Evidence-Based Preconceptional Lifestyle Interventions

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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 pre-defined search strategy was applied in electronic databases, and citation tracking was performed. Study selection was performed by 2 independent reviewers according to predefined criteria for eligibility: The intervention was performed preconceptionally on women regarding alcohol use, smoking, weight, diet/nutrition, physical activity, and folic acid status (fortification and supplementation) to achieve behavior change and/or improve pregnancy outcome. Quality and strength of evidence were assessed by 2 independent reviewers. A total of 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 based largely 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 periconceptional 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 predefined 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 offered mostly to these women with predefined risk factors. More evidence is needed regarding the effectiveness of interventions aimed at general lifestyle risk factors that are applicable to a large proportion of the couples aiming to conceive. This evidence would not only help women with predefined risks but also be a boost for implementation of PCC for the general population.

Abbreviations: CI, confidence interval; PCC, preconception care.
Furthermore, evidence for preconceptional health interventions is necessary to embed PCC as an available health service—for professionals and for couples wishing to conceive—among the general population. Also, concrete evidence is necessary to motivate policymakers, 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, no systematic review comprising 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 because of the behavior changes that 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 among preconceptional women in the general population.

MATERIALS AND METHODS

Search strategy

Studies were identified initially with an electronic search in the databases Medline, Embase, and Web of Science from inception to March 2012, restricted to the following languages (English, Dutch, German, French, and Spanish) and to 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. 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 from 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 anomalies other than neural tube defects); 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 neural tube defects 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 on the basis of 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 2 reviewers (S. T. and S. F. v. V.) with a third reviewer (S. D.) 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); flowchart of participants; loss to follow-up (number and reasons stated); baseline characteristics of the study population; setting of the intervention; definitions of prespecified 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 extracted largely from the Strengthening the Reporting of Observational Studies in Epidemiology (“STROBE”) statement (8) and the Cochrane Handbook (9). When there were questions regarding these items, the 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 on the basis of 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 randomized controlled trials (9, 10). Nine criteria were used across 5 quality domains. The criteria for quality assessment can be found in Appendix Table 1.

Studies were considered as highly susceptible to bias if 2 or more of the 5 domains were scored as susceptible to bias, or if 3 or more of the 5 domains were scored as unclear.

The strength of the evidence for each intervention was assessed by 2 reviewers (S. T., S. F. v. V.) according to predefined criteria adapted from the Canadian Task Force on the Periodic Health Examination (11). In case of disagreement, a third reviewer (S. D.) was asked to resolve the discrepancy. The applied classification for the strength of evidence can be found in Appendix Table 1.

Data analysis

Because of presumed clinical heterogeneity, no attempt for a meta-analysis was prespecified.
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).

Table 1 summarizes the included studies. Results are classified as follows. First, studies were grouped by the core risk factor that the interventions address and report. Multiple risk factor studies with multiple outcomes were classified separately. The 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. Second, 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., iodizing salt in prevention of hypothyroidism) (12).

The majority of studies focused on individual interventions (13–38), 3 studies focused on group interventions (39–41), 1 study focused on a mix of individual and group intervention (42), and 14 studies focused on collective interventions (43–56). Of 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 1 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); 1 study measured behavior change by using a combination of self-report and biomarkers (29), and 8 studies measured behavior change by using a combination of self-report and biomarkers (24, 28, 32, 35, 37, 38, 40, 55); 19 randomized controlled trials (13–22, 25, 26, 30, 31, 36, 38–41), 22 cohort studies (24, 27–29, 32, 35, 37, 42–56), 1 case-control study (34), 1 cohort controlled trial (23), and 1 cross-sectional study (33) were identified. Results are presented in Web Table 1 available at http://aje.oxfordjournals.org/ and discussed per (risk) behavior in the following section.

Data extraction

Alcohol. One randomized controlled trial reported on the effectiveness of a program to reduce alcohol-exposed pregnancies by reducing risky drinking (8 drinks/week or >5 drinks on 1 occasion) in women in whom conception could occur. Floyd et al. (36) assessed the effectiveness of a prevention program consisting of 4 counselling sessions with personalized feedback and goal setting regarding risky drinking. Participants
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, Union of Soviet Socialist Republics, United Kingdom, United States)

<table>
<thead>
<tr>
<th>First Author, Year (Reference No.)</th>
<th>Subject Area</th>
<th>Intervention Type</th>
<th>Study Design</th>
<th>Study Population, no.</th>
<th>Outcome</th>
<th>Pregnancy Outcome</th>
<th>High Susceptibility to Bias</th>
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<tbody>
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<td>Floyd, 2007 (36)</td>
<td>Alcohol</td>
<td>Individual</td>
<td>Randomized controlled trial</td>
<td>830</td>
<td>Self-reported</td>
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<tr>
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<td>Individual</td>
<td>Cohort</td>
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<td>Biomarkers</td>
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<td>Hughes, 2000 (38)</td>
<td>Smoking</td>
<td>Individual</td>
<td>Randomized controlled trial</td>
<td>94</td>
<td>Self-reported and biomarkers</td>
<td>Not reported</td>
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</tr>
<tr>
<td>de Weerd, 2001 (35)</td>
<td>Smoking</td>
<td>Individual</td>
<td>Cohort</td>
<td>111</td>
<td>Self-reported and biomarkers</td>
<td>Not reported</td>
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<tr>
<td>Caan, 1987 (34)</td>
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<td>Cena, 2008 (39)</td>
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<td>Mixed individual and group</td>
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<td>Individual: folic acid advice and provision</td>
<td>Randomized controlled trial</td>
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<td>Individual: folic acid advice and provision</td>
<td>Cohort</td>
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<td>Self-reported and biomarkers</td>
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<td>Self-reported and biomarkers</td>
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<td>Randomized controlled trial</td>
<td>322</td>
<td>Self-reported</td>
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Table continues
<table>
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<tr>
<th>First Author, Year (Reference No.)</th>
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<th>Outcome</th>
<th>Pregnancy Outcome</th>
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<td>Schwarz, 2008 (26)</td>
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<td>Individual: folic acid advice and provision</td>
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<td>Cohort</td>
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<td>Collective: fortification</td>
<td>Cohort</td>
<td>13,786 (cases)</td>
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<td>Cohort</td>
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<td>Cohort</td>
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<td>Cohort</td>
<td>5,630 (cases)</td>
<td>Not reported</td>
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<td>Collective: fortification</td>
<td>Cohort</td>
<td>5,200 (cases)</td>
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<td>Liu, 2004 (55)</td>
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<td>Cohort</td>
<td>825</td>
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<td>Cohort</td>
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<td>De Wals, 2007 (54)</td>
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<td>Cohort</td>
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<td>Randomized controlled trial</td>
<td>633</td>
<td>Self-reported</td>
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<td>Hammiche, 2011 (37)</td>
<td>Multiple risk factors</td>
<td>Individual</td>
<td>Cohort</td>
<td>419</td>
<td>Self-reported and biomarkers</td>
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<td>Ockhuijsen, 2012 (32)</td>
<td>Multiple risk factors</td>
<td>Individual</td>
<td>Cohort</td>
<td>101</td>
<td>Self-reported and biomarkers</td>
<td>Not reported</td>
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<td>Williams, 2012 (33)</td>
<td>Multiple risk factors</td>
<td>Individual</td>
<td>Cross-sectional study</td>
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<td>Self-reported</td>
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<td>Hillemeier, 2008 (40)</td>
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<td>Group</td>
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<td>362</td>
<td>Self-reported and biomarkers</td>
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<td>Weisman, 2011 (41)</td>
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<td>Group</td>
<td>Randomized controlled trial</td>
<td>315</td>
<td>Self-reported</td>
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</table>
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 who 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 9 months after intervention (odds ratio = 2.11, 95% confidence interval (CI): 1.47, 3.03). This outcome is based on self-reported behavior change.

Because 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: 1 randomized controlled trial (38) and 2 cohort studies (29, 35). One study assessed the effectiveness of a preconceptional health program in terms of behavior changes with a biomarker. Czeizel (29) assessed smoking cessation rates with urinary cotinine. The intervention, smoking cessation advice at a preconceptional consultation, resulted in a decrease of smoking rates after 3 months (17.9% vs. 12.4%). In the report by Hughes et al. (38), 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 prepregnancy smoking. de Weerd et al. (35) 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 report by Hughes et al. and with the biomarker cotinine in that by 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 the report by Hughes et al. were not proven effective in the 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 the study by Czeizel (29), overall susceptibility to bias was low. The study by de Weerd et al. (35) 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. (38) and de Weerd et al. (35) 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: 1 randomized controlled trial (39) and 2 case-control studies (34, 42). Caan et al. (34) assessed the effect of long-term enrollment in the Women, Infants, and Children (WIC) supplemental food program with short-term enrollment among women with low income and nutritionally at risk in their interpregnancy interval. Long-term (5–7 months) WIC support was associated with a positive effect on birth weight and birth length. Cena et al. (39) assessed the effect of nutrition lessons regarding folate among low-income, nonpregnant women. The comparison group underwent a lesson about resource management. Nutrition lessons led to increased self-reported intake of dietary folate.

Doyle et al. (42) assessed the effectiveness of a preconception nutrition counselling program (individual consultations, educational group events, and nutrition newsletters) among women with pregnancy intention and history of a prior low-birth-weight baby and an inadequate dietary intake. The interventions led to higher intake of certain micronutrients, except for folic acid from diet.

Doyle et al. (42) 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 as reporting on the effectiveness of folic acid supplementation and fortification. Sixteen studies were individual-based programs, of which 12 were randomized controlled trials (13–22, 25, 26), 1 was a cohort controlled trial (23), and 3 were 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 were restricted to advising only folic acid supplements.

From the 15 studies that provided supplements, there were 3 trials that provided folic acid supplements as well as counselling on folic acid: A significant beneficial effect of self-reported folic acid supplement use was shown (25–27). Counselling varied from brief folic acid counselling to a computerized educational session. Only Morgan et al. (27) succeeded in showing a significant increase in self-reported daily multivitamin intake. Morgan et al. and Schwarz et al. (26) showed an increase of self-reported use up to 6–10 months after the counselling and provision of supplements. Two trials, those by Watkins et al. (24) and de Weerd et al. (28), 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 among women planning a pregnancy. An elevated red cell folate level 4 months postintervention was found. All trials were conducted among 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 1 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 those by the Medical Research Council Vitamin

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Study Research Group (13) and Czeizel et al. (14–17, 19, 20), 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, 3 cohort studies reported on the effectiveness of a folic acid campaign (43–45). Chan et al. (43) reported on behavior change, and Myers et al. (44) and Gindler et al. (45) 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 neural tube defects 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% 1 year after the campaign.

Myers et al. (44) and Gindler et al. (45) 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 of miscarriages for women with folic acid use (relative risk = 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 and reported on the effectiveness of folic acid fortification. One study reported on behavior change assessed with biomarkers (55), and 10 studies evaluated changes in prevalence rates of congenital anomalies (46–54, 56).

Liu et al. (55) evaluated the effectiveness of folic acid food fortification among women of childbearing age and seniors over 65 years, recruited prefortification through a random telephone post. Postfortification, the annual rate of neural tube defects 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 neural tube defect 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 the incidence of neural tube defects postfortification. 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. (53) assessed prevalence rates of other congenital abnormalities besides neural tube defects postfortification. 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. (56) showed a significant decline of 6% in oro-facial 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 that reported on the effectiveness of multiple risk factors. The majority of these studies were individual-based programs, of which 2 were randomized controlled trials (30, 31), 2 were cohort studies (32, 37), and 1 was a cross-sectional study (33); there were 2 group-based randomized controlled trials (40, 41).

Williams et al. (33) 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 interconceptional women planning a pregnancy. Although the definition of PCC was broad, any receipt of PCC (content undefined) led to a higher self-reported intake of multivitamins 1 month before pregnancy and cessation of alcohol during the 3 months before pregnancy. Susceptibility to bias was assessed as low; the strength of evidence is II-2 (33). Hammiche et al. (37) assessed the effectiveness of a tailored lifestyle and dietary consultation in a hospital-sampled subfertile population that was planning pregnancy. Couples that attended a second counselling session after 3 months reported a higher intake of fruits and fish and reduction of their dietary risk score based on self-reported behaviors and biomarkers. However, only a selection of the sampled subfertile patients within a hospital-based setting attended the second consultation. Susceptibility of bias was assessed as low; the strength of evidence is II-2. Ockhuijsen et al. (32) assessed the effectiveness of PCC consultation in smoking cessation and weight reduction among subfertile women. The outcome was self-reported smoking cessation and self-reported and -weighed mean weight reduction. With consultations every 4 weeks during a follow-up period varying between 3 months and 1 year, 15 of 30 (50%) obese women lost weight (mean = 6.1 kg, standard deviation, 3.6) and 7 of 23 (30%) women quit smoking. Because the follow-up period varied among study participants, there is a susceptibility to a detection bias, as the study results are applicable only to a hospital-based population of subfertile women. Overall susceptibility of bias was assessed as low; the strength of evidence is II-2.

Two different multiple risk factor studies assessed effectiveness regarding pregnancy outcomes (30, 31). Lumley and Donohue (30) assessed the effect of a home visit with prepregnancy information, advice, and counselling given by midwives among 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 g lower in the intervention group, there was no significant difference in the outcomes; preterm birth (<32 weeks); low birth weight (<2,500 g); and small for gestational age (birth weight, <10th percentile). Quantitative outcomes showed a higher occurrence of preterm birth, low birth weight, and perinatal deaths. Because of 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.
Elsinga et al. (31) investigated the effectiveness of systematic PCC risk detection and intervention compared with the standard care given by general practitioners among women contemplating pregnancy. The study population consisted mainly of Dutch and high-educated women. The outcome was self-reported behavior change and an adverse outcome of subsequent pregnancy. Systematic counselling and intervention led to a significantly 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 g), small for gestational age (growth, <P2.3 (−2 standard deviations)), and congenital anomalies) was 16.2% in the intervention group versus 20.2% in the control group. The odds ratio 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.

Hillemeier et al. (40) assessed the effectiveness of a preconception group-based intervention program regarding nutrition and physical activity among 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. (41) performed a follow-up study to assess the maintenance of the aforementioned behavior changes 12-months after the intervention. After 12 months, women in the intervention group were more likely to use a daily multivitamin containing folic acid and to have a lower body mass index. Intervention effects on physical activity were not maintained, and effects on reading food labels for nutritional values diminished between the 6- and 12-month follow-up periods.

Allocation concealment in the studies by Hillemeier et al. (40) and Weisman et al. (41) 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.

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 1 single risk factor study was available. Women who 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 regarding alcohol consumption are proven effective for only 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 preconception smoking cessation is not clear. Hughes et al. (38) reported only maintenance of smoking cessation, verified by a biomarker, in the long term and only among a small subpopulation. 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. 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 assessed only among a selective group of women, for example, 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 proven effective only 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 4 months postintervention (28). On the basis of 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 with the provision of folic acid supplements. To compare the effectiveness of sole advice versus advice including provision of folic acid supplements, a randomized controlled trial would need to be conducted, preferably using biomarkers. Eleven randomized controlled trials reported on the effect of individual folic acid advice, mostly including provision on pregnancy outcomes. On the basis of 1 study (with nonsignificant 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 neural tube defects, 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. An increase of folic acid intake due to food fortification was further supported by the finding that folate biomarkers increased among women postfortification (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 neural tube defects (44, 46–54, 56).

Studies on multiple risk factors in reducing risky health behaviors all seemed to be effective in 1 or more targeted risk behaviors, for example, 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 among 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, they 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 the 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 in nature.

The evidence from the studies included in this review is likely to be at some risk of bias. Although studies made efforts to reduce bias by aspects of study design such as accounting for loss to follow-up and reporting predefined outcomes, the 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 who 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 19 studies relied only on self-report for information on behavior change postintervention. 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 that should be integrated in further research on 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 cutoff 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 subfertile 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 comprised 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 socioeconomic factors (1). Articles in this field often lack these details or lack reflection on the relation of these factors to 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, on the basis of 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 behavioral 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 as follows. Include 1) 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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REFERENCES


(Appendix follows)
APPENDIX

Search Strategy


Embase. ((preconception* OR prepregnan* OR pregestation* OR periconception* OR interconception* OR interpregnan* OR internatal* OR inter-gestation* OR preconception 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*)) AND (matern*[tw] OR mother*[tw] OR paternal*[tw] OR father*[tw] OR parent*[tw] OR man*[tw] OR woman*[tw] OR couple*[tw]) 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 inter-gestation* OR preconception OR pre-conceptional OR pre-pregnancy OR pre-pregnant OR pre-gestation OR pre-gestational OR periconception 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*[tw] OR mother*[tw] OR paternal*[tw] OR father*[tw] OR parent*[tw] 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 Table 1. Quality Assessment Criteria and Assessment of Strength of Evidence

<table>
<thead>
<tr>
<th>Domain</th>
<th>Quality Assessment Criteria&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Methods for selecting study participants</td>
<td>The source population was appropriate AND inclusion or exclusion criteria were defined.</td>
<td>Methodology was adequate to detect stated outcomes.</td>
</tr>
<tr>
<td>II. Methods for measuring exposure and outcome variables</td>
<td>(a) Randomized controlled trials: Allocation was concealed. (b) Selection bias: Patient selection and sampling (and in the case of a case-control or cross-sectional study case selection or when applicable matching) were adequate. (c) Detection bias: The length of follow-up was adequate to detect outcome and equally applied among all groups. (d) Attrition bias: Loss to follow-up/dropouts were reported and handled appropriately in analysis. (e) Reporting bias: Outcomes were prespecified, and there was no selective report on outcomes.</td>
<td>Statistical procedures were described adequately and if applicable adjustment for confounding factors was reported.</td>
</tr>
<tr>
<td>III. Design-specific sources of bias</td>
<td>Source of funding or conflicts of interests were reported.</td>
<td></td>
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<tr>
<td>IV. Statistical methods</td>
<td>Classification of Strength of Evidence&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>V. Conflicts of interest</td>
<td>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</td>
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<sup>a</sup> Adapted from references (10, 58).

<sup>b</sup> Adapted from the Canadian Task Force on the Periodic Health Examination (11).