# Prenatal Multivitamin Supplementation and Rates of Congenital Anomalies: A Meta-Analysis

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## Abstract

**Background:** The use of folic acid-fortified multivitamin supplements has long been associated with decreasing the risk of neural tube defects. Several studies have also proposed the effectiveness of these supplements in preventing other birth defects; however, such effects have never been systematically examined.

**Objective:** We conducted a systematic review and meta-analysis to evaluate the protective effect of folic acid-fortified multivitamin supplements on other congenital anomalies.

**Methods:** We searched Medline, PubMed, EMBASE, Toxline, Healthstar, and Cochrane databases for studies describing the outcome of pregnancies in women using multivitamin supplements that were published in all languages from January 1966 to July 2005. The references from all collected articles were reviewed for additional articles. Two independent reviewers who were blinded to the source and identity of the articles extracted data based on predetermined inclusion and exclusion criteria. Using a random effects model, rates of congenital anomalies in babies born to women who were taking multivitamin supplements were compared with rates in the offspring of controls who were not.

**Results:** From the initial search, 92 studies were identified; 41 of these met the inclusion criteria. Use of multivitamin supplements provided consistent protection against neural tube defects (random effects odds ratio[OR] 0.67, 95% confidence intervals [95% CI] 0.58–0.77 in case control studies; OR 0.52, 95% CI 0.39–0.69 in cohort and randomized controlled studies), cardiovascular defects (OR 0.78, 95% CI 0.67–0.92 in case control studies; OR 0.61, 95% CI 0.40–0.92 in cohort and randomized controlled studies), and limb defects (OR 0.48, 95% CI 0.30–0.76 in case control studies; OR 0.57, 95% CI 0.38–0.85 in cohort and randomized controlled studies). For cleft palate, case control studies showed OR 0.76 (95% CI 0.62–0.93), and cohort and randomized controlled studies showed OR 0.42 (95% CI 0.06–2.84); for oral cleft with or without cleft palate, case control studies showed OR 0.63 (95% CI 0.54–0.73), and cohort and randomized controlled studies showed OR 0.58 (95% CI 0.28–1.19); for urinary tract anomalies, case control studies showed OR 0.48 (95% CI 0.30–0.76), and cohort and randomized controlled studies showed OR 0.68 (95% CI 0.35–1.31); and for congenital hydrocephalus case control studies showed OR 0.37 (95% CI 0.24–0.56), and cohort and randomized controlled studies showed OR 1.54 (95% CI 0.53–4.50). No effects were shown in preventing Down syndrome, pyloric stenosis, undescended testis, or hypospadias.

**Conclusion:** Maternal consumption of folic acid-containing prenatal multivitamins is associated with decreased risk for several congenital anomalies, not only neural tube defects. These data have major public health implications, because until now fortification of only folic acid has been encouraged. This approach should be reconsidered.

**Key Words:** Prenatal multivitamins, congenital anomalies, meta-analysis

Competing Interests: None declared.

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## Résumé

**Contexte :** L'utilisation de suppléments multivitaminiques fortifiés à l'acide folique est depuis longtemps associée à la baisse du risque d'anomalies du tube neural. Plusieurs études ont également proposé l'efficacité de ces suppléments pour la prévention d'autres anomalies congénitales; cependant, ces effets n'ont jamais fait l'objet d'un examen systématique.

**Objectif :** Nous avons mené un examen et une méta-analyse systématiques afin d'évaluer l'effet protecteur des suppléments multivitaminiques fortifiés à l'acide folique sur d'autres anomalies congénitales.

**Méthodes :** Nous avons mené des recherches dans les bases de données Medline, PubMed, EMBASE, Toxline, Healthstar et Cochrane afin d'y recenser les études (qui ont été publiées, toutes langues confondues, entre janvier 1966 et juillet 2005) décrivant les issues de grossesse chez les femmes qui ont utilisé des suppléments multivitaminiques. Les références de tous les articles recensés ont fait l'objet d'une analyse afin d'y trouver des articles additionnels. Deux analystes indépendants, n'ayant pas été mis au courant de la source ni de l'identité des articles en question, ont procédé à l'extraction de données en fonction de critères d'inclusion et d'exclusion prédéterminés. Les taux d'anomalies congénitales chez les enfants nés de femmes ayant pris des suppléments multivitaminiques ont été comparés, au moyen d'un modèle à effets aléatoires, à ceux de témoins n'en ayant pas pris.

**Résultats :** La recherche initiale a permis l'identification de 92 études; 41 d'entre elles ont satisfait aux critères d'inclusion. L'utilisation de suppléments multivitaminiques a offert une protection uniforme contre les anomalies du tube neural (rapport de cotes des effets aléatoires [RC], 0,67, intervalles de confiance [IC] à 95 %, 0,58–0,77, dans les études cas-témoins; RC, 0,52, IC à 95 %, 0,39–0,69, dans les études de cohorte et les essais

comparatifs randomisés), les anomalies cardiovasculaires (RC, 0,78, IC à 95 %, 0,67–0,92, dans les études cas-témoins; RC, 0,61, IC à 95 %, 0,40–0,92, dans les études de cohorte et les essais comparatifs randomisés) et les anomalies affectant les membres (RC, 0,48, IC à 95 %, 0,30–0,76, dans les études cas-témoins; RC, 0,57, IC à 95 %, 0,38–0,85, dans les études de cohorte et les essais comparatifs randomisés). Dans le cas de la fente palatine, les études cas-témoins ont indiqué un RC de 0,76 (IC à 95 %, 0,62–0,93) et les études de cohorte et les essais comparatifs randomisés ont indiqué un RC de 0,42 (IC à 95 %, 0,06–2,84); dans le cas de la fente orale avec ou sans fente palatine, les études cas-témoins ont indiqué un RC de 0,63 (IC à 95 %, 0,54–0,73) et les études de cohorte et les essais comparatifs randomisés ont indiqué un RC de 0,58 (IC à 95 %, 0,28–1,19); dans le cas des anomalies du tractus urinaire, les études cas-témoins ont indiqué un RC à 0,48 (IC à 95 %, 0,30–0,76) et les études de cohorte et les essais comparatifs randomisés ont indiqué un RC de 0,68 (IC à 95 %, 0,35–1,31); et dans le cas de l'hydrocéphalie congénitale, les études cas-témoins ont indiqué un RC de 0,37 (IC à 95 %, 0,24–0,56) et les études de cohorte et les essais comparatifs randomisés ont indiqué un RC de 1,54 (IC à 95 %, 0,53–4,50). Aucun effet préventif n'a été constaté en ce qui concerne le syndrome de Down, la sténose du pylore, la cryptorchidie ou l'hypospadias.

**Conclusion :** La consommation de multivitamines prénatales contenant de l'acide folique par la mère est associée à une baisse non seulement du risque d'anomalies du tube neural, mais également de celui d'anomalies congénitales graves. Ces données entraînent d'importantes conséquences en matière de santé publique puisque, jusqu'à présent, seule la fortification à l'acide folique a été favorisée. Cette approche devrait être remise en question.

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## INTRODUCTION

One in 33 children born in Canada and the United States has a birth defect.[1,2] In 2005, it was estimated that about 150 000 babies are born in North America each year with a birth defect.[3] The burden of illness and the economic cost of birth defects are extremely high.[4,5] More than a decade ago, the preventative role of maternal folate supplementation on the occurrence and the recurrence of neural tube defects was documented in several studies.[6,7,8] Subsequently, preconceptional fortification with folic acid has been shown to reduce the rates of neural tube defects in North America.[9]

During the last decade, several studies have suggested that folic acid-fortified multivitamins may also prevent other congenital anomalies.[10] Botto et al. suggested, on the basis of several studies, that there was a decreased risk for orofacial clefts, limb deficiencies, and cardiovascular abnormalities in babies whose mothers received multivitamin supplementation.[11] To date, however, no systematic review has been conducted to examine existing evidence for the potential of folic acid-containing multivitamins to decrease the risk of congenital anomalies other than neural tube defects. The objective of the present study was to conduct a meta-analysis of studies comparing rates of congenital malformation among women taking vitamin supplements with the rates in controls.

## METHODS

We conducted a search of existing studies that focused on pre- and periconceptional maternal ingestion of multivitamins and the rates of malformation in the offspring. The outcome of interest was congenital malformations. All original research articles using randomized controlled trial, case control, or cohort studies were included. All selected articles contained reports of maternal intake of multivitamins during pregnancy, a control group, and raw data describing rates of healthy and malformed children. Articles that did not report usage of multivitamins during pregnancy, articles that focused on specific vitamins, articles describing mothers exposed to other known teratogens, review articles, letters to the editor, and data reports from abstracts or meetings were excluded.

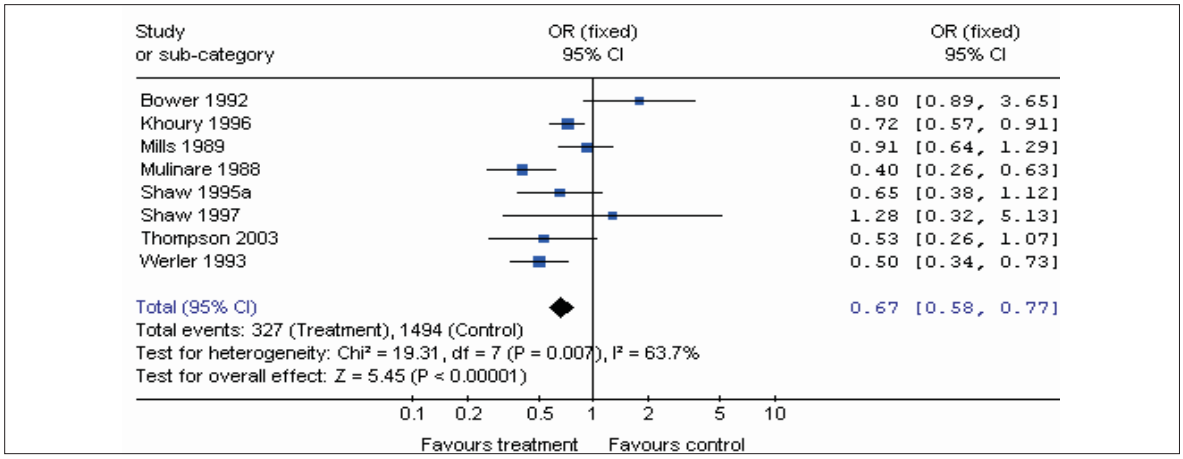
Articles were searched using the terms "multivitamin," "pregnancy," and "malformation" in Medline (January 1966–July 2005), PubMed (1950–July 2005), EMBASE (January 1980–July 2005), Toxline (January 1960–July 2005), Healthstar (January 1966–July 2005), and Cochrane database in all languages. The references from all collected articles were reviewed to locate other original studies.

Two reviewers blinded to authors' names, institution, and journal title assessed all of the articles collected using the selection criteria described above. Data were extracted from these articles to collection forms in 2 × 2 tables. In cases of discrepancy between the reviewers that were not resolved by discussion, the article in question was reviewed by a third blinded reviewer. The odds ratios and 95% confidence intervals were calculated for each study using Review Manager 4.2.7 (2004, The Cochrane Collaboration). Homogeneity among effects was tested by calculating chi-square.

## RESULTS

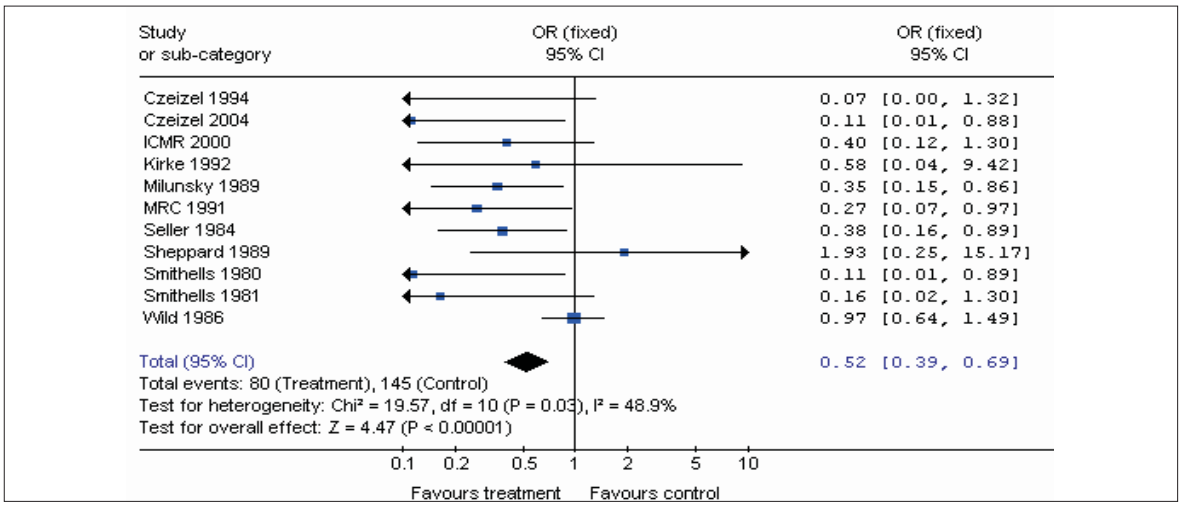
Ninety-two articles were compiled from initial searches of the databases and reference review. Forty-one studies were eligible for the meta-analysis based on the inclusion and exclusion criteria.[12–53] There were 27 case control studies, four randomized control trials, and 10 cohort studies. Fifty-one articles were excluded because they did not report malformation rates, focused specifically on folic acid, did not contain a control group, were review articles, or contained data that were identical to previous studies by the same authors. The use of multivitamin supplementation by the mothers from before the time of conception was associated with a consistent protective effect against neural tube defects (odds ratio [OR] 0.67, 95% confidence interval [CI] 0.58–0.77 in case control studies; OR 0.52, 95% CI 0.39–0.69

**Figure 1. Maternal multivitamin consumption before and in first trimester of pregnancy and risk of NTD in their children (case control studies)**



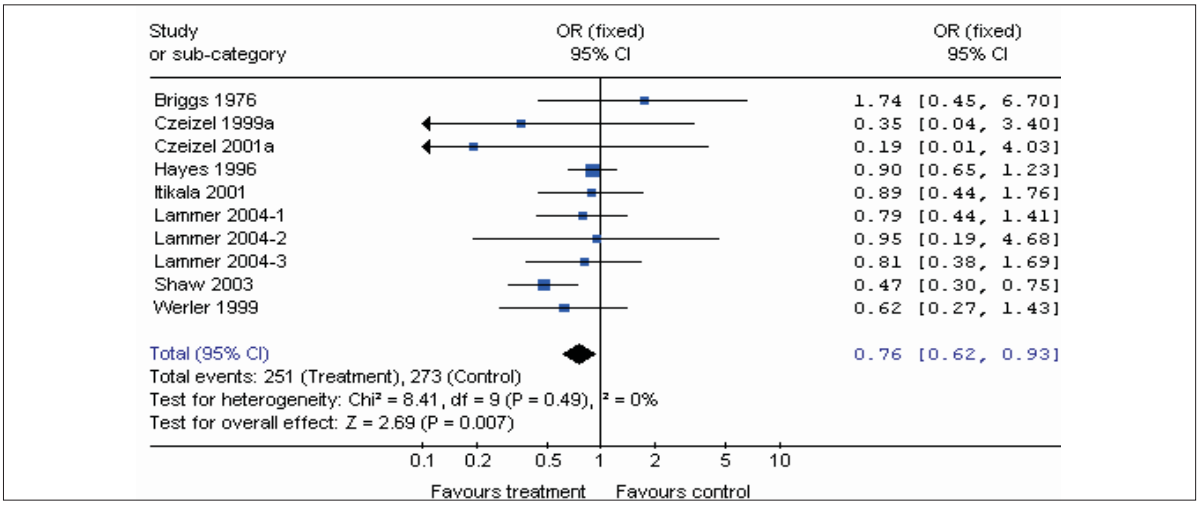

NTD: neural tube defects; OR: odds ratio; CI: confidence interval.

**Figure 2. Maternal multivitamin consumption before and in first trimester of pregnancy and risk of NTD in their children (cohort and RCT studies)**



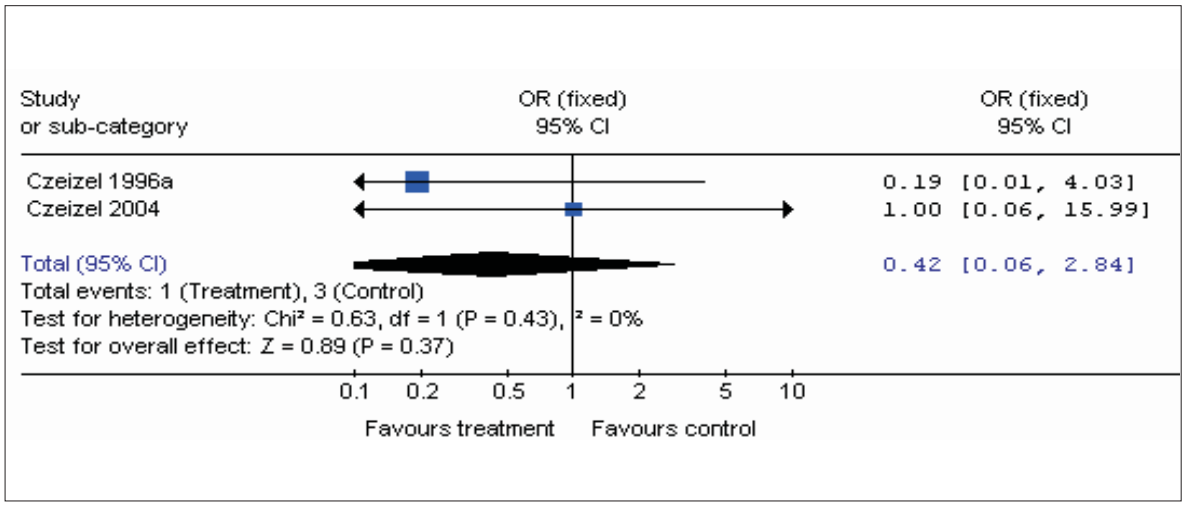

NTD: neural tube defects; RCT: randomized controlled trials; OR: odds ratio; CI: confidence interval.

**Figure 3. Maternal multivitamin consumption before and in first trimester of pregnancy and risk of cleft palate in their children (case control studies)**



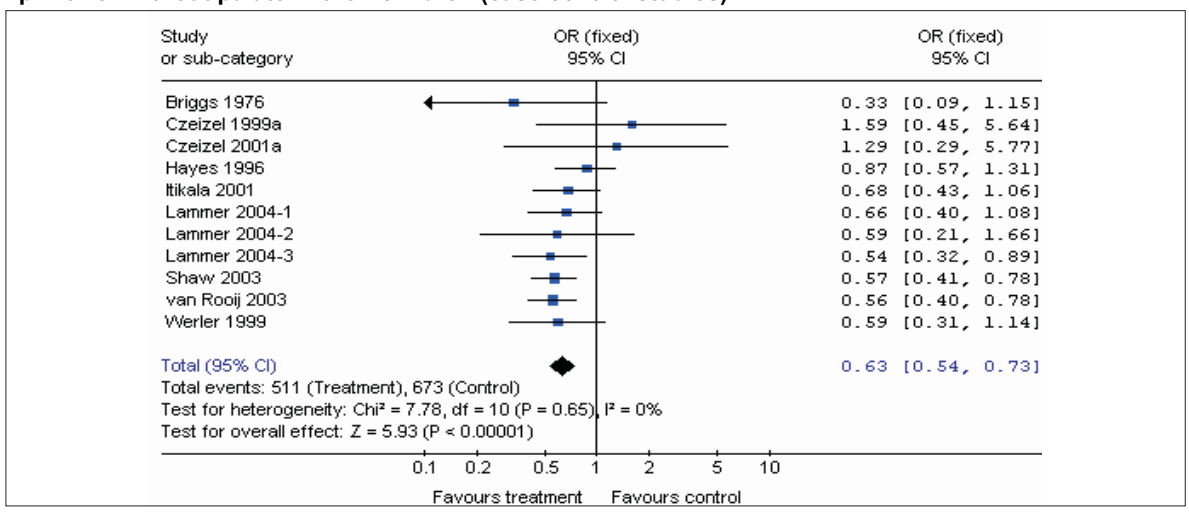

OR: odds ratio; CI: confidence interval

**Figure 4. Maternal multivitamin consumption before and in first trimester of pregnancy and risk of cleft palate in their children (cohort and RCT studies)**



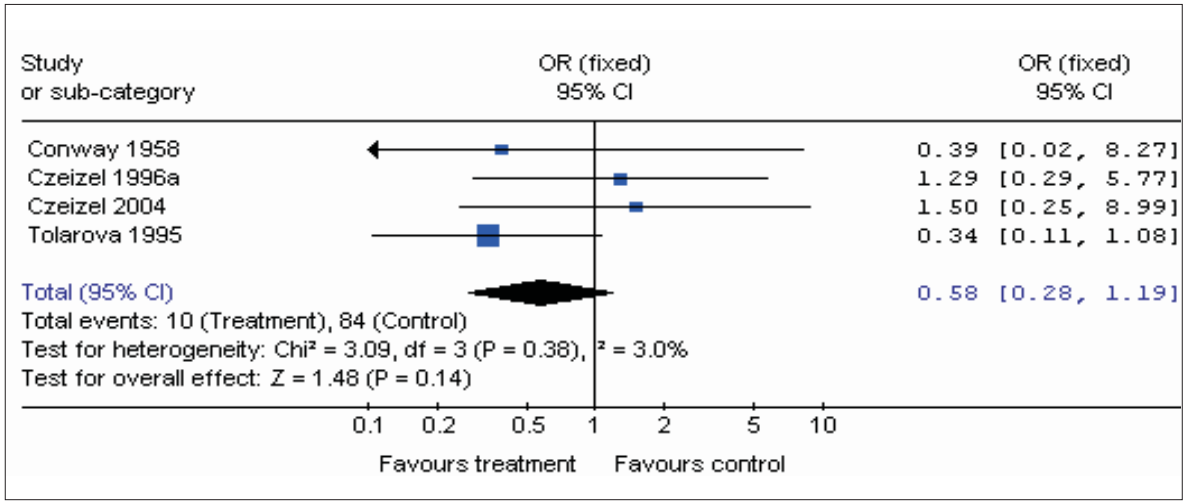

RCT: randomized controlled trials; OR: odds ratio; CI: confidence interval.

**Figure 5. Maternal multivitamin consumption before and in first trimester of pregnancy and risk of cleft lip with or without palate in their children (case control studies)**



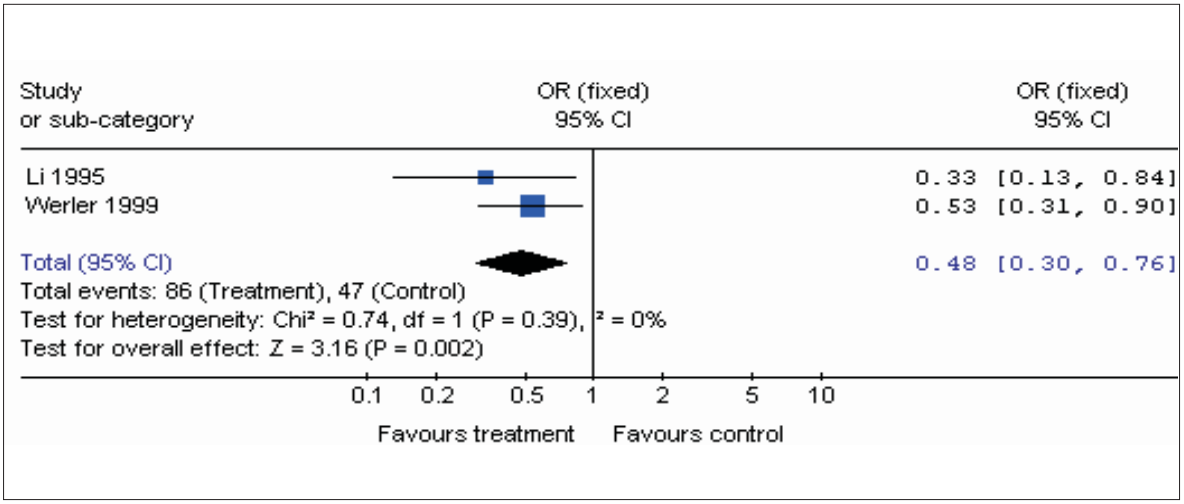

OR: odds ratio; CI: confidence interval.

**Figure 6. Maternal multivitamin consumption before and in first trimester of pregnancy and risk of cleft lip with or without palate in their children (cohort and RCT studies)**



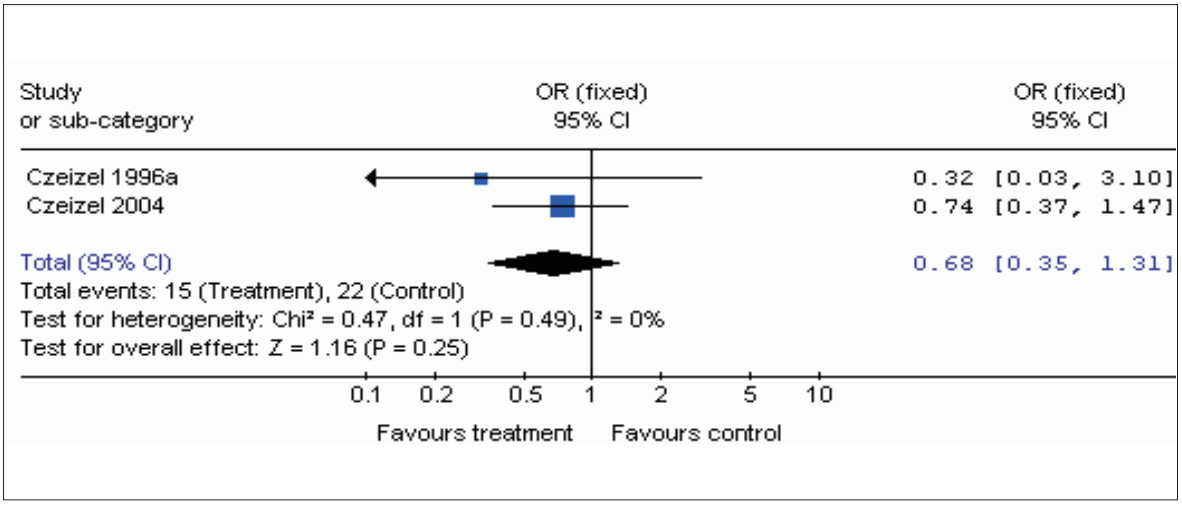

RCT: randomized controlled trials; OR: odds ratio; CI: confidence interval.

**Figure 7. Maternal multivitamin consumption before and in first trimester of pregnancy and risk of urinary tract anomalies in their children (case control studies)**



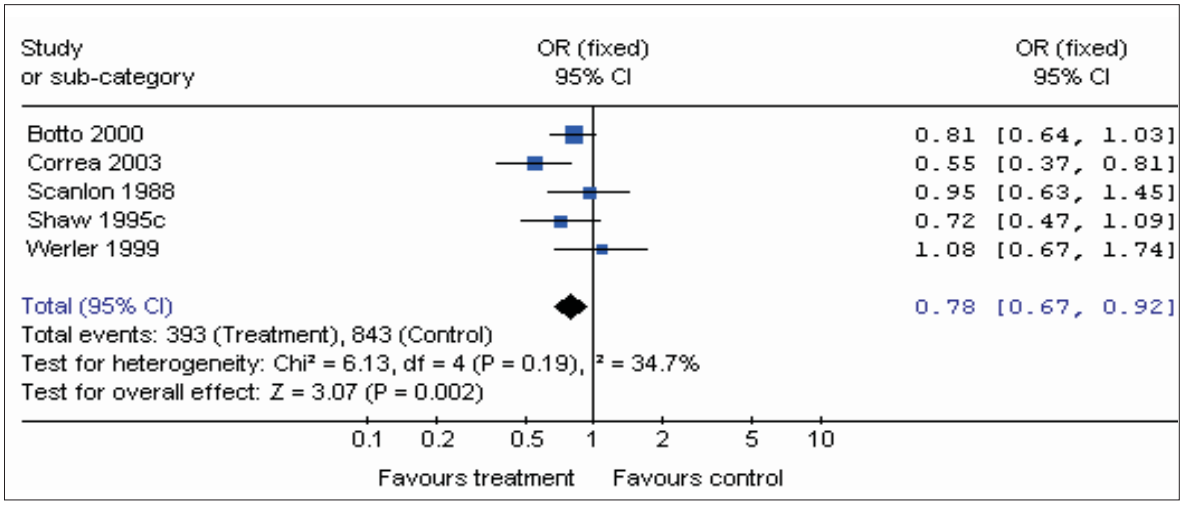

OR: odds ratio; CI: confidence interval.

**Figure 8. Maternal multivitamin consumption before and in first trimester of pregnancy and risk of urinary tract anomalies in their children (cohort and RCT studies)**



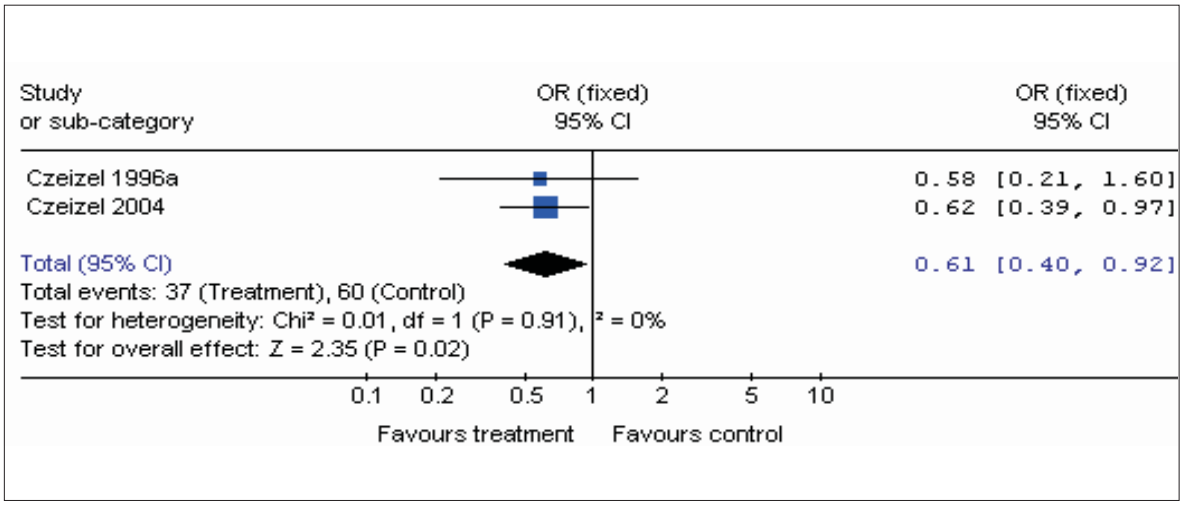

RCT: randomized controlled trials; OR: odds ratio; CI: confidence interval.

**Figure 9. Maternal multivitamin consumption before and in first trimester of pregnancy and risk of cardiovascular defects in their children (case control studies)**



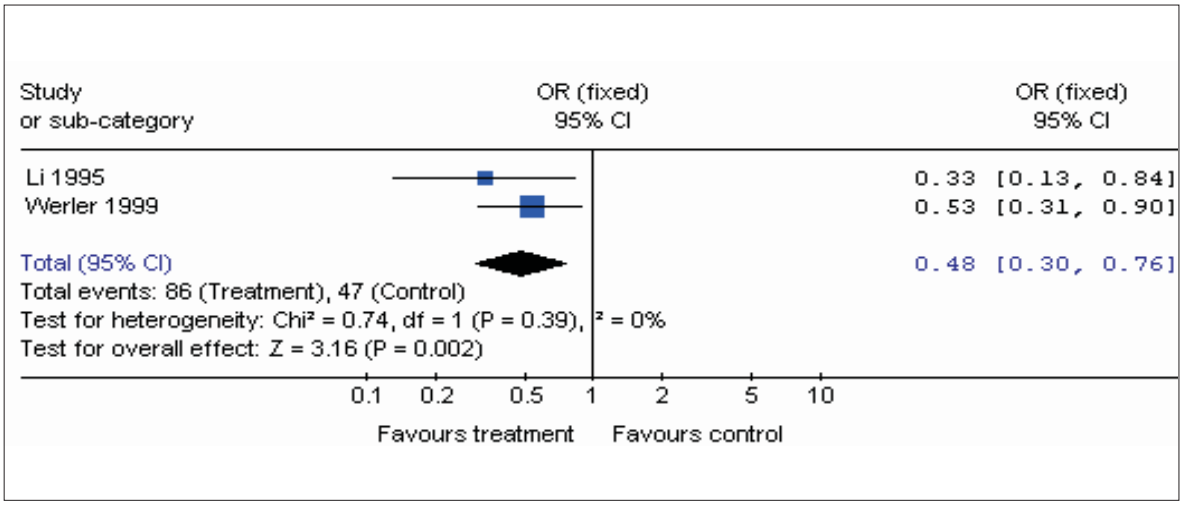

OR: odds ratio; CI: confidence interval.

**Figure 10. Maternal multivitamin consumption before and in first trimester of pregnancy and risk of cardiovascular defects in their children (cohort and RCT studies)**



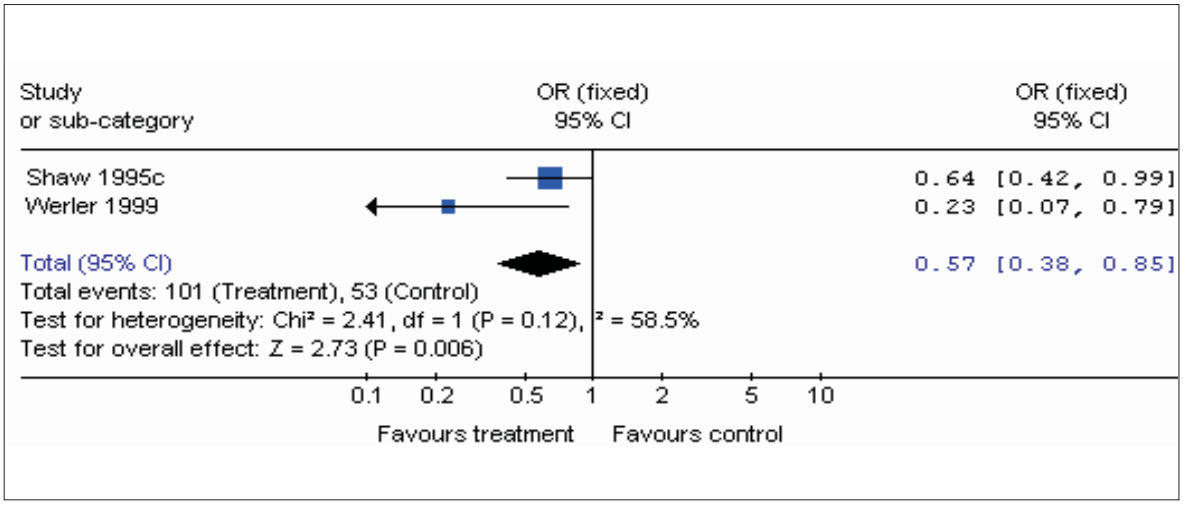

RCT: randomized controlled trials; OR: odds ratio; CI: confidence interval.

**Figure 11. Maternal multivitamin consumption before and in first trimester of pregnancy and risk of limb defects in their children (case control studies)**



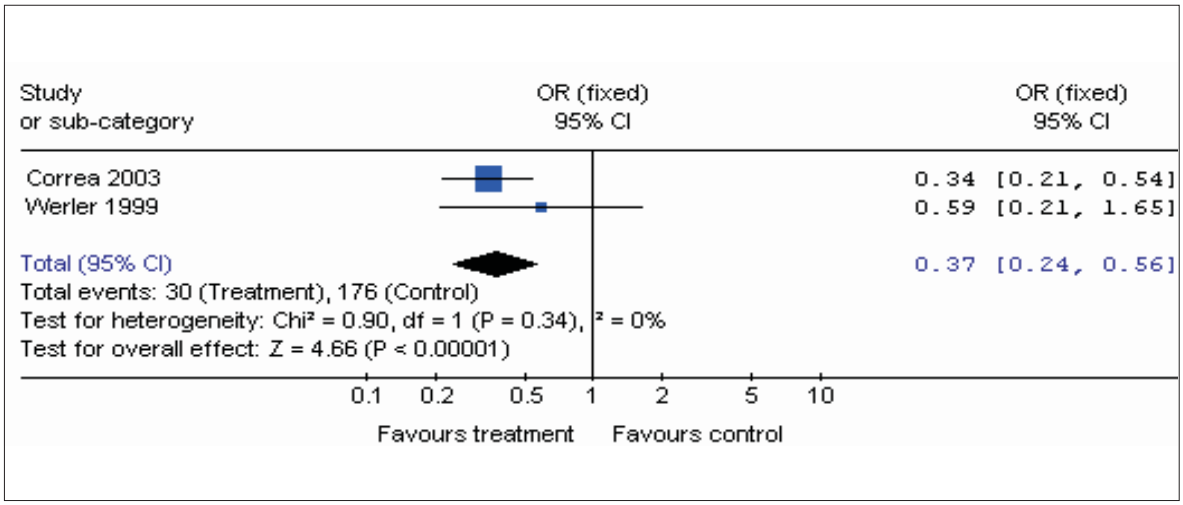

OR: odds ratio; CI: confidence interval.

**Figure 12. Maternal multivitamin consumption before and in first trimester of pregnancy and risk of limb defects in their children (cohort and RCT studies)**



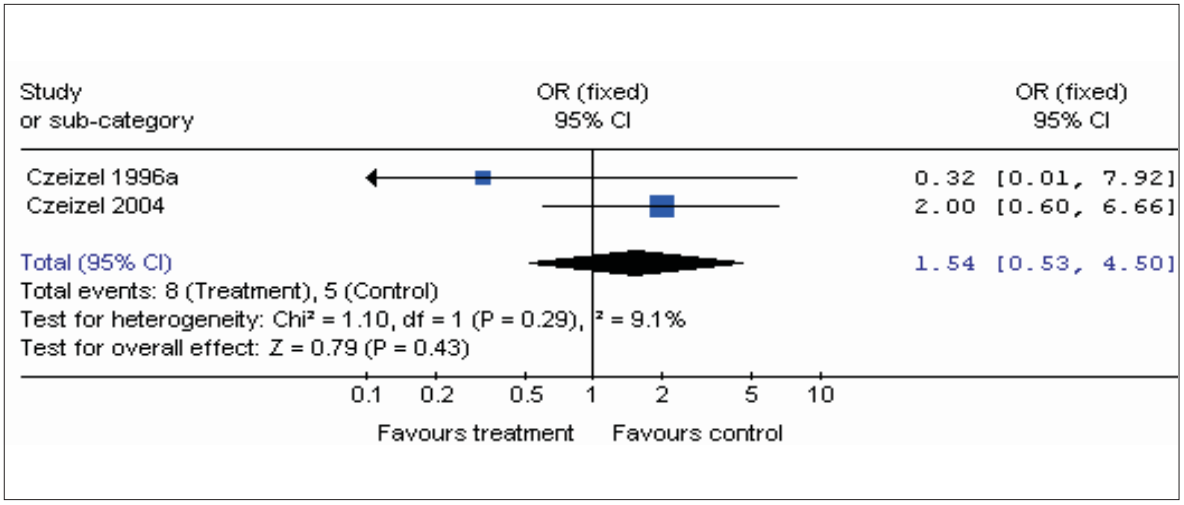

RCT: randomized controlled trials; OR: odds ratio; CI: confidence interval.

**Figure 13. Maternal multivitamin consumption before and in first trimester of pregnancy and risk of congenital hydrocephalus in their children (case control studies)**



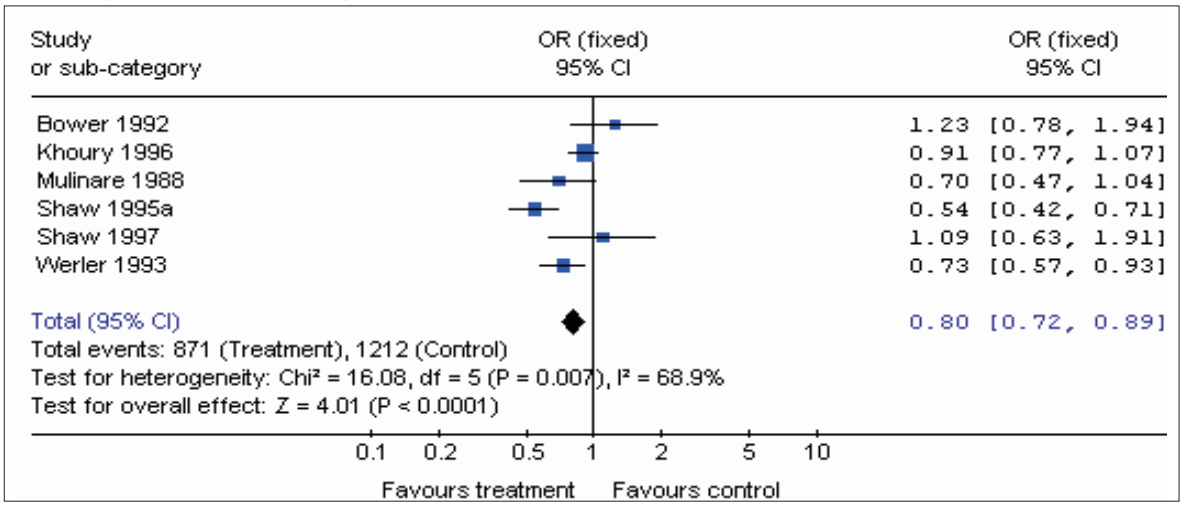

OR: odds ratio; CI: confidence interval.

**Figure 14. Maternal multivitamin consumption before and in first trimester of pregnancy and risk of congenital hydrocephalus in their children (cohort and RCT studies)**




RCT: randomized controlled trials; OR: odds ratio; CI: confidence interval.

**Figure 15. Maternal multivitamin consumption in first trimester of pregnancy and risk of NTD in their children (case control studies)**




NTD: neural tube defects; OR: odds ratio; CI: confidence interval.

in cohort and randomized controlled studies), cardiovascular defects (OR 0.78, 95% CI 0.67–0.92 in case control studies; OR 0.61, 95% CI 0.40–0.92 in cohort and randomized controlled studies), and limb defects (OR 0.48, 95% CI 0.30–0.76 in case control studies; OR 0.57, 95% CI 0.38–0.85 in cohort and randomized controlled studies). Multivitamin supplementation beginning before pregnancy showed a less consistent protective effect against cleft palate (OR 0.76, 95% CI 0.62–0.93 in case control studies; OR 0.42, 95% CI 0.06–2.84 in cohort and randomized controlled studies), oral cleft with or without cleft palate (OR 0.63, 95% CI 0.54–0.73 in case control studies; OR 0.58, 95% CI 0.28–1.19 in cohort and randomized controlled studies), urinary tract anomalies (OR 0.48, 95% CI 0.30–0.76 in case control studies; OR 0.68, 95% CI 0.35–1.31 in cohort and randomized controlled studies), and congenital hydrocephalus (OR 0.37, 95% CI 0.24–0.56 in case control studies; OR 1.54, 95% CI 0.53–4.50 in cohort and randomized controlled studies) (Figures 1–14). In addition, women who began supplementation in the first trimester after learning of the pregnancy showed a protective effect for neural tube defects (OR 0.80, 95% CI 0.72–0.89) (Figure 15). There was no heterogeneity among the studies.

In contrast, multivitamin supplementation was not associated with a protective effect for Down syndrome (OR 0.56, 95% CI 0.26–1.19 in cohort and randomized controlled studies), congenital pyloric stenosis (OR 1.10, 95% CI 0.79–1.53 in case control studies; OR 0.20, 95% CI 0.02–1.68 in cohort and randomized controlled studies), undescended testis (OR 0.81, 95% CI 0.40–1.64 in cohort studies), and hypospadias (OR 0.44, 95% CI 0.13–1.43 in cohort and randomized controlled studies).

## DISCUSSION

The present meta-analysis confirms initial impressions that the use of multivitamins fortified with folic acid by women before conception and continuing through the first trimester is associated with a decrease in several serious major malformations. To our knowledge, this is the first systematic review and meta-analysis to examine and document these protective effects.

The majority of the studies included in the meta-analysis were case control studies, although there were also several randomized controlled trials and cohort studies. Not surprisingly, case control studies are more sensitive in showing significant effects for preventing specific malformations than cohort or randomized studies. The observation that all the studies for the majority of endpoints were statistically homogenous lends credibility to the documented effects. There was heterogeneity in the case control studies and cohort studies examining neural tube defects (8 and 11 studies, respectively). Exclusion of one small case control study (Bower and Stanley[17]) and one small cohort study (Sheppard et al.[45]), each of which showed no protective effect, renders the results homogeneous without changing the overall effect size. Moreover, we could not detect a publication bias by employing the funnel plot. Our study, however, is limited by the fact that multivitamin supplements in differing studies may have varied in their composition.

Presently, there are widely publicized recommendations by various authorities for women to supplement with folate at daily doses of at least 0.4mg (4 mg for women at higher risk) to reduce the risk of delivering a child with neural tube defects. In many centres women are advised to begin taking prenatal vitamin supplements when they decide to attempt to conceive, merely to allow them sufficient folate supplementation. It is currently impossible to discern whether folic acid or other vitamins are critical in the prevention of other birth defects.

Only a fraction of women currently take prenatal vitamin supplements at the time of conception, partly because one half of all pregnancies are unplanned. Serious consideration should be given to fortification of flour or other food staples with other vitamins in addition to folate. With increased surveillance of changes in malformation rates as a result of folate fortification, and subsequently larger cohorts, it will be possible to determine whether folate fortification itself is capable of protecting against birth defects other than neural tube defects.

## CONCLUSION

The results of the present meta-analysis support the use of prenatal multivitamin preparations containing folic acid to reduce the incidence of several congenital anomalies, including neural tube defects, cardiovascular anomalies, oral cleft, urinary tract anomalies, congenital hydrocephalus, and limb defects. Randomized trials will be necessary to prove which specific vitamin(s) render protective effects.

## ACKNOWLEDGEMENTS

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