## Introduction

1. Sleep is associated with a number of health outcomes.
   * Sleep deficiency, which includes insufficient and poor quality sleep, represents a growing public health problem in the United States. Nearly 30% of adults report sleeping 6 or fewer hours per night (Ram 2010), 20% report excessive daytime sleepiness, and 20-30% experience insomnia symptoms (Roth 2007).
   * A growing body of literature links sleep duration and quality to a number of health outcomes, including all-cause mortality (Gallicchio 2009, Cappuccio 2010), as well as incidence of type 2 diabetes (Cappuccio 2010, Ayas 2003), hypertension (Gangwisch 2006), coronary heart disease (Ayas 2003), stroke (Yaggi 2005). Specifically, a “U-shaped” association in which both short and long sleep (generally <6 and >8 hours, respectively) are related to elevated all-cause mortality risk is supported by meta-analyses (Cappuccio 2010, Gallicchio 2009).
2. An important factor linking sleep and many chronic diseases may be low-grade, chronic inflammation, commonly measured by immune-related biomarkers such as interleukin-6 (IL-6), fibrinogen, tumor necrosis factor-a, and c-reactive protein (CRP).
   * ~~Subclinical inflammation indicated by peripheral blood levels of IL-6, CRP, and fibrinogen predict diabetes, CHD, and all cause and CHD-related mortality (intro of Grunewald 2009).~~
   * Extensive experimental and observational evidence links inflammatory processes to atherogenesis, the primary pathogenic process underlying coronary heart disease (CHD) (Libby 2002).
   * The most extensively studied biomarker of inflammation is c-reactive protein (CRP), an acute phase reactant (biochemicals accompanying inflammatory pathway activation), for which high sensitivity assays are widely avaiable (Roberts 2001).
   * CRP is best characterized in relation to CVD, as it is a strong predictor of cardiovascular events (Ridker 1998, 2003); however, it is also a potent risk factor for all-cause mortality (Marsik 2008), and is associated with incidence of metabolic syndrome (Ridker 2003), colorectal cancer (Erlinger 2004),and endstage renal disease (Arici 2001).
   * Based on mendelian randomization studies, CRP itself is unlikely to be a causal risk factor of metabolic syndrome (Timpson 2015) or ischemic vascular disease (Zacho 2008), although limited human experimental evidence suggests it has an etiologic role in atherosclerosis (Bisoendial 2005). CRP has a complex role in inflammation and its primary function may be anti-inflammatory (Marnell 2005); nonetheless, it is useful biomarker corresponding to general, potentially subclinical risk.
3. Sleep duration and quality have been linked to inflammation, which may be important link in its association with mortality and chronic disease.
   * Sleep duration and quality has been shown to affect inflammation in experimental studies (Meier-Ewert 2004, Vgontzas 2004) and to be associated with CRP and IL-6 in observational studies (Prather 2013, Jackowska 2013, Hall 2014).
   * Sleep restriction induces changes in glucose tolerance, thyrotropin concentration, evening cortisol concentrations, and sympathetic nervous activity, alterations which have implications in inflammation (Spiegel 1999).
4. Socioeconomic disparities in inflammatory markers have been extensively document
   * Adult socioeconomic status is associated with risk for CVD, diabetes, hypertension, all cause mortality (CDC 2013).
   * CRP, IL-6, fibrinogen elevated in lower SES (intro of Grunewald 2009),
5. Socioeconomic disparities in sleep have been extensively documented
   * Sleep restriction (Piccolo 2013) and poor quality sleep (Patel 2010, Mezick 2008) have been found to be more prevalent among individuals of low SES .
   * Low income and low education are associated with adverse social and environmental conditions that impede adequate sleep (Gradner 2010) and a growing number of lower-paid jobs involve shift work and non-standard hours (Alterman 2012).
6. No one has tested whether sleep is a mediator of the SES->inflammation association
   * Sleep is a modifiable risk factor for which efficacious non-pharmocological interventions exist (Montgomery 2004, Montgomery 2003)
   * Commonly hypothesized pathways for SES-->inflammation are health status, behavioral (smoking, physical activity) and psychosocial (stress etc.) factors (intro of Grunewald 2009). Kershaw 2010 also demonstrated that exercise, tobacco, physical activity, diet, and chronic diseases mediate this relationship.

* ~~CVD is the leading cause of death in the United States and a number of countries, and remains expensive to treat (Overview of the risk equivalents and established risk factors for cardiovascular disease, UpToDate)~~

## Methods

* How is sleep measured in NHANES?
  + Mental Health / Depression screener (DPQ)
    - DPQ030 [Over the last 2 weeks, how often have you been bothered by the following problems:] trouble falling or staying asleep, or sleeping too much?
  + Sleep disorders (SLQ)
    - SLD010H How much sleep {do you/does SP} usually get at night on weekdays or workdays?
    - SLQ050 {Have you/Has SP} ever told a doctor or other health professional that {you have/s/he has} trouble sleeping?
    - SLQ060 {Have you/Has SP} ever been told by a doctor or other health professional that {you have/s/he has} a sleep disorder?
    - SLQ070A-D What was the sleep disorder?
    - SLQ080 In the past month, how often did {you/SP} have trouble falling asleep?
    - SLQ090 [In the past month, how often did {you/SP}] wake up during the night and had trouble getting back to sleep?
    - SLQ100 [In the past month, how often did {you/SP}] wake up too early in the morning and {were/was} unable to get back to sleep?
    - SLQ110 [In the past month, how often did {you/SP}] feel unrested during the day, no matter how many hours of sleep {you have/s/he has} had?
    - SQL120 [In the past month, how often did {you/SP}] feel excessively or overly sleepy during the day?
    - SLQ130 [In the past month, how often did {you/SP}] not get enough sleep?
    - SLQ140 [In the past month, how often did {you/SP}] take sleeping pills or other medication to help {you/him/her} sleep?
    - SLQ150-190: Leg cramps, difficulty with activities due to lack of sleep
    - **Check reliability statistics for this.**
* How is CRP measured in NHANES?
  + Note F 2003-6, Note G 2007-10
* How is SES measured in NHANES?
  + Demographics:
    - INDHHIN2 - Total household income
    - INDFMINC - Total family income
    - INDFMPIR - Poverty income ratio (PIR) - a ratio of family income to poverty threshold
    - DMDHREDU -- Highest level of education completed
  + Questionnaire (CBQPFC\_E / INQ\_E / OCQ):
    - CBD765 - Which of the following best describe your highest education level?
    - INDFMMPC - Family monthly poverty level index categories.
    - IND235 - Monthly family income (reported as a range value in dollars).
    - OCD392 - OCD392 Thinking of all the paid jobs or businesses {you/SP} ever had, what kind of work {were you/was s/he} doing the longest? (For example, electrical engineer, stock clerk, typist, farmer.)
    - OCD241 What kind of work {were you/was SP} doing? (For example: farming, mail clerk, computer specialist.)
    - OCD231 What kind of business or industry is this? (For example: TV and radio management, retail shoe store, state labor department, farm.)
  + Occupation (OCQ)
* Counfounders of Sleep->CRP:
  + Diet
  + Physical Activity
  + Smoking
  + BMI
  + Psychosocial stress
  + Chronic diseases
  + Medications
    - Oral contraceptives
  + Coffee drinking!!!!
  + Race ethnicity????
  + Age
* Confounder of SES->CRP
  + Likely few confounders, possibly chronic diseases, although SES is more likely to cause chronic diseases.
* Exclusions
  + Age: I could just do this in adolescents, although all the literature I’ve looked has been about adults. Let’s say over 18. I would control for age, I could also look at an interaction with age to see if there were consistent effects.
  + Chronic diseases. I could exclude chronic diseases because I’m interested in subclinical CRP. However, this might exclude the sickest people, which may bias the results if the sick people in the low SES group tend to be sicker, and there is more of a distinction between the survivors and the sick people. I could opt to adjust for chronic disease, although this may be a collider.
  + CRP >= 10, acute infection (Kershaw 2010)
  + Pregnancy
* Statistical analysis
  + AHA and CDC recommend a cutoff of >3 mg/L as elevated CRP (Kershaw 2010).
  + Sleep duration = <6, 6, 7, 8 >8, Hall 2014)
  + Sleep quality:
    - Bansil 2011: Participants were classified as having poor sleep (poor quality) if they answered “often” or “almost always” (together defined as 5–30 times a month) to any of the 6 items on sleeping habits as follows: (1) having trouble falling asleep; (2) waking up during the night and having trouble getting back to sleep; (3) waking up too early in the morning and being unable to get back to sleep; (4) feeling unrested during the day, no matter how many hours of sleep were obtained; (5) feeling excessively or overly sleepy during the day; and (6) not getting enough sleep.
  + SES income tertiles? Education categories??
    - Healthy People 2020 uses poor (below FLP), nearly poor (100-199% FPL), and middle and high income (200%+ FPL) (<http://www.healthypeople.gov/2010/Document/HTML/tracking/THP_PartA.htm>)
    - Education should be used after age 25, based on guidance from the U.S. Census Bureau
  + Age groups or linear??
  + Total indirect effect = quantity of interest.
    - [P(Y1M1=1)] – [P(Y1M0=1)]
    - Calculate a risk difference from logistic regression models predicting the risk:
      * If everyone were exposed and had the mediator they would have had if they were exposed [P(Y1M1=1)]
        + This quantity is estimated by the observed risk in the exposed, with values of the confounders held constant (at the means?)
      * Minus
      * If everyone were exposed and had the mediator they would have had if they were unexposed [P(Y1M0=1)]
        + This quantity is estimated by a weighted average of the observed risk in the exposed, mediator positive, and exposed, mediator negative, with weights based on the probability of the mediator in the unexposed, and confounders held constant (at the means?)
        + This probability could be estimated at the population level from the survey design. I don’t think it would need any inference.