SOF Analysis Plan #771

SOF Analysis Plan Submission Form

Date: August 7, 2013

Investigator's Name: Ahmed Kassem

Clinical Center: Pittsburgh

Sponsor (if not a SOF investigator): Jane Cauley

Telephone: 917-500-7160  e-mail: amk192@pitt.edu

Other investigators who will be working on this analysis: Kris Ensrud

Analysis Plan Title: Association of Anxiety and Anxiolytics with Cognitive Impairment

Data sets to be used: Visit 8 (Year 16), Visit 9 (Year 20)

Primary variables to be used in the analysis: Anxiety, Anxiolytics and Cognition

Does this analysis plan involve a consortium or meta-analysis project? ☒ YES  ☐ NO
If YES,
1. Does this plan propose to use GWAS data? ☐ YES  ☒ NO
2. Who is the investigator leading the analysis?
   a. If not a SOF investigator, please note the lead investigator’s affiliations.
3. What other cohorts are involved in the consortium or meta-analysis?
4. What are the definitions of the primary phenotypes of interest?
5. Describe any authorship policies of the consortium.

Do you plan to submit an abstract based on these results? ☒ YES  ☐ NO
If YES, when is the abstract due? February 1, 2014

Who will perform the analyses?
☒ Coordinating Center
☐ Other local analyst, please specify: Ahmed Kassem

Is this the first analysis plan you are submitting to utilize SOF data? ☒ YES  ☐ NO
If YES, please provide 2-3 sentences about your professional background and research interests.

Ahmed M. Kassem is a physician with an interest in population-level health research. He completed medical training at Cairo University and public health training at New York University. He is currently pursuing a PhD in Epidemiology at the University of Pittsburgh and is working on research projects addressing mental health and mental-physical co-morbidity. He plans to work with Professor Jane Cauley on his doctoral dissertation.
Background and Rationale

Dementia is a significant public health problem that affects 5.4 million people in the United States and 35.6 million people worldwide (1, 2). Dementia is a complex disorder with both genetic and environmental determinants (3). Accumulating evidence suggests that depression increases risk of dementia (4, 5), but literature had a little focus on other common mental disorders, such as anxiety (6), as potential risk factors for dementia.

The United States National Comorbidity Survey Replication (NCS-R) highlighted the high co-occurrence of anxiety disorders and mood disorders including major depressive disorder (7). In addition, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, assessed by elevated cortisol levels, is implicated in both anxiety and depression (6). Therefore, it is plausible to consider that anxiety may operate, with or without depression, to increase risk of dementia. Furthermore, use of benzodiazepine, an anxiolytic medication, has been shown in some studies to increase risk of cognitive impairment, however, other studies did not show similar finding (8). Finally, current evidence suggests that gender may be a critical factor in psychopathology with women being disproportionately far more affected than men (6, 7).

Therefore, it is important to better understand impact of anxiety and medications used to treat anxiety on dementia risk among women, particularly the oldest old who are understudied. As such, this study will utilize data from the Study of Osteoporotic Fractures (SOF) to confirm whether baseline anxiety is associated with an increased risk of dementia and whether pharmacologically treating anxiety alleviates such risk. We will use Goldberg Anxiety Scale, Medication Inventory Form, Geriatric Depression Scale and Mini-mental State Exam to evaluate Anxiety, Anxiolytic Medications, Depression and Cognition at baseline (SOF visit 8) and at 5-year follow-up (SOF visit 9). We will use adjudicated MCI and dementia diagnosis at 5-year follow-up (SOF visit 9)

Research Aims

Specific Aim 1: To assess whether anxiety, independent of depression, at baseline is associated with an increased risk for future cognitive impairment

Hypothesis: controlling for depression, women with anxiety at baseline will be at an increased risk of cognitive impairment at follow-up compared to women without anxiety at baseline.

Specific Aim 2: To evaluate impact of anxiolytic medication use at baseline on risk for future cognitive impairment

Specific Aim 2.1: To assess whether anxiolytic medication use at baseline is associated with a reduced risk for future cognitive impairment

Hypothesis: women with anxiety who use anxiolytic medications at baseline will be at a reduced risk of cognitive impairment at follow-up compared to women with anxiety who do not use anxiolytic medications at baseline

Specific Aim 2.2: To assess whether non-benzodiazepine anxiolytic medication use at baseline is associated with a reduced risk for future cognitive impairment

Hypothesis: women with anxiety who use non-benzodiazepine anxiolytic medications at baseline will be at a reduced risk of cognitive impairment at follow-up compared to women with anxiety who use benzodiazepine anxiolytic medications at baseline
Selection Criteria

Specific Aim 1 and Specific Aim 2

Only participants who were cognitively intact at baseline (SOF visit 8) will be included in the analyses. Participants falling under any of the following criteria will be excluded: 1) self-report of a physician diagnosis of dementia; 2) dementia medication use or 3) a Mini-Mental State Examination (MMSE) score of 23 or lower.

Specific Aim 2

Only participants who had clinically significant anxiety symptoms and reported anxiolytic medication use at baseline (SOF visit 8) will be included in the analyses. Clinically significant level of anxiety symptoms is defined as a Goldberg Anxiety Scale (GAS) score of 5 or more. Participants who reported anxiolytic medication use in previous visits will be excluded.

Variables

Predictor Variables:

1) Goldberg Anxiety Scale (ANXSC) assessed as a categorical variable (score >5) and as a continuous variable
2) Anxiolytic Medications extracted from the Medication Inventory Form (MIF). Two medication classes will be used in the analyses: benzodiazepine anxiolytic medications (BZD) and non-benzodiazepine anxiolytic medications (NBZD). Non-benzodiazepine anxiolytic medications include non-barbiturate non-benzodiazepine sedative-hypnotics, trazodone, tricyclic anti-depressants, selective serotonin re-uptake inhibitors and other antidepressants.

Outcome Variables:

1) Cognitive decline (Mini-mental State Exam; SHT3MS) assessed as a 5-point change between the 2 visits
2) Mild Cognitive Impairment (MCI) diagnosis
3) Dementia diagnosis

Potential Confounders:

We will use covariates from SOF visit 8 and if unavailable, we will use previous visits. We will consider the following factors as potential confounders (SOF variable name in parenthesis):

1) Demographics: Age (AGE), Education (EDUC), Race (RACE), Marital Status (MARRY)
2) Geriatric Depression Scale (GDS15) and antidepressant medications (SSRIs and TCAs): we will adjust for depression and antidepressants to estimate the independent contribution of anxiety to cognitive impairment risk
3) Health status: Self-rated Health (COMP), Medical Conditions (EOA, ECANCER, ESTRK, EHEART, EHYPER, EDIAB, ECOPD, EPARK) Sleep Disorders (SLPDIS), Pittsburgh Sleep Quality Index (PSQI)
4) Substance use: Alcohol (DR30), Caffeine (CAFGDC), Smoking (SMOKE)
5) Physical activity: walking for exercise (EXER)
6) Functional status: IADL impairments (FXST61)
**SOF Analysis Plan #771**

**Statistical Methods**

First, we will calculate descriptive statistics for all variables and explore bivariate associations between each covariate and outcomes using chi-squared tests or ANOVA, as appropriate. Then, we will fit a series of age-adjusted and multivariable logistic regression models of the relationship between each of our exposures (anxiety, anxiolytic medications, NBZD) and our outcomes (cognitive decline, MCI, dementia). In all analyses, we will adjust for demographics, depression and sleep disorder. We will additionally adjust for each covariate that is associated with both outcomes and exposures at alpha = 0.20 level.

**Mock Tables**

Table 1. Descriptive Statistics and Bivariate Associations between Each Covariate and Cognitive Impairment for Older Women

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Normal</th>
<th>MCI</th>
<th>Dementia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
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<td>Upper tertile</td>
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<td>Mid tertile</td>
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<td>Lower tertile</td>
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<tr>
<td>Anxiolytic use</td>
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<td>Any</td>
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<tr>
<td>Non-BZD</td>
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<tr>
<td>BZD</td>
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<td>Depression</td>
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<td>Demographics…</td>
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<td>Health status…</td>
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<td>Substance use…</td>
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Tables 2-4. Multivariable Logistic Regression Models of Association of Anxiety and Non-Benzodiazepine Use with Cognitive Decline, MCI and Dementia for Older Women

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Cognitive Decline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude Model (OR, 95% CI)</td>
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<tr>
<td>Anxiety (categorical)*</td>
<td></td>
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<tr>
<td>Anxiety (continuous)</td>
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<tr>
<td>Any anxiolytic use</td>
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<tr>
<td>Non-Benzodiazepine Use***</td>
<td></td>
</tr>
</tbody>
</table>

*Reference group = no anxiety
**Reference = no anxiolytic use
***Reference group = BZD use
## Mild Cognitive Impairment (MCI)

<table>
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<th>Age-adjusted Model (OR, 95% CI)</th>
<th>Multivariate-adjusted Model (OR, 95% CI)</th>
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## Dementia

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### References


