

## ADA Evidence Analysis Worksheet

<b>Date of review</b>	November 1st, 2010
<b>Reviewer</b>	Kalyn Eden and Brittney Patera
<p><b>Author/Year:</b> Bjelland, Tell, Vollset, Refsum, Ueland/2003  <b>Complete Reference:</b> Bjelland I, Grethe S, Vollset S, et al. Folate, Vitamin B<sub>12</sub>, Homocysteine, and the <i>MTHFR</i> 677C→T Polymorphism in Anxiety and Depression. Arch Gen Psychiatry. 2003; 60:618-626</p>	
<b>Design Type:</b> Cross-sectional. study : :	
<b>Class</b> D	
<b>Purpose/Population Studied/Practice Studied</b>	
<p><b>Purpose</b> To examine the associations between folate, total homocysteine, vitamin B12, and the MTHFR gene on anxiety and depression.</p>	
<p><b>Inclusion Criteria:</b></p> <ul style="list-style-type: none"> <li>•Men and women ranging from ages 46-49 years old and 70-74 years old.</li> <li>•Previously participated in the Hordaland Homocysteine Studies in 1992-1993.</li> </ul>	
<p><b>Exclusion Criteria</b></p> <ul style="list-style-type: none"> <li>•None specifically mentioned</li> </ul>	
<p><b>Study Protocol</b></p> <ul style="list-style-type: none"> <li>•Recruitment: Subjects from the Hordaland Homocysteine Study, Norway.</li> <li>•Design: Cross-sectional study. Subjects received a self-administered questionnaire</li> <li>•Blinding used: Not applicable</li> <li>•Intervention: Not applicable</li> <li>•Statistical analysis: A 2-sided P&lt;.05 was chosen to indicate statistical significance. Two logistic regression models were used, one with adjustments for age and sex (model 1) and one with additional adjustments for smoking status and educational level (model 2).</li> <li>•Dependent variables: Anxiety, depression, and levels of folate, total homocysteine, vitamin B12, and MTHFR gene.</li> <li>•Independent variables: Scores of HADS-A and HADS-D</li> <li>•Confounders such as coffee consumption, physical exercise, BMI, and self-reported CVD was examined by adding them in one by one to model 2.</li> <li>•To examine whether use of B-vitamin supplements was associated with anxiety or depression, logistic regression analyses were used to estimate OR for being a case, comparing non-users with users after adjusting for age, sex, smoking status, and educational level.</li> </ul>	
<p><b>Data Collection</b></p> <ul style="list-style-type: none"> <li>•Timing of measurements</li> </ul> <p>Anxiety and depression questionnaire scores were examined in relation to levels of folate in blood, total homocysteine, vitamin B12, and MTHFR gene. The questionnaire used to assess</p>	

anxiety and depression was HADS. HADS is a self-administered questionnaire consisting of 14 items, 7 for anxiety and 7 for depression. Anxiety disorder was defined as a HADS-A score of 8 or more restricted to a HADS-D score less than 8 to avoid comorbid disorders. Accordingly, depression was defined as HADS-D score of 8 or more restricted to a HADS-A score less than 8.

- At the start subjects underwent physical examination and a blood sample was stored and analyses were performed 1-3 years later.

### Primary Outcome(s) /Results & Significance

#### Actual Sample

- 2291 men and 2558 women aged 46-49 years old
- 1868 men and 2470 women aged 70-74 years old
- 5948, 77% of these numbers finished the study: (84%) of these individuals returned questionnaires with valid ratings of anxiety and depression
- Location: Norway

#### Results

- Plasma tHcy level correlated with plasma folate and modestly with plasma vitamin B12 ( $P < .001$ )
- Plasma folate and plasma vitamin B12 levels correlated poorly ( $P < .001$ )
- In the MTHFR T/T genotype the value of plasma tHcy was significantly increased compared to the C/C and C/T genotypes (13.66 $\mu$ mol/L vs 10.62 $\mu$ mol/L and 10.98 $\mu$ mol/L)
- AND mean plasma folate significantly decreased (7.49 nmol/L vs 8.46 nmol/L and 8.15 nmol/L)
- Mean plasma vitamin B12 did not show significant differences between the genotypes
- The association with depression was strongest at high plasma tHcy levels ( $>15.0\mu$ mol/L)
- Neither folate nor vitamin B12 was significantly related to anxiety disorder or depression
- Depression but not anxiety disorder was related to the C677T MTHFR genotype.
- There was no significant associations between; levels of plasma folate, vitamin B12 or tHcy and comorbid anxiety disorder and depression.
- Nonusers of B-vitamin supplements were not more prone to anxiety or depression than users
- The relationship with tHcy was weaker for anxiety disorder and stronger for depression (neither was significant)
- Significant effects of MTHFR T/T genotype were not obtained for anxiety disorder, but they were for depression.
- The strongest relationship was observed between the T/T MTHFR genotype and depression
- Associations were observed between tHcy and depression
- Associations were observed between the lowest level of vitamin B12 ( $<230.0$  pmol/L) and depression with high ratings of anxiety and depression on questionnaire
- Associations were observed specifically in middle aged women between depression and folate status
- Only a weak relationship or no relationship was seen between anxiety disorder and tHcy, folate, or vitamin B12 level or MTHFR genotype

#### Conclusions

**Author's Conclusions**

- Other studies (usually case-controlled) have showed stronger relationships between folate status and depression, due to selection bias. A population-based cross-sectional study eliminates selection of population.
- Participation rate of study might have been affected by mental disorders themselves, since persons with anxiety disorders and depression might be less likely to participate in the study.
- We conclude from this large population-based study that there is a role of impaired 1-carbon metabolism in depression without comorbid anxiety disorder. The conclusion is supported by increased risk among subjects with the MTHFR T/T genotype, which has an effect of folate distribution and thereby tHcy level. The observation that the T/T genotype confers increased risk suggests that altered B-vitamin status may be a risk factor for, rather than the result of, depression.

**Reviewer's Comments**

This study has interesting findings however I agree with the authors and believe that people with anxiety and depression wouldn't typically volunteer to be in a study leading to a higher participation rate of those who do not suffer as severely from anxiety and depression.