**PROTOCOL**

# Systematic review and meta-analysis on the association between prenatal folic acid and the risk of asthma in children

## Research Question

- Is prenatal folic acid intake associated with an increased risk of asthma or other allergic outcomes in children?

## Objective

- To perform a systematic review and meta-analysis of the association of folate and/or folic acid intake during pregnancy and the risk of asthma and other allergic outcomes in children.

## Methods

- *Search Strategy*
  - All original research articles assessing the association between folate and/or folic acid and cancer will be sought
  - A research librarian from the CDC Public Health Library will be consulted and will perform the literature search based on the following criteria:
  - Research articles from inception of database to March 2012 will be identified, with an updated search being performed close to publication
  - No limits set in terms of gender, age, language of publications or publication type
  - The following databases will be searched: Medline, Embase, CINAHL, Cochrane Library, Web of Science, POPLINE, and ERIC
  - The following search terms will be used:
    - Category A: Folate OR "folic acid"
    - Category B: asthma OR respiratory OR respiratory illness OR atopy OR allergy
  - Each search term in Category A, Category B will be linked together with AND
- *Inclusion Criteria*
  - Exposure: folate or folic acid (including MV supplement containing FA and blood folates)
  - Exposure Timing: Before or during pregnancy
  - Outcome: Asthma or related respiratory illness/disease, atopy, or allergy in offspring
  - Study Type: RCT, Cohort, Case-control, Cross-sectional
- *Exclusion Criteria*
  - Exposure is limited to comparison of genotypes
  - Article does not include one of outcomes of interest

- Studies dealing only with the effect of folic acid as a treatment for one of outcomes of interest
- No comparison group (e.g., ecological, case studies, case reports, review, letter, news article, conference abstract etc.)
- The timing of exposure is postnatal (i.e., study does not assess prenatal exposure)

➢ *Screening*

- The abstracts of all retrieved articles will be reviewed independently in duplicate (KC, AC) to determine potential relevance (if no abstract, title only or full text)
- The two reviewers (KC, AC) will compare results and agree upon articles for which full text should be reviewed, with any differences being resolved through discussion and consensus
- Full text of identified articles will be reviewed independently in duplicate (KC, AC) against inclusion criteria
- The two reviewers (KC, AC) will compare results and agree upon articles that merit inclusion, with any differences being resolved through discussion and consensus
- Reference lists of all full text articles retrieved will be reviewed for additional articles

➢ *Data abstraction*

- A data abstraction form will be created and piloted that includes the following information:
  - Study design information
    - ♦ Study design
    - ♦ Population-based (y/n)
    - ♦ Study population
    - ♦ Study time period
    - ♦ Study location
    - ♦ Study name
  - Subjects
    - ♦ Number of children
  - Exposure
    - ♦ Type of folic acid exposure (e.g., dietary folate, folic acid supplement, total folate, blood folate, etc.), defined, with units
    - ♦ How exposure assessed/measured (e.g., food frequency questionnaire, maternal self-report, blood assay, etc.)
    - ♦ Timing of exposure (week or trimester of pregnancy)
  - Outcome
    - ♦ Name of outcomes (s)
    - ♦ How outcome(s) defined/measured

        - ♦ Age of child at outcome assessment
    - Measure of association
        - ♦ Adjusted effect measure
        - ♦ Confidence intervals
    - Confounders adjusted for in the analyses
  - One author will abstract data (AC) into the piloted form and a second author (KC) will review all abstracted data for accuracy
- *Risk of Bias*
  - Will be assessed using the Newcastle Ottawa Scale
  - Two authors will independently assess studies, compare results, and come to consensus through discussion
- *Statistical Analysis*
  - The meta-analysis software package to be used is Comprehensive Meta-Analysis (CMA)
  - A random effects meta-analysis will be used to combine studies with similar exposures (in terms of type of folic acid exposure, timing of exposure, and how exposure analyzed) and outcomes
  - Risk ratios and 95% confidence intervals will be calculated
  - Publication bias will be assessed with the use of funnel plots
  - Heterogeneity of effects will be assessed using the $I^2$ statistic
  - Sub-analyses
    - Sub-analyses performed will depend on the number of studies eligible for inclusion in the meta-analysis, as this number is expected to be limited.
    - Potential sub-analyses include
        - ♦ Assessing whether the summary effect differs for studies with low risk of bias compared to studies with high risk of bias
        - ♦ Assessing changes in the summary effect due to how outcomes are grouped
    - Other sub-analyses may be performed as appropriate and will be reported on in the manuscript.