2010-2013 | 4 |
| Assisted in the organization of two Expert Meetings for Preconception Care | 2012 | 2 |
| Assisted in the organization and training of 30 GPs and five midwives for Preconception care | 2012 | 4 |

## ABOUT THE AUTHOR

Sevilay Temel was born on the 6th of May 1984 in Tiel, the Netherlands. After graduation of pre-university education (Atheneum, Lingecollege, Tiel) in 2002, she started her study Medicine at the Erasmus University of Rotterdam. One of her last internships was carried out at the department of Obstetrics and Gynaecology of the Capa University Hospital in Istanbul, Turkey. After attaining her medical degree in February 2009 she worked as an ANIOS at the department of Obstetrics and Gynaecology of the Ikazia Hospital in Rotterdam.

In 2009, the Ready for a Baby program started to improve perinatal outcome in Rotterdam- a joint initiative of the Erasmus Medical Center and the municipality of Rotterdam. Sevilay was dedicated to the execution and evaluation of the preconception care study between February 2010 and May 2013. Her PhD thesis was supervised by prof. dr. E.A.P. Steegers (promotor) and dr. S Denktaş (co-promotor) at the Erasmus Medical Center where she performed the studies that are described in this thesis. In September 2013, she started her residency in General Practice at the Utrecht University.

Sevilay Temel is married to Shakib Sana and the proud mother of Lina Roza.

## DANKWOORD

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