SOF Analysis Plan Submission Form

Date: March 17, 2011

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Analysis Plan Title: Leptin, Mild Cognitive Impairment and Dementia Among the Oldest Old Women

Datasets to be used: Visits 8 and 9.

Primary variables to be used in the analysis: leptin and dementia

Do you plan to submit an abstract based on these results? No

If YES, when is the abstract due?

Who will perform the analyses?
  Coordinating Center
  Other local analyst, please specify: Adina Zeki Al Hazzouri

Please attach a 1-2 page description of your analysis plan. Please include the following:
  1) Short background/rationale for addressing the research question
  2) Brief description of statistical methods
  3) Mock tables

E-mail this completed form (as an attachment) to Dana Kriesel (dkriesel@sfccpmc.net).
Background and Rationale
Adipose tissue is a primary source for the production and secretion of leptin. While leptin was originally considered an anti-obesity protein; a growing body of evidence suggests that leptin might act on the brain. Leptin has been implicated through various mechanisms to influence cognitive decline and potentially Alzheimer disease (AD). For example, through its modulation of synaptic plasticity, leptin was found to positively influence memory and learning processes in mice modules. Moreover, leptin was found to decrease the production of beta-amyloid and to mediate its clearance, further suggesting a role in the pathogenesis of AD.

Despite the intriguing and complex role of leptin, the majority of previous work examining the link between leptin and cognitive function has been limited to experimental study designs. Very few were population-based studies. Results from a cross-sectional study suggested that higher serum leptin was associated with lower risk of AD. While the latter study could not make any causal inference due to its cross-sectional nature, results from two prospective population-based studies suggested an inverse relationship between serum leptin, cognitive decline, and dementia incidence. Given that these associations remain relatively unexplored, we propose to examine the association between serum leptin levels and the risk of Mild cognitive Impairment (MCI) and dementia among women enrolled in the Study of Osteoporotic Fracture (SOF).

Research Aims
To determine the associations between baseline (visit 8) leptin level and the risk of dementia/MCI over 5 years of follow-up of women

Hypothesis
We hypothesize an inverse relationship between leptin level and risk of dementia/MCI.

Variables
Outcome variables:
- Normal cognitive functioning, Mild Cognitive Impairment (MCI), or dementia at visit 9.

Predictor variables:
- Serum leptin level at visit 8.

Covariates:
- Socio-demographic factors: age, race, education, marital status
- Health-related behaviors: alcohol consumption, smoking, physical activity
- Medical conditions: depressive symptoms, stroke, type-2 diabetes
- Body composition factors: body mass index, waist-to-hip-ratio

Analytic Plan
For the purpose of the current analysis, baseline will be defined as visit 8 when leptin was measured. The outcome of interest would be incidence of MCI/dementia (combined into one outcome) over 5 years of follow-up. Covariates with repeated measures at visits 8 and 9 such as BMI, diabetes, depression, and stroke will be modeled as time-varying covariates.

First, univariate descriptive analyses will be performed on variables of interest to identify normality. The latter will help us decide on how to best model leptin, in particular. Second, we
will examine the distribution of the characteristics of the study population across the various leptin categories- if it is categorized into tertiles. Third, bivariate logistic regression models will be constructed to examine the associations between various covariates and the incidence of MCI/dementia. Similarly, bivariate associations between various covariates and leptin level will be explored. In addition to those commonly known in the literature, covariates with significant bivariate associations with both leptin level and MCI/dementia will be included at the multivariate level. Fourth, we will check for the possibility of effect measure modification (significant statistical interaction term) of the leptin-MCI/dementia association by other covariates based on the literature, such as body mass composition covariates. Finally, we will run multivariate logistic regression models to determine the adjusted associations between baseline leptin level and the risk of MCI/dementia over 5 years of follow-up. All analyses will be performed using SAS v.9.2.
Mock tables

Table 1: Baseline characteristics of the SOF study population by categories (tertiles) of leptin

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Overall</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>N= n=</td>
<td>n=</td>
<td>n=</td>
<td>n=</td>
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<tr>
<td>Race, % White</td>
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<tr>
<td>Education, mean (SD), y</td>
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<tr>
<td>Marital Status, % married</td>
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<tr>
<td>Alcohol consumption, mean (SD), glasses/week</td>
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<tr>
<td>Smoking, % current</td>
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<tr>
<td>Physical activity, % regular</td>
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<tr>
<td>Body Mass Index, kg/m², mean (SD)</td>
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<tr>
<td>Waist-to-hip ratio, cm, mean (SD)</td>
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<tr>
<td>Diabetes, % yes</td>
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<tr>
<td>Depressive symptoms, % yes</td>
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<tr>
<td>Stroke, % yes</td>
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<tr>
<td>APOE e4 allele, % yes</td>
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</tbody>
</table>

*a Only a subset of women were tested for APOE.
Table 2: Results from polytomous logistic regression models for the multivariate associations between leptin and risk of MCI/dementia

<table>
<thead>
<tr>
<th>Leptin</th>
<th>Model 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Model 2&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MCI/dementia RR (95% CI)</td>
<td>MCI/Dementia RR (95% CI)</td>
</tr>
<tr>
<td>Independent</td>
<td>N</td>
<td></td>
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<tr>
<td>Leptin</td>
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<tr>
<td>Low</td>
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<tr>
<td>Medium</td>
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<tr>
<td>High</td>
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<td>1.00</td>
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</table>

<sup>a</sup> Model 1 is unadjusted
<sup>b</sup> Model 2 additionally adjusts for confounders as well as other variables thought to be on the pathway between leptin and dementia/MCI
References


