



Effects of Stage of Reproduction, Nutrients, and Genes on Serum Total Homocysteine Concentrations in Reproductive Age Women (17-44 Years) in the United States from the Third National Health and Nutrition Examination Survey DNA Bank

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Background

- Poor pregnancy outcomes can be caused by deficiencies or excesses of various micronutrients, such as the association between neural tube defects and decreased folate consumption
- Elevated serum homocysteine concentrations have been associated with adverse pregnancy outcomes, such as prematurity, stillbirth, and low birth weight
- Serum homocysteine concentrations can be affected by age, as well as environmental (e.g., cigarette smoking, caffeine intake, intake of certain B vitamins) and genetic factors
- Several common polymorphisms in genes encoding enzymes involved in folate and homocysteine metabolism have been shown to influence homocysteine concentrations and disease risks

Objectives

- (1) To describe the serum homocysteine concentrations among reproductive age women in relation to stage of reproduction (currently pregnant, pregnant in the previous two years, pregnant more than two years ago, and never pregnant), race/ethnicity, and age
- (2) To evaluate the influence of genetic variants on the serum homocysteine concentration in women within each of four reproductive stages and three major racial/ethnic groups.

NHANES III

- Complex multistage cross-sectional sample survey
 - Conducted by the National Center for Health Statistics (NCHS) for the CDC from 1988-1994
 - Stratified multistage probability design to provide national estimates of common diseases and respective risk factors
 - Components: (1) household interview, (2) physical examination and (3) laboratory measurements
- In Phase 2 of NHANES III (1991-1994), blood was collected for immortalizing cell lines and creating a DNA bank, which contains specimens from 7159 participants, aged 12 years and older

Methods

- Mean serum homocysteine concentrations were compared for women (aged 17-44 years) within the different reproductive stages (total N=1725)
- Linear regression was used to test the association between logarithmically transformed homocysteine concentration and each of five genetic variants: MTHFR 1298A-C, MTHFR 677C-T, MTHFR 116C-T, MTRR 66A-G, and CBS 844ins68
- Sample weighted and adjusted geometric means and 95% confidence intervals for homocysteine concentrations were estimated from a linear regression model with the genetic model (dominant, recessive, complete overdominant, or codominant) that best fit the data for each variant

Methods (continued)

- Models were adjusted for age, smoking status, caffeine intake, folate intake and vitamin B6 intake from food and dietary supplements, and serum vitamin B12 concentration
- Models were stratified by stage of reproduction or race/ethnicity
- Models were further stratified by folate intake of ≤ 20 th percentile ($\leq 131 \mu\text{g}/\text{day}$) and >20 th percentile

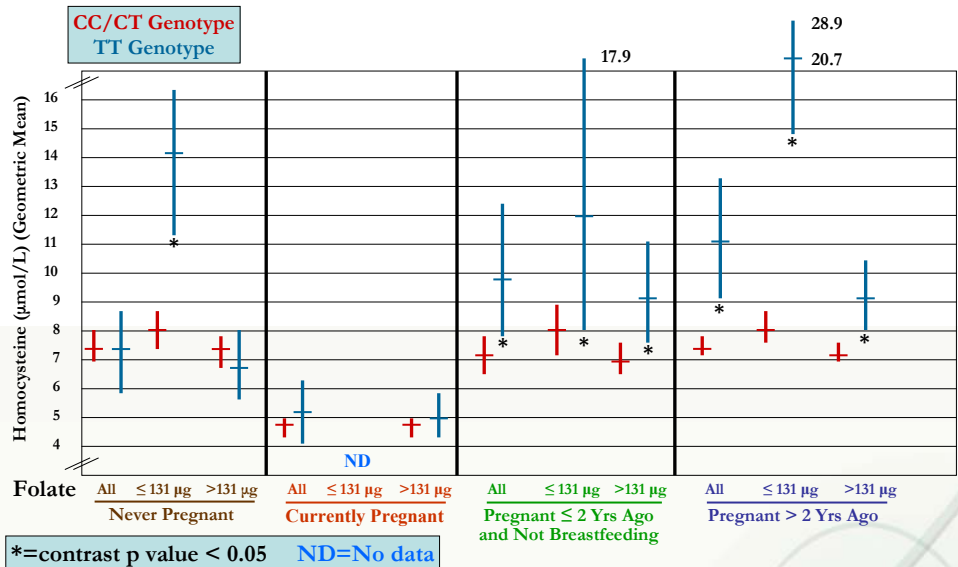
Results

| | Mean Homocysteine (SE) | Geometric Mean Homocysteine (95% CI) |
|-------------------------------------|------------------------|--------------------------------------|
| Never Pregnant (N=370) | 7.7 (0.2) | 7.4 (6.9-7.8) (ref) |
| Currently Pregnant (N=101) | 5.2 (0.3) | 4.8 (4.2-5.4) |
| Pregnant ≤ 2 Years Ago (N=327) | 7.8 (0.4) | ND |
| Breastfeeding (N=37) | 6.3 (0.3) | ND |
| Not Breastfeeding (N=266) | 7.9 (0.4) | 7.3 (6.6-8.0) |
| Pregnant > 2 Years Ago (N=927) | 8.4 (0.2) | 7.7 (7.4-8.0) |
| Non-Hispanic White (N=492) | n/a | 7.5 (7.2-7.9) (ref) |
| Non-Hispanic Black (N=642) | n/a | 7.4 (7.1-7.7) |
| Mexican American (N=529) | n/a | 6.8 (6.5-7.2) |

Yellow font = significant difference from referent group by unpaired Student's t-test

Homocysteine values are $\mu\text{mol}/\text{L}$
 n/a=data not available
 ND=category not included in regression analyses

- When analyses were performed for each of the five gene variants
 - Significant pairwise differences in mean homocysteine concentrations were seen only between genotypes for MTHFR 677C-T
 - The pattern of differences suggested a recessive model (CC/CT vs. TT)
 - Further analyses were restricted to the recessive model for MTHFR 677C-T



Conclusions

- The MTHFR 677TT genotype was associated with a significant increase in the serum homocysteine concentration among women who were pregnant in the previous 2 years and not breastfeeding, as well as among women who were pregnant more than 2 years ago
- Among women in all stages of reproduction except for those currently pregnant, the effects of the 677TT genotype were significantly more pronounced in women with a reduced daily intake of folate; this effect was partially to completely corrected in women with a folate intake of $>131 \mu\text{g}$.
- These effects showed interactions with stage of reproduction, which bears further investigation