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 I² 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.