SOF Analysis Plan

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Title: Patterns of estrogen use, $ER\alpha$ genotypes and sleep disturbance.

Investigators Names: Greg Tranah, Katie Stone, Terry Blackwell, Jane Cauley, Kris Ensrud and others who are interested.

Center: SFCC
Telephone: 415-600-7410

Research Questions:

1) Is estrogen use associated with sleep disturbance?
2) Are $ER\alpha$ polymorphisms associated with sleep disturbance?

Background and Significance:

There are significant differences in the prevalence of sleep disorders between men and women, suggesting that sleep physiology could be influenced by sex (reviewed by Manber and Armitage ¹). In general, women have a greater prevalence of insomnia ² and men have approximately twice the prevalence of sleep apnea ³. The differences in sleep characteristics between men and women may be explained by differences in the levels of sex hormones, notably estrogen and progesterone.

It has been proposed that increased estrogen levels may improve sleep by reducing the impact of stress or nocturnal disturbances ⁴, ⁵. Estrogen replacement therapy (ERT) has been shown to reduce sleep disturbance and insomnia ⁶, ⁷ and produce shortened sleep latencies, reduced nocturnal restlessness and reduced wake after sleep onset ⁴. Manber et al. ⁸ found that estrogen confers a beneficial effect on measures of sleep disordered breathing in postmenopausal women while Itil et al. ⁹ and Fries et al. ¹⁰ have shown that exogenous administration of progesterone produces sedative effects in both women and men.

Sleep disturbances during menopause have been attributed to hot flashes and ‘night sweats’ (reviewed by Moe ¹¹). While it is hypothesized that the beneficial effects of estrogen on sleep are mediated via a reduction in hot flashes ⁵, the beneficial effects of estrogen may not be mediated only via a reduction in hot flashes or other symptoms. For instance, ERT administration has been reported to improve sleep in asymptomatic perimenopausal women ⁴. Sleep complaints commonly associated with menopause may be largely subjective as demonstrated by Young et al. ¹². Using polysomnography, the gold-standard objective measure of sleep, Young et al. ¹² found that objective sleep quality is better during and after menopause than before.

A single small study by Malacara et al. ¹³ (N=177) found that the $ER\alpha$ Pvull polymorphism was associated with hot flashes but not sleep alteration (both assessed by questionnaire). To our knowledge no studies have assessed the association between $ER\alpha$ polymorphisms and objectively measured sleep data.

Given the large number of women experiencing sleep disturbance and consequent decreases in waking functions, this is an area of significant concern that has not, to date, been adequately addressed.

Datasets to be used: Baseline, SOF genetics, and Visit 8.

Subjects: Participants with both Visit 8 actigraphy data and $ER\alpha$ genotype data (n~2600).
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Predictor variables: Oral estrogen use, ERα genotypes.

Covariates: Variables to be considered will include age, menopause years, age at menopause, surgical vs. natural menopause, medical history (self-rated health, cardiovascular disease, cancer, hypertension, and diabetes), depression and anxiety, BMI, race, smoking, alcohol use, physical activity and indicators of socioeconomic status (years of education, income, and marital status), use of sleep medications and SSRIs.

Outcome Variables: Our primary analyses will assess associations with total sleep time, sleep efficiency, wake after sleep onset, sleep latency, napping behavior and day-to-day actigraphic variability. In addition, we will examine genetic associations with circadian parameters supplied by actigraphy (such as amplitude, mesor and acrophase of the rest/activity rhythm).

Study Design and Methods:

Estrogen use: We will analyze three patterns of estrogen use: never users; past users (use at baseline and Visit 8); current users (use at baseline and stopped prior to Visit 8). In exploratory analyses we may analyze past early users (started under age 60), past late users (started at age 60 or later) current early users (started under age 60) and current late users (started at age 60 or later).

ERα genotypes: We will analyze additive and dominant models for ERα genotypes.

Standard linear regression models will be used for analyses involving estrogen use and genotype associations with continuous outcome measures such as wrist actigraphy.

For categorical outcome variables (e.g. total sleep time < 5 hrs.) we will compare allele frequencies between ‘cases’ and ‘non-cases’ by χ² tests and will analyze our results for associations using logistic regression models.

Literature Cited:
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