SLEEP DURATION, SLEEP INSUFFICIENCY, AND CAROTID INTIMA-MEDIA THICKNESS

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Cardiovascular disease is the leading cause of death in the United States. Chronic short sleep duration is also a significant public health problem and has been linked to several markers and outcomes of cardiovascular disease. To date, inconsistency of assessments of sleep duration and insufficiency, use of covariates, and cardiovascular disease measurement across studies limits strong conclusions about the relationship between sleep duration, sleep insufficiency, and cardiovascular disease. The current study examined the association between sleep duration, sleep insufficiency, and a marker of preclinical coronary heart disease (i.e., carotid intima-media thickness) in a community sample using a cross-sectional design. Some evidence for a relationship between sleep duration and cIMT was found, with longer sleep duration predicting higher cIMT in some segments. Additionally, the interaction between sleep duration and sleep insufficiency was significant. However, neither of these effects were significant after adjusting for age and in some cases race/ethnicity, suggesting demographics may explain this association. Actigraphy and sleep diary duration assessments demonstrated significantly different correlations with cIMT in some segments, suggesting the nature of the assessment method may impact the strength or direction of the relationship between sleep duration and cIMT. Limitations and future directions are discussed.
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“Each night, when I go to sleep, I die. And the next morning, when I wake up, I am reborn.”

--Mahatma Gandhi
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CHAPTER I
INTRODUCTION

Statement of the Problem

Cardiovascular disease is the leading cause of death in the United States (Kung, 2008) and is becoming a global health problem (Murray & Lopez, 1997). Chronic short sleep duration is also a significant public health problem and has been linked to several markers and outcomes of cardiovascular disease (Mullington, Haack, Toth, Serrador, & Meier-Ewert, 2009). To date, inconsistency of assessment of sleep duration and insufficiency, use of covariates, and cardiovascular disease measurement across studies limits strong conclusions. The current review examines the relationship between short sleep duration and a preclinical marker of cardiovascular disease (i.e., carotid intima-media thickness) and provides guidance about potential directions for future research to begin filling in gaps in the literature.

Stress and Cardiovascular Disease

Stressors (e.g., short sleep duration) trigger responses designed to help the individual survive, which can be beneficial in acute stress situations (e.g., threat of immediate physical harm) but can have negative biological consequences when prolonged or chronic (Sih, 2011). These consequences, including elevated nervous system activity (e.g., blood pressure), stress hormones (e.g., cortisol), and inflammation (e.g., interleukin-6), can lead to shear stress injuries within the arterial walls (Cunningham & Gotlieb, 2004). Over time, the buildup of fatty and waxy deposits within these lesions is known as atherosclerosis, which is one of the most significant contributors to coronary heart disease (CHD; Libby, 2006), the most common cardiovascular disease (Go et al., 2013). Insufficient sleep related to chronic short sleep duration, either as a result of stress or as an event itself, may contribute to or be a modifiable risk factor for
atherosclerotic progression or increased CHD risk (Grandner, Chakravorty, Perlis, Oliver, & Gurubhagavatula, 2014).

Sleep Duration and Coronary Heart Disease Risk

Although short sleep duration has been associated with a variety of poor physical health outcomes including type 2 diabetes (Cappuccio, D'Elia, Strazzullo, & Miller, 2010a), obesity (Cappuccio, Taggart, Kandala, & Currie, 2008), higher all-cause mortality risk (Cappuccio, D'Elia, Strazzullo, & Miller, 2010b; Gallicchio & Kalesan, 2009), and cardiovascular disease (Cappuccio, Cooper, D'Elia, Strazzullo, & Miller, 2011), the literature linking short sleep and cardiovascular outcomes (e.g., heart attack, stroke, cardiovascular mortality) has been mixed (Grandner, Hale, Moore, & Patel, 2010). A recent systematic review and meta-analysis of 15 prospective studies (see Table 1) revealed short sleep duration (primarily ≤5 – 6 hours per night) was associated with increased risk of developing or dying of CHD (RR = 1.48; 95% C.I.: 1.22 – 1.80) or stroke (RR = 1.15; 95% C.I.: 1.00 – 1.31) but not overall cardiovascular disease (RR = 1.03; 95% C.I.: 0.93 – 1.15) based on pooled adjusted estimates (Cappuccio et al., 2011). This suggests short sleep duration may be related to CHD, but may not be associated with other forms of cardiovascular disease. One reason may be atherosclerosis, which underlies CHD, does not underlie all cardiovascular diseases. It is unclear whether short sleep duration is a mechanism driving atherosclerotic disease progression or a factor associated with disease outcomes. In order to better understand this relationship, research examining the relationship between sleep duration and preclinical markers of disease progression (e.g., carotid intima-media thickness) is necessary.

Current Proposal

The current study examined the association between sleep duration, sleep insufficiency,
and a marker of preclinical coronary heart disease in order to determine how sleep duration and insufficiency are associated with atherosclerotic progression. This question was addressed in a community sample using a cross-sectional design. Sleep duration was assessed via three methods: single time-point retrospective estimate, daily sleep diaries, and actigraphy. Sleep insufficiency was assessed via questionnaire. The outcome measure, carotid intima-media thickness, was assessed via high resolution B-mode ultrasonography using recent recommendations (Dogan et al., 2010b; Dogan et al., 2011).

Background

Sleep Overview

Sleep is a necessary biological function that is behaviorally modifiable. Sleep is associated with significant physiological changes including electroencephalographic, breathing, heart rate, and blood pressure (Colten & Altevogt, 2006). Sleep duration is not static across the lifetime, with high variability depending on factors like age, gender, genetic profile, and environmental influences (Ferrara & De Gennaro, 2001). In addition to sleep duration, other sleep factors (e.g., sleep insufficiency) may play an important role in health outcomes (Grandner, Patel, Gehrman, Perlis, & Pack, 2010).

Sleep physiology. In addition to significant changes in electroencephalographic activity, normal sleep produces significant physiological changes associated with cardiovascular functioning (Snyder, Hobson, Morrison, & Goldfrank, 1964). In healthy individuals, heart rate and respiratory rate decreases (Aldredge & Welch, 1973), heart rate variability increases (Huikuri et al., 1990), and systolic blood pressure drops initially and then steadily rises during sleep (Snyder et al., 1964). Individuals with cardiovascular disease progression (e.g., myocardial infarction) do not always demonstrate these changes, even when their risk profiles appear normal.
during wake (Vanoli, Adamson, Pinna, Lazzara, & Orr, 1995). Experimentally-induced short sleep duration (i.e., 4 hours per night for 6 nights) is associated with increased sympathetic nervous system activity, suggesting short sleep duration may negatively affect cardiac function and regulation of blood pressure (Spiegel, Leproult, & Van Cauter, 1999).

**Sleep duration.** Sleep duration is determined by a number of factors. For instance, average sleep duration decreases across the lifetime, with infants sleeping on average 14.2 hours ($SD=1.9$) per night (Iglowstein, Jenni, Molinari, & Largo, 2003) and adults over 75 sleeping on average 7.2 hours ($SD=1.7$) per night (Ohayon & Vecchierini, 2005). Additionally, sleep duration can be voluntarily curtailed due to sleep timing related to traits (e.g., circadian rhythm preference; Goel, 2011) or social or occupational pressures (Bliwise, 1996).

Short sleep duration is commonly examined in relation to poor health outcomes, but it is inconsistently defined in the literature (Grandner, Patel, et al., 2010). Moreover, there is substantial controversy about whether short sleep duration is necessarily equivalent to insufficient sleep, resulting in poor health outcomes. This debate is further confounded in part by the inconsistency and low quality of sleep duration measurement used in many studies (Grandner, Patel, et al., 2010).

Prevalence estimates for short sleep duration (typically defined as less than 6 hours) in adults range from 16% – 28% (Krueger & Friedman, 2009) (NSF, 2005). However, these estimates rely on subjective data and may not accurately reflect the true population prevalence of short sleep duration. Although no formal cutoff currently exists, 6 hours or less has been proposed as a standardized value (Grandner, Patel, et al., 2010). Many studies of health and alertness have found significant impairments at or below this level (Ferrara & De Gennaro,
2001), which may be one reason to use this cutoff. However, to our knowledge no strong theoretical backing supporting this cutoff has been described in the literature.

Short sleep duration vs. insufficient sleep. Understanding of short sleep duration is further complicated by the controversy over sleep need, or the average daily amount of sleep needed to prevent sleep debt (Ferrara & De Gennaro, 2001). Sleep debt refers to the buildup of sleep pressure that results in decrements in daily functioning and health (e.g., decreased alertness, increased propensity for accidents, increased mortality rate; Bonnet & Arand, 1995; Van Dongen, Rogers, & Dinges, 2003). Findings from naturalistic and experimental studies support the idea that shortened sleep results in changes including sleep architecture (e.g., Mullaney, Johnson, Naitoh, Friedmann, & Globus, 1977), sleepiness, and cognitive performance (e.g., Van Dongen, Maislin, Mullington, & Dinges, 2003). However, most associations between short sleep duration and negative health effects (e.g., hormonal, cardiovascular, metabolic, immunological) have been largely mixed, making it difficult to determine if short sleep duration has a long-term causal relationship with these health consequences (Ferrara & De Gennaro, 2001).

These mixed findings may be because chronic short sleep is not inherently problematic, but rather sleep duration is an individualized need determined by factors such as age, gender, and genetic profile (Ferrara & De Gennaro, 2001). Therefore, short sleep may not necessarily reflect the accumulation of sleep debt for all individuals. Conversely, some individuals with a higher individual sleep need who fall in the “normal” range of sleep duration may be receiving insufficient sleep. This suggests short sleep duration may overlap with but not fully encompass insufficient sleep. Therefore, instead of examining population-based short sleep duration, examining the amount of sleep necessary for optimal functioning and health and the significance
of diverging from that amount (i.e., receiving insufficient sleep) may be more accurate and meaningful. However, few studies have attempted to disentangle short sleep duration and sleep insufficiency (Grandner, Patel, et al., 2010).

**Insufficient sleep and CHD.** Studies examining the relationship between CHD and sleep typically focus only on sleep duration and ignore the question of sleep insufficiency, as well as other factors involved in sleep (e.g., shift work, apnea symptoms; Cappuccio et al., 2011). To date, no study of the relationship between sleep duration and CHD has differentiated between individuals who are regularly receiving less sleep than they need to feel rested (i.e., receiving insufficient sleep) and individuals who biologically require less sleep (i.e., do not accumulate sleep debt with short sleep duration). This is problematic because exclusively examining short sleep duration may minimize a stronger relationship between insufficient sleep and CHD. One potential reason previous studies have not focused on insufficient sleep may be that it is difficult to operationally define.

For instance, the International Classification of Sleep Disorders (ICSD-2) describes Insufficient Sleep as: 1) complaints of excessive daytime sleepiness for at least 3 months; 2) the typical sleep episode is shorter than would be developmentally expected; and 3) when the restrictive sleep schedule is not maintained (e.g., vacation or weekends), individuals sleep longer than typical (AASM, 2005). Unfortunately, they do not define how much shorter the sleep duration needs to be or operationalize “developmentally expected” sleep durations. Given the previous argument that sleep need varies by individual, it would be difficult to do the latter.

Limited data exists on prevalence of insufficient sleep, perhaps due in part to its ambiguous definition. Hublin, Kaprio, Partinen, and Koskenvuo (2001) defined insufficient sleep as a difference of one hour or more between self-reported sleep need (i.e., “How many hours of
sleep do you need during the night to be alert the next day?”) and obtained sleep (i.e., “How many hours do you usually sleep per 24 hours?”), and found a prevalence of 20.4% in an adult Finnish sample (N=12,423). Broman, Lundh, and Hetta (1996) defined persistent insufficient sleep as a sleep sufficiency index (i.e., ratio of amount of habitual sleep to the amount of estimated need for sleep) below 80% and insufficient sleep more than twice per week, and found a prevalence of 12.0% in an adult Swedish sample (N=600). In addition to limited or infrequent measurement of insufficient sleep, few studies assess sleep duration sufficiently.

Sleep Measurement

Three primary types of sleep measurement are feasible to use in large-scale studies of sleep duration and CHD. Most studies examining the relationship between sleep duration and CHD use brief, subjective measures like single-point retrospective estimates (Cappuccio et al., 2011). To our knowledge, daily sleep diaries have not been used in this research, and actigraphy has been used infrequently. These three measures demonstrate different strengths and limitations, and the accuracy of these measures is affected by various factors.

**Single-point retrospective estimates.** Most studies assessing the relationship between sleep duration and CHD use a single-point retrospective assessment (Cappuccio et al., 2010b) such as a single question (e.g., “On average, how many hours do you sleep per night?”) to assess the past week, month, or several months of sleep. Single-point retrospective estimates used in studies assessing CHD often give ordinal (e.g., “Less than 5 hours, 5-6 hours, etc.”) response sets (e.g., Abe, Aoki, Yata, & Okada, 2011). Single-point retrospective estimates allow for inexpensive, brief assessment of sleep, which is beneficial in large epidemiological studies that assess many variables (Schwarz, 2007) but greatly limits response variability and therefore
power. This makes single-point retrospective estimates a poor choice for precise measurement of sleep duration.

Single-point retrospective estimates of sleep duration also typically fail to account for napping, variability of sleep duration (e.g., night-to-night differences), and potential sleep disorders (Schwarz, 2007). One study has shown that single-point retrospective estimates of sleep were highly correlated with daily sleep diaries ($r = .832$). However, these authors used a much more detailed approach to assessing sleep duration than a single question (i.e., calculating time in bed, subtracting sleep onset latency and wake after sleep onset), which may have improved their measurement error (Libman, Fichten, Bailes, & Amsel, 2000).

Single-point retrospective estimates of sleep duration are only moderately correlated ($r = 0.45$) with objective measures of sleep. One study (Lauderdale, Knutson, Yan, Liu, & Rathouz, 2008) found single-point retrospective estimates tend to be systematically biased towards over-reporting sleep duration compared to an objective measure (i.e., actigraphy). This effect was more pronounced for individuals reporting shorter sleep duration (e.g., 1.3 hours overestimated for 5 hours of sleep vs. 0.3 hours overestimated for 7 hours of sleep).

Accuracy of single-point retrospective estimates can also be affected by question format. First, using two questions to differentiate between weekend and weekday sleep, as opposed to a single question assessing a daily average, yields higher average sleep duration (Lauderdale, 2014). Second, assessing sleep duration via an hour estimate (e.g., “How many hours do you sleep per night?”) versus bedtime and risetime estimates (e.g., “What time do you typically go to bed/wake up?”) can yield consistently different results. A recent meta-analysis examining sleep duration and mortality found studies using an hour estimate demonstrated a U-shaped relationship between sleep duration and overall mortality, whereas studies that used bedtime and
risetime estimates to calculate average sleep duration failed to find the U-shaped relationship (i.e., found a linear relationship or no relationship). This indicates there may be a systematic bias across studies based in way in which sleep duration questions are asked (Kurina et al., 2013). Taken together, these findings suggest the ease of using single-point retrospective estimates of sleep duration may come at the price of accuracy, and a more thorough method of assessment is indicated.

**Sleep diaries.** To our knowledge, no studies have used sleep diaries to assess sleep duration related to CHD. Sleep diaries are an inexpensive, subjective, prospective measure of sleep duration that are typically completed by participants assessing recent (e.g., the previous night) sleep variables, such as bedtime, risetime, sleep onset latency, number of awakenings, wake after sleep onset, and early morning awakenings (Carney et al., 2012). Although sleep diaries contribute to increased participant burden and time compared to single-point retrospective estimates, their increased accuracy and comparable cost makes them a favorable alternative.

Sleep diaries, when used by participants correctly, can account for napping, variability of sleep duration (e.g., night-to-night differences), differences between weekend and weekday sleep, and patterns associated with some sleep disorders (e.g., insomnia, shift work; Rogers, Caruso, & Aldrich, 1993). Sleep diaries demonstrate acceptable agreement with the gold standard of sleep assessment (i.e., polysomnography) in a community sample (kappa = .87; Rogers et al., 1993). Sleep diary sleep duration estimates correlate moderately ($r = 0.57$) with actigraphy used over the same time period (Lockley, Skene, & Arendt, 1999). Sleep diaries are considered the gold standard of subjective sleep assessment (Carney et al., 2012).

Accuracy of sleep diaries can be affected by factors such as type of sleep diary and participant compliance (e.g., filling out sleep diaries every morning upon awakening). Although
a standardized research sleep diary exists (Carney et al., 2012), this sleep diary is not used consistently across studies. Additionally, one study in a related field (i.e., chronic pain) demonstrated daily-collected diaries are associated with 93.6% participant compliance compared to 10.9% with weekly-collected diaries (Stone, Shiffman, Schwartz, Broderick, & Hufford, 2003). Low compliance may affect accurate reporting due to expectations about sleep, recall bias, or memory impairments (Martin & Hakim, 2011). These limitations indicate use of a concurrent objective measure, to assess subjective difficulties with sleep diaries, may be warranted.

**Actigraphy.** Few studies that assess sleep duration related to CHD use actigraphy. Actigraphy is a moderate-cost (e.g., $1000 - $5000), objective, prospective measure of sleep duration that can be used to assess days, weeks, or months of sleep (Sadeh & Acebo, 2002). Actigraphs are wrist-worn, wristwatch-like devices that use an accelerometer to capture motion. Computer software uses an algorithm to analyze activity and estimate sleep parameters such as total sleep time, sleep onset latency, number of awakenings, wake after sleep onset, and terminal wakefulness (Ancoli-Israel et al., 2003). Like single-point retrospective estimates and sleep diaries, actigraphy is an unobtrusive measure that does not significantly interfere with the individual’s routine, which allows for increased external validity compared to polysomnography (de Souza et al., 2003). Actigraphy, although more costly than sleep diaries and single-point retrospective estimates, is significantly less expensive than polysomnography and offers increased accuracy over subjective measures.

Actigraphy can account for napping, variability of sleep duration, differences between weekend and weekday sleep, patterns associated with some sleep disorders, and variables the participant may be unable to subjectively assess accurately (e.g., wake after sleep onset; de
Souza et al., 2003). However, unlike polysomnography, actigraphy does not assess sleep architecture. Actigraphy correlates well (*rs > .90*) with polysomnography in a laboratory setting (Ancoli-Israel et al., 2003; Sadeh, Hauri, Kripke, & Lavie, 1995). Actigraphy has higher sensitivity (i.e., sleep detection) than specificity (i.e., wake detection), rendering it less useful in sleep-disordered populations (Ancoli-Israel et al., 2003). Actigraphy overestimates sleep duration compared to polysomnography by an average of 0.80 hours (Lauderdale et al., 2008).

The accuracy of actigraphy may be improved when it is used in combination with a subjective measure (e.g., sleep diaries; Kushida et al., 2001).

Accuracy of actigraphy can also be affected by type of device, type of computer software and algorithm, and participant adherence. Several mainstream devices used to assess sleep duration and other sleep variables differ on factors such as type of accelerometer or software compatibility (Ancoli-Israel et al., 2003). Devices from different manufacturers estimate sleep duration differently (Cellini, Buman, McDevitt, Ricker, & Mednick, 2013), although agreement between devices is generally high (>90%; Ancoli-Israel et al., 2003). Algorithms for scoring actigraphy data have not been standardized, and no published studies have examined differences between different algorithms (Ancoli-Israel et al., 2003). Participant adherence (e.g., completing concurrent sleep diaries, pressing event marker buttons, wearing the device consistently) and environmental factors (e.g., bed partners, pets, bedroom light exposure) can also impact accuracy (Sadeh & Acebo, 2002). Despite these limitations, actigraphy and sleep diaries used concurrently yield reliable sleep duration data in situations in which polysomnography is not practical (Ancoli-Israel et al., 2003) such as studies of sleep duration and CHD.

**Coronary Heart Disease Overview**

CHD is a significant global health problem. CHD is the leading cause of death worldwide
and expected to remain the leading cause of death through 2030 (Mathers & Loncar, 2006). Almost 16 million Americans have coronary heart disease (NHLBI, 2012), and CHD was responsible for 405,309 deaths in 2008 (NHLBI, 2012). Total CHD prevalence in the United States is 6.4%, with higher prevalence rates for men (7.1%) than women (5.9%; Go, 2013). Moreover, CHD is the most common form of cardiovascular disease, accounting for approximately half of cardiovascular-related deaths (NHLBI, 2012).

CHD refers to a type of cardiovascular disease that is a progression of coronary artery disease (CAD). CAD primarily results from atherosclerosis progression in the arteries of the heart (Falk, Shah, & Fuster, 1995). Atherosclerosis is a lifelong systemic disease process, and evidence of its progress can be detected as early as adolescence (Strong et al., 1999). Atherosclerosis is the process of damage and inflammation in the heart that leads to buildup of fatty deposits, cells, and scar tissue within the arterial walls over time (Go et al., 2013). This buildup can create blockages that impede the flow of blood to the heart, leading to negative downstream consequences (NHLBI, 2012). Atherosclerotic progression is associated with significant negative health outcomes like myocardial infarction, stroke, and death (Lorenz, Markus, Bots, Rosvall, & Sitzer, 2007).

Many individuals with atherosclerosis do not show outward symptoms of the disease process—50% of men and 64% of women who die unexpectedly of CHD demonstrated no prior symptoms (Loria et al., 2007). Since 1950, United States CHD death rates have declined by 72% (NHLBI, 2012), with an estimated 47% of this decrease directly related to treatments and 44% due to modifications in risk factors (Ford & Capewell, 2007). There is some evidence that early screening of atherosclerosis can improve individuals’ risk factor profiles which may reduce negative health outcomes (Rozanski et al., 2011).
CHD Measurement

In epidemiological studies, CHD is examined as a health outcome (i.e., disease diagnosis, cardiovascular event, or death) typically measured via medical records, individual self-report, or death records (Cappuccio et al., 2011). Although these outcomes provide information about the latter stages of disease progression, they do not provide an opportunity for early-stage intervention. Once atherosclerosis has culminated in a cardiovascular event (e.g., myocardial infarction), the disease process is difficult to reverse (Libby & Theroux, 2005). Thus, it is important to examine preclinical markers of CHD so behavioral modifications (e.g., sleep extension) can be effectively implemented early in disease progression.

Preclinical atherosclerosis measurements include coronary artery calcification scans, cardiovascular magnetic resonance, brachial artery reactivity testing, and carotid intima-media thickness (CIMT; Redberg et al., 2003). Although CHD refers specifically to atherosclerotic progression in the heart, atherosclerosis develops in multiple arteries across the body (e.g., carotid artery; Go et al., 2013). Measurement in these areas can be less invasive and more cost-effective than direct measurement of atherosclerosis in the heart while still providing good prediction of future events (Redberg et al., 2003).

cIMT. Atherosclerotic progression occurs within the innermost walls of the artery (i.e., intimal and medial layers; Pignoli, Tremoli, Poli, Oreste, & Paoletti, 1986). Measurement of the thickness of these walls within the carotid artery (i.e., the distance from the lumen-intima interface to the media-adventitia interface of the arterial wall) is called carotid intima media thickness (CIMT; Polak et al., 2011). cIMT is a widely-used, safe, highly sensitive, non-invasive objective assessment of atherosclerosis development that can be used to quantify subclinical
cardiovascular disease progression (Bisoendial et al., 2002; Dogan et al., 2010b; Finn, Kolodgie, & Virmani, 2010).

Clinically significant intimal-medial thickness does not instantaneously lead to cardiovascular events but reflects the presences of atherosclerosis in the entire arterial system including the heart (Bots et al., 2007). The correlation between cIMT and coronary atherosclerosis ranges from $r = 0.30 – 0.50$ (Bots et al., 2007). Intimal thickening is one of the earliest signs of atherosclerosis (Finn et al., 2010) and change in cIMT progression can be reliably detected over time in large samples (O'Leary & Polak, 2002). cIMT is positively related to CHD progression with larger values indicating greater cardiovascular risk (Kablak-Ziembicka et al., 2004; Redberg et al., 2003), although this relationship may not be linear in all populations (Lorenz et al., 2007). cIMT assessment can help define the burden of atherosclerosis before significant outcomes (e.g., myocardial infarction, stroke, death) occur (Go et al., 2013). cIMT is frequently used in psychosocial and treatment research due to its reproducibility, relationship to other risk factors, ability to detect change over time, and consistent relationship with cardiovascular outcomes (Bots & Sutton-Tyrrell, 2012; Matthews, 2005).

cIMT can be used to predict cardiovascular outcomes (e.g., myocardial infarction, stroke). The American Heart Association has endorsed cIMT as offering improved risk assessment above traditional prognostic profiles (Greenland et al., 2010). One meta-analysis found, after adjusting for age and sex, for every 0.1mm increase in cIMT, relative risk for myocardial infarction was 1.15 (95% C.I.: 1.12-1.18) and for stroke was 1.17 (95% C.I.: 1.15-1.21) (van den Oord et al., 2013). However, heterogeneity amongst study procedures may somewhat attenuate these relative risk ratios (Lorenz et al., 2007).
Assessment of cIMT. The assessment of cIMT via B-mode ultrasound was first introduced in the 1980s as a research tool (Pignoli et al., 1986). cIMT can be assessed in a variety of ways, which makes comparison across studies difficult (see Figure 1). cIMT can be assessed in three segments: the common carotid artery (CCA), the carotid bifurcation (BIF), and the internal carotid artery (ICA). cIMT can also be assessed in two places: the arterial wall closest (i.e., near wall) or farthest (i.e., far wall) from the ultrasound. The assessment can be expressed in two ways: mean thickness across a fixed segment (e.g., 10mm), called the mean common cIMT, or as a maximum thickness in a specific wall and segment, called the mean maximum cIMT. The outcome assessment used for analysis can be a single assessment (e.g., mean near wall ICA) or a mean assessment of all segments and walls (e.g., mean maximum CIMT; Bots et al., 2007). Finally, assessments can be made at different angles (e.g., 90°, 120°, 150°, 180°; Dogan et al., 2010b). Recent recommendations (Dogan et al., 2010b; Dogan et al., 2011) indicate the optimal mean common cIMT is the mean of both near and far wall CCA using ≥2 angles, and the optimal mean maximum cIMT is the mean maximum of both near and far walls of all three segments based on factors like high reproducibility and ability to capture progression/change over time. However, studies do not consistently report these values, making comparison across studies difficult (Dogan et al., 2010b).

cIMT and known correlates. In addition to CVD outcomes, cIMT is significantly related to traditional biological (e.g., age, body mass index, cholesterol), behavioral (e.g., smoking, alcohol use, exercise), and psychosocial (e.g., depression) cardiovascular risk factors. Examples of the strength of these various relationships can be seen in Table 2 (Davis, Dawson, Riley, & Lauer, 2001; Ebrahim et al., 1999; Stewart, Janicki, Muldoon, Sutton-Tyrrell, & Kamarck, 2007). The strength of some of these associations differs for men and women, suggesting
differing factors may affect heart disease risk for men and women differentially (Davis et al., 2001). Furthermore, certain segments of the carotid artery care more predictive of certain outcomes than other segments. For example, behavioral/psychosocial risk factors tend to be more strongly associated with cIMT progression in the BIF compared to the CCA (Roepke et al., 2012; Urbina et al., 2002). However, examination of behavioral and psychosocial correlates of cIMT has thus far been limited, and some risk factors (e.g., sleep duration) have received little attention in the literature.

**cIMT and Sleep Duration**

Relatively few studies have examined the relationship between sleep duration and cIMT, and the existing body of literature has significant limitations. Furthermore, comparison between studies is difficult due to variety in sleep assessment methodology, cIMT assessment, statistical analyses used, and covariates. For an overview of the literature in this area, see Table 3. Studies are ordered from most limited to strongest, as rated by the current author.

Results examining sleep duration and cIMT are mixed (for a range of effect sizes, see Table 3). It appears a linear relationship between sleep duration and cIMT exists, with shorter sleep duration associated with higher levels of cIMT. There is also some evidence that a quadratic model may fit this data as well. It appears the relationship between sleep duration and cIMT is stronger in men than in women, and may be stronger in the BIF than in other segments. However, the evidence is too limited to make strong conclusions.

One major limitation of previous studies examining sleep duration and cIMT is the insufficiency and inconsistency of assessment methods, which may be partially responsible for the mixed findings in this area. Some studies in this area (e.g., Abe et al., 2011; Wolff et al., 2008) demonstrate significant limitations in either study procedures (e.g., examining sleep
duration as a categorical variable) or in reporting (e.g., failing to report duration of actigraphy assessment). For example, the use of reference groups is inconsistent across studies as is not presented with theory-guided rationale. Additionally, categorizing cIMT into “clinical disease progression” or “no disease” groups eliminates the advantage of assessing subclinical disease progression.

Despite increased methodological rigor, limitations of other studies in this area are still potentially impactful. For example, studies using actigraphy did not report concurrent use of sleep diaries, which may increase measurement error (Ma et al., 2013; Nakazaki et al., 2012; Sands et al., 2012; Schwartz et al., 2012). Additionally, no study examines the relationship between insufficient sleep and cIMT. Studies used various protocols for assessing different aspects of cIMT. These inconsistencies make comparison across studies difficult.

Conclusions. Taken together, the findings of this literature indicate a need for further research examining sleep duration and cIMT. The effects of inconsistency of sleep duration and cIMT assessment methods, and inconsistency of categorical vs. continuous variables in this literature is unknown. In order to better understand the relationship between sleep duration and cIMT, improvement in consistency and rigor of sleep duration and cIMT assessment is necessary.

The Current Study

The current study examined the association between sleep duration, insufficient sleep, and cIMT in order to determine if and how short sleep duration and sleep insufficiency are associated with atherosclerotic progression. The current study also examined whether assessment method significantly impacted the nature of the relationship between sleep duration and cIMT. These questions were addressed in an adult community sample using a cross-sectional design.
Sleep duration was assessed via three methods: single time-point retrospective estimate, daily sleep diaries, and actigraphy. Sleep insufficiency was assessed via questionnaire. cIMT was assessed via high resolution B-mode ultrasonography using recent recommendations (Dogan et al., 2010b; Dogan et al., 2011).

Specific Aims and Hypotheses

**Aim 1:** The current study seeks to examine whether sleep duration is significantly associated with preclinical atherosclerosis.

**Hypothesis 1:** Sleep duration will be inversely related to cIMT levels (i.e., shorter sleep duration will be associated with higher levels of cIMT).

**Aim 2:** The current study seeks to examine whether insufficient sleep is significantly associated with preclinical atherosclerosis.

**Hypothesis 2:** Insufficiency of sleep (habitual average sleep time – ideal sleep time) will demonstrate a stronger inverse relationship between sleep duration and cIMT than individuals with short sleep and no evidence of sleep insufficiency (i.e., insufficient sleep will be a moderator in the relationship between sleep duration and cIMT).

**Aim 3:** The current study seeks to examine whether type of sleep duration assessment (i.e., single-point retrospective estimate, sleep diary, actigraphy) affects the relationship between sleep duration and cIMT.

**Hypothesis 3:** Sleep diary and actigraphy assessments will yield higher relationships between sleep duration and cIMT than single-point retrospective estimates.
CHAPTER II

METHODS

Sample

Data for the current study was collected as part of a larger parent study, the North Texas Heart Study (NTHS). The major aims of NTHS were to examine social vigilance as a cross-sectional and longitudinal predictor of change in subclinical atherosclerosis as well as examine ambulatory blood pressure as a mediator among a sample of healthy community volunteers. Participants were 300 adults (150 women) ages 21-70 years with no history of cardiovascular disease. The sample is stratified by age within gender and race/ethnicity. The sample is diverse, including 60% non-Hispanic Whites, 15% non-Hispanic Blacks, 6% non-Hispanic Other, and 19% Hispanic/Latinos.

Key Procedures

All sessions were conducted at a single-site, staffed, vascular medicine clinic located in the community and which functions as a general clinical research center. All laboratory sessions were conducted on Thursday mornings followed by a 2-day/1-night ambulatory/ecological momentary assessment (EMA) study.

Following arrival at the laboratory study and consent, all participants underwent a brief physical exam which includes a review of systems, personal and family medical history, current medications and conditions, health behaviors, and detailed cardiac disease history. Participants were rescheduled in cases of acute illness/infection. A fasting blood draw to assess lipids and inflammatory markers was performed after which participants received a light snack. A vascular technologist performed a complete bilateral ultrasound imaging of the extracranial vasculature including the internal and external carotid arteries and related vasculature. Finally, participants
completed a psychosocial survey which included measures of vigilance, social experiences, personality, health behaviors, and single-point retrospective estimates of sleep.

Prior to leaving, all participants were fitted with an actigraph monitor (Phillips-Respironics, Inc), an ambulatory blood pressure monitor (ABPM: Oscar II; Suntech, Inc.), and given a cellular phone for the 2-day/1-night, ambulatory/ecological momentary assessment (EMA) study. Participants were instructed to complete two EMA-based surveys: 1) an end-of-day survey completed at bedtime, and 2) a morning survey upon awakening in order to obtain sleep diary data.

Key Measures

Sleep Duration

Sleep duration was assessed via three methods in the current study, in order to allow for comparison across methods.

Single-point retrospective estimates. Participants reported the hours and minutes of their typical sleep duration (i.e., “How much sleep do you usually get at night [or your main sleep period] on weekdays/workdays?” and “How much sleep do you usually get at night [or your main sleep period] on weekends/off days?”).

Sleep diaries. Participants were asked to keep sleep diaries, derived from the work of Carney et al. (2012), in combination with actigraphy (below) to obtain prospective estimates of their sleep on the previous night (e.g., bedtime, sleep onset, wake time, etc.). Participants recorded sleep diary information for two days via EMA on a cell phone provided by the study.

Actigraphy. Participants were asked to wear Actiwatches for the same two days sleep diary data was recorded. AW Spectrum Actiwatches (Mini Mitter, Bend, OR) are compact, wrist-worn, battery-operated activity monitors that look similar to a wristwatch. The monitor
uses a motion sensor known as an “accelerometer” to monitor the occurrence and degree of motion. This type of sensor integrates the degree and speed of motion and produces a small signal where magnitude and duration depend on the amount of motion. The device also collects data about the strength and color of light. This information is stored in memory, downloaded to a computer, and analyzed. In addition, AW Spectrum has an on-board event marker button which the patient presses to identify bedtime and risetime, in order to assist the researcher in capturing the intended sleep interval.

Sleep Insufficiency

Participants answered a question assessing desired sleep duration (i.e., “How much sleep do you feel you need to get at night to feel rested?”). A measure of “typical sleep insufficiency” was calculated by subtracting actigraphy assessed sleep duration from desired sleep duration. Values could be negative, indicating sleep insufficiency, or positive, indicating more sleep than one believes they need.

cIMT

B-mode ultrasonography of the left and right carotid arteries was performed by experienced sonographers. Briefly, Dicom images were captured for the common (CCA), bifurcation (BIF), and the internal carotid artery (ICA) segments interrogated from 4 standard angles (90º, 150º, 210º, 270º). Consistent with recommendations (Dogan et al., 2010b; Dogan et al., 2011; Stein et al., 2008) a Meijer’s Carotid Arc (Meijer Medical Ultrasound; Voorschoten, The Netherlands) was used to improve the precision of measurement points and to improve reliability of within-participant measurement over time.

Two readers blinded to the characteristics of the participants interrogated the Dicom images for intima media thickness (IMT) off-line using Vascular Research Tools, Version 5.0
(Medical Imaging Applications, Coralville, IA). This software uses a semi-automated edge
detection algorithm to ascertain the thickness of the intima in the designated region of interest
(ROI) for each frame in the series of the clip. Consistent with the literature, IMT was defined as
the distance between the intimal-luminal and the medial-adventitial interfaces of the arterial
segment. Each segment was analyzed for the presence or absence of plaques. Plaques were given
a quality score using the following criteria: 1) size (small, medium, large), 2)
heterogeneity/homogeneity, and 3) fibrous, fatty, and calcified. If cIMT was measureable
adjacent to the plaque, a score was measured and recorded. If no cIMT was measureable adjacent
to the plaque, no score was recorded as including the plaque in the measurement artificially
inflates results. The software generates average, minimum, and maximum IMT scores for each
segment at each angle. The maximum IMT value was chosen as the marker of focus in
accordance with prior recommendations (Allan, Mowbray, Lee, & Fowkes, 1997) and the parent
study’s authors’ (Allison, Laughlin, & Barrett-Connor, 2006; Roepke et al., 2012). Mean of the
maximums (mean of the maximum scores for each of the 4 angles for a given segment) were
derived for the CCA, BIF, and ICA.

Potential Covariates

Additional potential covariates, identified as cardiovascular risk factors within the
broader literature (Ali et al., 2014; Breton et al., 2011; Chaer, Kip, Mulukutla, Aryan, & Reis,
2012; Davis et al., 2001; Ebrahim et al., 1999; Youn et al., 2011), were collected using self-
report (i.e. age, sex, race/ethnicity, alcohol use, smoking, sleep apnea risk, sleeping medication
use, insomnia symptoms), history and physical (i.e., BMI, blood pressure), and traditional
laboratory methods (i.e., total cholesterol, interleukin-6 [IL-6], high sensitivity C-reactive protein
[hsCRP], tumor necrosis factor alpha [TNF-α]).
CHAPTER III
ANALYTIC STRATEGY

Hypothesis 1

Sleep duration will be inversely related to cIMT levels (i.e., shorter sleep duration will be associated with higher levels of cIMT). To test this hypothesis, four hierarchical linear regressions were conducted. The dependent variable was cIMT assessed in four ways: mean maximum far common carotid artery (CCA), mean maximum bifurcation (BIF), mean maximum internal carotid artery (ICA), and mean maximum bifurcation/internal carotid artery (BIF/ICA). Independent variables were identical for each analysis. Sleep duration (assessed by actigraphy) was entered into the first block (Model 1). The covariates age, gender, and race/ethnicity were entered into the second block (Model 2). If sleep remained a significant predictor in Model 2, other covariates (detailed above) determined to be related to sleep duration and cIMT (see Table 5) were entered into the third block (Model 3).

Hypothesis 2

Insufficient sleep (habitual average sleep time – ideal sleep time) will be a moderator in the relationship between sleep duration and cIMT). To test this hypothesis, four hierarchical linear regressions were conducted. The dependent variable was cIMT assessed in four ways (CCA, BIF, ICA, BIF/ICA). Independent variables were identical for each analysis. Habitual average sleep duration (assessed by actigraphy) and insufficient sleep were entered into the first block (Model 1). The interaction term (computed by multiplying centered insufficient sleep and centered sleep duration) was entered into the second block (Model 2). The covariates age, gender, and race/ethnicity were entered into the third block (Model 3). If sleep remained a significant predictor in Model 2, other covariates (detailed above) determined to be related to sleep duration and cIMT were entered into the third block (Model 3).
Hypothesis 3

Sleep diary and actigraphy assessments of sleep duration will yield stronger relationships between sleep duration and cIMT than single-point retrospective estimates (survey). First, correlations (Pearson’s $r$) were computed to test the relationships of sleep duration, assessed in three ways (survey, sleep diary, actigraphy) with cIMT assessed in four ways (CCA, BIF, ICA, BIF/ICA). To test the magnitude of differences between these relationships, Fisher’s $Z$ (Meng, Rosenthal, & Rubin, 1992) was calculated for each comparison.

Data Cleaning

Data were inspected for accordance with regression assumptions. Influential outliers, determined by studentized deleted residual analysis and standardized DfBeta influence analysis, were removed from analyses ($n = 9$). The dependent variables were positively skewed, and a natural log transformation was performed to normalize the data. This transformation prevents the meaningful interpretation of individual coefficients, but does not interfere with significance interpretations for models or predictors.
CHAPTER IV
RESULTS

Data was collected for 300 community volunteers in North Texas. Sample characteristics are presented in Table 4. Participants were 21 – 70 years old, primarily non-Hispanic White (60%), married (65.5%), and overweight (70.9%). Average sleep duration ranged from 6.71 to 7.05 hours per night depending on assessment method. Average sleep insufficiency was 46.90 minutes. Average cIMT ranged from 0.78 to 0.92mm depending on segment.

Hypothesis Testing

Hypothesis 1: Sleep duration will be inversely related to cIMT levels (i.e., shorter sleep duration will be associated with higher levels of cIMT).

CCA

Model 1 testing the unadjusted relationship between sleep duration and cIMT in the CCA was significant, $F(1, 241) = 8.58, p = .004$, adjusted $R^2 = 0.03$ (see Table 6). Counter to expectations, longer unadjusted sleep duration was a significant predictor of greater cIMT in the CCA, $\beta = .19, t = 2.93, p = .004$. Model 2 which adjusted for gender, age, and race/ethnicity was significant, $F(4, 238) = 23.94, p < .001$, adjusted $R^2 = 0.28$, $R^2$ change = 0.25, and the inclusion of this step reduced the relationship between sleep duration and cIMT to a trend, $\beta = 0.11, t = 1.85, p = .066$. Older age was associated with higher cIMT in the CCA, $\beta = 0.48, t = 8.62, p < .001$ (Figure 2), and a main effect of race/ethnicity and cIMT in the CCA was also observed, $\beta = 0.16, t = 2.45, p = .006$. Post hoc tests (Tukey’s Honestly Significant Difference) indicate this association was driven by the non-Hispanic other group, which demonstrated significantly lower cIMT in the CCA than both the Non-Hispanic White ($p = .007$) and Non-Hispanic Black ($p = .017$) groups (Figure 3). No other racial groups differed significantly on levels of cIMT in the
CCA. These two Model 2 findings suggest age and race/ethnicity may account for the relationship between sleep duration and cIMT in the CCA. Because sleep duration was no longer a significant predictor of cIMT in the CCA in Model 2, no further models were examined.

**BIF/ICA, BIF, ICA**

Model 1 testing the unadjusted relationship between sleep duration and cIMT in the combined BIF/ICA was significant, $F(1, 231) = 4.28, p = .040$, adjusted $R^2 = 0.01$ (see Table 6). Counter to expectations, longer unadjusted sleep duration was related to higher levels of cIMT in the BIF/ICA, $\beta = 0.14, t = 2.07, p = .040$. Model 2 which adjusted for gender, age, and race/ethnicity was significant, $F(4, 228) = 25.98, p < .001$, adjusted $R^2 = 0.30$, $R^2$ change = 0.30, and the inclusion of this step rendered the relationship between sleep duration and cIMT non-significant, $\beta = 0.01, t = 0.24, p = .809$. Older age was associated with higher cIMT in the BIF/ICA, $\beta = 0.55, t = 9.80, p < .001$ (Figure 2), but race/ethnicity was not. This indicates age may account for the relationship between sleep duration and cIMT in the BIF/ICA. Because sleep duration was no longer a significant predictor of cIMT in the BIF/ICA in Model 2, no further models were examined.

Model 1 testing the unadjusted relationship between sleep duration and cIMT in the BIF showed a trend, $F(1, 224) = 3.69, p = .056$, adjusted $R^2 = 0.01$. Similar to findings in the combined BIF/ICA, longer unadjusted sleep duration was related to higher levels of cIMT in the BIF, $\beta = 0.06, t = 1.92, p = .056$. Model 2, which adjusted for gender, age, and race/ethnicity, was significant, $F(4, 221) = 21.02, p < .001$, adjusted $R^2 = 0.26$, $R^2$ change = 0.26, and the inclusion of this step eliminated the trend between sleep duration and cIMT in the BIF, $\beta = 0.02, t = 0.40, p = .687$. Older age was associated with higher cIMT in the BIF, $\beta = 0.52, t = 8.78, p < .001$ (Figure 2), but race/ethnicity was not. This Model 2 finding suggests age may account for
the relationship between sleep duration and cIMT in the BIF. Because sleep duration was no longer a significant predictor of cIMT in the BIF in Model 2, no further models were examined.

Model 1 testing the unadjusted relationship between sleep duration and cIMT in the ICA was not significant, $F(1, 198) = 1.89, p = .170$, adjusted $R^2 = 0.00$. Therefore, no further models were examined.

Hypothesis 2: Insufficient sleep will be a moderator in the relationship between sleep duration and cIMT.

CCA

Model 1 testing the relationship of sleep duration and sleep insufficiency with cIMT in the CCA was significant, $F(2, 234) = 4.87, p = .008$, adjusted $R^2 = 0.03$ (see Table 7), despite no single variable emerging as a significant predictor, all $\beta$’s $< 0.13$, all $t$’s $< 1.49$, all $p$s $= ns$.

Model 2 which added the interaction of sleep duration and sleep insufficiency was significant, $F(3, 233) = 4.94, p = .002$, adjusted $R^2 = 0.05$. The interaction between sleep duration and sleep insufficiency was the only significant predictor, $\beta = -0.15, t = -2.22, p = .028$. Further examination of this interaction indicates for individuals who reported higher insufficient sleep (>30m), longer sleep duration was associated with higher cIMT in the CCA, $R^2 = 0.06$. For individuals reporting sufficient sleep or more sleep than they said they needed, there was no relationship between sleep duration and cIMT, $R^2 < 0.01$ (Figure 4). Model 3 which adjusted for gender, age, and race/ethnicity was significant, $F(6, 230) = 15.53, p < .001$. The inclusion of this step reduced the interaction with cIMT in the CCA to a trend, $\beta = -0.10, t = -1.75, p = .082$.

Similar to Hypothesis 1, age, $\beta = 0.46, t = 7.97, p < .001$ and race/ethnicity, $\beta = 0.16, t = 2.70, p = .008$ were the only significant predictors of cIMT in the CCA (see Figures 2 and 3). These results indicate although sleep insufficiency appears to moderate the relationship between sleep
duration and cIMT in the CCA, age and race/ethnicity may account for this relationship. Because sleep duration, sleep insufficiency, and their interaction were no longer significant predictors of cIMT in the CCA in Model 3, no further models were examined.

ICA, BIF, BIF/ICA

Model 1 testing the relationship of sleep duration and sleep insufficiency with cIMT in the ICA was not significant, $F(2, 192) = 0.94, p = .391$, adjusted $R^2 = 0.00$ (see Table 7). Neither sleep duration nor sleep insufficiency were significant predictors, all $\beta$'s < 0.10, all $t$'s < 1.09, all $ps = ns$. Model 2 which added the interaction of sleep duration and sleep insufficiency was not significant, $F(3, 191) = 2.23, p = .082$, adjusted $R^2 = 0.02$. However, the interaction between sleep duration and sleep insufficiency was a significant predictor, $\beta = -0.17, t = -2.21, p = .028$. Further examination of this interaction indicates for individuals who reported insufficient sleep (>30 minutes), or more sleep than they said they needed (>30 minutes), longer sleep duration was associated with higher cIMT in the ICA, both $R^2 = 0.02$. For individuals reporting sufficient sleep, there was no relationship between sleep duration and cIMT, $R^2 < 0.01$ (Figure 4). Model 3 which adjusted for gender, age, and race/ethnicity was significant, $F(6, 194) = 7.21, p < .001$. The inclusion of this step rendered the relationship between the interaction and cIMT in the ICA non-significant, $\beta = 0.06, t = 0.68, p = .500$. Results suggest older age was associated with higher cIMT in the ICA, $\beta = 0.39, t = 5.69, p < .001$ (see Figure 2). Although sleep insufficiency appeared to moderate the relationship between sleep duration and cIMT in the ICA, age may account for this relationship. Because sleep duration, sleep insufficiency, and their interaction were no longer significant predictors of cIMT in the ICA in Model 3, no further models were examined.
Model 1 testing the relationship of sleep duration and sleep insufficiency with cIMT in the BIF was not significant, $F(2, 217) = 1.73, p = .179$, adjusted $R^2 = 0.01$ (see Table 7). Neither sleep duration nor sleep insufficiency were significant predictors, all $\beta$’s < 0.13, all $t$’s < 1.44, all $p$s = ns. Model 2 which added the interaction of sleep duration and sleep insufficiency was not significant, $F(3, 216) = 1.64, p = .182$. Because none of the predictors were significant, all $\beta$’s < 0.12, all $t$’s < 1.34, all $p$s = ns, no further models were examined.

Model 1 testing the relationship of sleep duration and sleep insufficiency with cIMT in the combined BIF/ICA was not significant, $F(2, 224) = 2.12, p = .122$ (see Table 7). Neither sleep duration nor sleep insufficiency were significant predictors, all $\beta$’s < 0.14, all $t$’s < 1.57, all $p$s = ns. Model 2 which added the interaction of sleep duration and sleep insufficiency was not significant, $F(3, 223) = 2.25, p = .083$. Because none of the predictors were significant, all $\beta$’s < 0.13, all $t$’s < 1.58, all $p$s = ns, no further models were examined.

Hypothesis 3: Sleep duration as assessed by sleep diary and actigraphy will demonstrate stronger correlations with cIMT than single-point retrospective estimates.

Actigraphy assessed sleep duration demonstrated *positive* correlations with all segments of cIMT, but the only significant correlation was with CCA (Table 8). These results indicate that in general, greater *objectively* assessed higher sleep duration was associated with higher cIMT levels. Sleep diary assessed sleep duration demonstrated *negative* correlations for all but CCA, but the only significant correlation was with BIF. These results indicate that in general, greater subjectively and prospectively assessed higher sleep duration was associated with lower cIMT levels. Finally, the survey sleep duration questions demonstrated *positive* correlations for all but BIF, and none were significant. These results indicate that in general, when assessed with single-time point subjective methods, higher sleep duration was associated with higher cIMT levels.
Of note, significant differences were found between actigraphy assessed sleep duration and sleep diary sleep duration for CCA ($p = .042$), BIF ($p < .001$), and BIF/ICA ($p < .001$). No differences were found between survey assessment of sleep and either sleep diary or actigraphy assessed sleep. As can be seen in Table 9, the CCA difference appeared to be driven by discrepancy in magnitude between the two methods (sleep diary $r = 0.05$, actigraphy $r = 0.19$), suggesting actigraphy assessed sleep duration shows a stronger relationship with cIMT in the CCA than sleep diary assessed sleep duration. The BIF and BIF/ICA differences were driven by a discrepancy in directionality (e.g., sleep diary $r = -0.14$, actigraphy $r = 0.13$), suggesting whereas actigraphy assessed sleep duration demonstrates a positive relationship, sleep diary assessed sleep duration demonstrates an inverse relationship with cIMT in the BIF and BIF/ICA. Taken together, these data suggest sleep duration assessment method may significantly alter the apparent nature of the relationship between sleep duration and cIMT, and this effect may occur differentially across segments.
CHAPTER V
DISCUSSION

The current study explored the relationship between sleep duration, sleep insufficiency, and cIMT. There was no support for the proposed hypotheses that short sleep duration and insufficient sleep would be related to higher levels of cIMT. Instead, longer sleep duration was associated with higher levels of cIMT in some areas of the carotid artery (i.e., CCA, BIF/ICA). In some segments (i.e., CCA, ICA), sleep insufficiency was a moderator in the relationship between sleep duration and cIMT. None of these sleep and cIMT relationships remained significant after accounting for age and in some cases race/ethnicity. Finally, assessment method moderated the relationship between sleep duration and cIMT for some methods (i.e., actigraphy and sleep diary) in some segments (i.e., CCA, BIF, BIF/ICA).

Sleep Duration and cIMT

The current findings did not support our hypotheses and were not in agreement with previous studies that found evidence for a relationship between short sleep duration and cIMT (Nakazaki et al., 2012; Sands et al., 2012; Wolff et al., 2008). This may be due to the relative heterogeneity of the current sample compared to previous studies. Previous studies have examined samples with narrower age ranges, typically middle-aged (Ma et al., 2013; Sands et al., 2012) or older (Nakazaki et al., 2012; Schwartz et al., 2012) adults. The age range in the current study was 21-70, which may have reduced power if an effect exists only for middle-aged or older adults. A study with a similar age range to the current study (Ma et al., 2013) also failed to find a significant relationship after controlling for demographics variables. Although cIMT is a robust measure for detecting pre-clinical atherosclerosis in younger individuals (Finn et al., 2010), the buildup of cIMT due to sleep duration may be overshadowed by the buildup of cIMT over the
lifespan. A study examining older individuals (Nakazaki et al., 2012) did not find age was a significant covariate, but did find sleep duration was a significant covariate. This suggests this relationship may only be present in older individuals, and the age range of the current study was too large to allow for detection of a significant relationship in this subgroup.

The current findings were in agreement with previous studies that found evidence for a relationship between long sleep duration and cIMT (Abe et al., 2011; Ma et al., 2013). These results were consistent with researchers who have found a link between long sleep duration and CVD outcomes (Cappuccio et al., 2010b). Foley (2004) and Grandner, Patel, et al. (2010) suggest there may be different causal mechanisms driving the relationship between long sleep duration and CVD than short sleep duration and CVD, making it important to examine these effects differentially. For example, individuals with longer sleep durations may be more likely to have medical conditions, which confounds the relationship with cIMT (Foley, 2004). Given previous research showing some both long and short sleep could be detrimental to health (Grandner, Hale, et al., 2010), and some previous evidence of a J- or U-shaped relationship (Abe et al., 2011; Ma et al., 2013) between sleep duration and cIMT, the current data should be examined to determine if there is a curvilinear relationship (i.e., both long and short sleeper have higher cIMT than intermediate sleepers).

The current study failed to replicate the Sands et al. (2012) study, which suggested a relationship between short sleep duration and cIMT existed only in the BIF. The current study instead found some evidence for a relationship between long sleep duration and cIMT in the CCA and combined BIF/ICA, but not in the BIF or ICA individually. It is unclear why this may have been, but may be related to the aforementioned curvilinear relationship or inadequate power for these analyses. With regards to power, the largest number of participants (n = 243) had
complete data for the CCA, which is the easiest portion to measure reliably (Dogan et al., 2010a). This made this the highest powered analysis of the study. Additionally, Dogan et al. (2010a) found that individuals for whom cIMT data were incomplete had significantly higher BMI and waist circumference. This finding suggests these missing data may be qualitatively different from cases with complete data, which may have affected the outcome in the ICA and BIF analyses. Further analysis of the different segments of the carotid artery in relation to sleep duration is necessary in order to better understand these findings.

The current study found that the Non-Hispanic Other group had lower levels of cIMT compared to Black and White individuals. To our knowledge, no studies have compared Hispanic or Non-Hispanic Other groups to White and Black groups on cIMT and sleep duration. Sands et al. (2012) also found Black women have higher cIMT than White women and no difference amongst men, whereas Ma et al. (2013) found no differences in cIMT across race. Sands et al. (2012) and Ma et al. (2013) found Black individuals have significantly shorter sleep duration than White individuals. These findings suggest race/ethnicity may play an important role in the relationship between sleep duration and cIMT, and further examination is required.

Sleep Insufficiency and cIMT

The current study found some evidence that sleep insufficiency is a moderator in the relationship between sleep duration and cIMT. A weak relationship was found in the CCA and ICA for this interaction, although the direction was contrary to the proposed hypothesis. For individuals with insufficient sleep (>30m), shorter sleep duration was related to lower cIMT in the CCA and ICA. One possible explanation for this unexpected finding is that short and long sleepers may report sleep insufficiency for different reasons. For example, short sleepers with high sleep insufficiency may believe they need more sleep than they actually receive based on
popular notions of adequate sleep duration. In contrast, long sleepers with high sleep insufficiency may have medical conditions that make them feel sleepy and therefore believe they need more sleep to mitigate that feeling (Grandner, Hale, et al., 2010). The causal mechanism differentiating these groups may also be related to cIMT outcomes. However, the current study was unable to test these explanations, and further examination of this interaction is warranted.

Sleep Duration Assessment Method and cIMT

Most studies examining sleep duration and CVD outcomes use subjective estimates of sleep, but these estimates are not as accurate as objective measures (Lauderdale et al., 2008). As hypothesized, this study provides evidence to suggest sleep assessment method may impact the relationship between sleep duration and cIMT. One previous study found objectively assessed sleep duration had a stronger relationship with cIMT than subjectively assessed sleep duration (Ma et al., 2013). In the current study, significant differences were found between actigraphy and sleep diary in the CCA, BIF, and BIF/ICA. Results suggest in the CCA, there was a difference in magnitude of the relationship, indicating actigraphy assessed sleep duration demonstrates a stronger relationship with cIMT in the CCA than sleep diary assessed sleep duration. In the BIF and BIF/ICA, instead of a difference in magnitude, a difference in directionality of the relationship was demonstrated. Whereas actigraphy assessed sleep duration demonstrated a positive linear relationship with cIMT in these segments, sleep diary assessed sleep duration assessed demonstrated an inverse linear relationship. For actigraphy, longer sleep duration was associated with higher cIMT, and for sleep diary, shorter sleep duration was associated with higher cIMT. Sleep diary is a subjective measure (Lauderdale et al., 2008), which may mean individuals’ perception of their sleep duration, but not the actual amount of sleep obtained, is related to disease outcome for shorter sleepers. In contrast, actigraphy is an objective measure
(Sadeh & Acebo, 2002), which may mean individuals’ actual sleep duration is related to disease outcome for longer sleepers. This gives further support to the view that short and long sleep durations may be related with disease outcome via different mechanisms. No significant differences were found between sleep diary or actigraphy and survey. It is not clear what these nonsignificant findings indicate, but they may be related to low power. Further examination of the differential effects of sleep duration assessment on the relationship between sleep duration and cIMT is warranted.

Limitations

The primary limitation of the current study was that power to detect an effect was low across all analyses. Compared to similar studies, sample size was smaller and demographic heterogeneity (i.e., age, race/ethnicity) was higher which resulted in low power in the current study. For example, for hypothesis 1, the observed power for the relationship between sleep duration on cIMT in the CCA was 0.34, requiring a sample size of 787 to detect an effect. This sample size is comparable to Sands et al ($N = 617$), who found a significant effect of short sleep duration with a similar effect size to the current study (for men in BIF, $\beta = 0.03$; current study in BIF, $\beta = 0.02$). Additionally, the age range in the current study (21-70) may have further limited power to detect an interaction between age and sleep duration, as the relative number of individuals in each decade was fairly small ($n = 60$). Taken together, the sample size and relative heterogeneity of the current sample may have had effects on statistical power that rendered analyses non-significant.

Sleep duration was examined via actigraphy over two nights (Thursday and Friday night), which may not have been representative of an individual’s habitual sleep duration. Although actigraphy is an objective measure, it can only report data for the time during which it was used.
Participants’ typical sleep schedules cannot be thoroughly assessed with only two days of data. Furthermore, combining a weekday and weekend night’s sleep may introduce further error, as sleep durations on weekdays and weekends have been shown to be significantly discrepant (Hale, 2005). Unfortunately, the other measures of sleep in the current study did not provide a methodological advantage—sleep diaries were also utilized for only two days, and single-point retrospective estimates have been shown to have poor correlations with objective data (Lauderdale et al., 2008), and showed no relationship to cIMT in the current study. Using two days of actigraphy data to represent a “typical” sleep schedule is inaccurate and may have impacted statistical power due to increased measurement error.

Although the parent study was a longitudinal design, data for the present study was limited to cross-sectional analyses. It is likely that sleep duration changes across the lifespan commensurate with the demands of a given life stage. For example, an individual who worked 60 hours per week and slept 4 hours per night during young adulthood may sleep 8 hours per night after retirement. A cross-sectional design cannot capture this lifespan variability, which may be an important factor in the prediction of cIMT, and does not allow for the determination of causality. Further examination using longitudinal data is warranted.

Future Directions

Future studies should continue to examine the relationship between sleep duration, sleep insufficiency, and cIMT with consideration for assessment methods. Curvilinear relationships should be assessed, or short and long sleepers should be examined separately as suggested by Grandner, Hale, et al. (2010). Important potential moderators, such as age and race/ethnicity, should be examined in larger samples. Future studies should utilize multiple, rigorous assessment methods in large samples to better understand the nature of the complex relationship between
sleep duration and cIMT. For example, collecting one month of actigraphy and sleep diary data, as opposed to two days, may provide a more accurate assessment of habitual sleep duration. Examination of other sleep variables, such as sleeping medication usage, sleep quality, sleep efficiency, sleep onset latency, or wake after sleep onset may add further depth to findings from the current study. Potential mechanisms driving the relationship between sleep duration and cIMT should also be examined. One avenue for examination may be the impact of differences between subjective perceptions of sleep and objective sleep obtained on cIMT. Finally, future studies will ideally use prospective, longitudinal designs to examine causality in the relationship between sleep duration and cIMT.
### TABLES AND FIGURES

*Studies Used in Meta-Analysis and Systematic Review by Cappuccio (2011), Updated to Include Articles Published since June 2009*

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Cohort</th>
<th>Year of baseline</th>
<th>Sleep category</th>
<th>Total events CHD/stroke/CVD</th>
<th>Age</th>
<th>Quality Score</th>
<th>Exposure assessment</th>
<th>Outcome assessment</th>
<th>Adjusted variables</th>
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<tr>
<td>Qureshi</td>
<td>1997</td>
<td>USA</td>
<td>NHANES I (NHEFS)</td>
<td>1982</td>
<td>&lt;6h</td>
<td>413/285/--</td>
<td>31+</td>
<td>17</td>
<td>Questionnaire</td>
<td>Hospitalizations and death certificates</td>
<td>Age, sex, race, BMI, education, smoking, SBP, cholesterol, diabetes</td>
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<td>Heslop</td>
<td>2002</td>
<td>Scotland</td>
<td>Scottish workplaces</td>
<td>1970-74</td>
<td>&lt;7h</td>
<td>--/--/1182</td>
<td>&lt;66</td>
<td>16</td>
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<td>Death certificate</td>
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<tr>
<td>Mallon</td>
<td>2002</td>
<td>Sweden</td>
<td>County of Dalarna</td>
<td>1983</td>
<td>&lt;6h</td>
<td>71/--/--</td>
<td>45-65</td>
<td>18</td>
<td>Questionnaire</td>
<td>Death certificate</td>
<td>Age, shift work, high cholesterol, BMI, diabetes, hypertension, smoking, snoring, exercise, alcohol consumption, depression, aspirin use, HRT, family history of MI</td>
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<td>Ayas</td>
<td>2003</td>
<td>USA</td>
<td>Nurses’ Health Study</td>
<td>1986</td>
<td>≤5h</td>
<td>934/--/--</td>
<td>40-65</td>
<td>18</td>
<td>Questionnaire</td>
<td>National Death Index plus Medical Records</td>
<td>Age, sex, social class, country origin, smoking, alcohol use, physical activity, self-appraised health status, diabetes, CHD, stroke, congestive heart failure, blood pressure, BMI, serum glucose, creatinine, albumin, total and HDL cholesterol, thiocyanate, plasma homocysteine</td>
</tr>
<tr>
<td>Burazeri</td>
<td>2003</td>
<td>Israel</td>
<td>Kiryat Yovel Community Health Study</td>
<td>1985-88</td>
<td>--</td>
<td>--/--/77</td>
<td>50+</td>
<td>17</td>
<td>Questionnaire</td>
<td>Death certificate</td>
<td>Age, SBP, total cholesterol, BMI, smoking, alcohol consumption, education, marital status</td>
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<tr>
<td>Amagai</td>
<td>2004</td>
<td>Japan</td>
<td>Jichi medical school cohort study</td>
<td>1992-95</td>
<td>&lt;6h</td>
<td>26/34/--</td>
<td>40-69</td>
<td>15</td>
<td>Questionnaire</td>
<td>Death certificate</td>
<td>Age, SBP, total cholesterol, BMI, smoking, alcohol consumption, education, marital status</td>
</tr>
<tr>
<td>Patel</td>
<td>2004</td>
<td>USA</td>
<td>Nurses’ Health Study</td>
<td>1986</td>
<td>≤5h</td>
<td>--/--/1084</td>
<td>30-55</td>
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<td>Questionnaire</td>
<td>National Death Index</td>
<td>Age, smoking, alcohol consumption, physical activity, depression, snoring, BMI, history of cancer, CVD,</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Country</td>
<td>Study</td>
<td>Start-End</td>
<td>≤5h</td>
<td>5h-9h</td>
<td>≥9h</td>
<td>9h-16h</td>
<td>Cases</td>
<td>Controls</td>
<td>Follow-up</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td>---------</td>
<td>-------</td>
<td>----------</td>
<td>-----</td>
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<td>-------</td>
<td>-------</td>
<td>----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Ferrie</td>
<td>2007</td>
<td>England</td>
<td>Whitehall II Study</td>
<td>1985-88</td>
<td>--/--168</td>
<td>35-55</td>
<td>18</td>
<td>Questionnaire</td>
<td>Death certificate</td>
<td>Age, sex, marital status, employment grade, smoking, physical activity, alcohol consumption, self-rated health, BMI, SBP, total cholesterol, physical illness, GHQ, prevalent CHD</td>
<td></td>
</tr>
<tr>
<td>Lan</td>
<td>2007</td>
<td>Taiwan</td>
<td>Survey of Health and Living Status of the Elderly</td>
<td>1993-94</td>
<td>--/--209</td>
<td>64+</td>
<td>17</td>
<td>Questionnaire</td>
<td>Death certificate</td>
<td>Age, marital status, income, smoking, alcohol, BMI, exercise, depression</td>
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<tr>
<td>Meisinger</td>
<td>2007</td>
<td>Germany</td>
<td>MONICA/KORA Augsburg Study</td>
<td>1984-95</td>
<td>--/--170</td>
<td>45-74</td>
<td>17</td>
<td>Questionnaire</td>
<td>Death certificate and coronary event registry</td>
<td>Age, survey, BMI, education, dyslipidemia, alcohol intake, FH of MI, physical activity, smoking, hypertension, diabetes, (menopause in women)</td>
<td></td>
</tr>
<tr>
<td>Chen</td>
<td>2008</td>
<td>USA</td>
<td>Women’s Health Initiative</td>
<td>1994-98</td>
<td>--/1166/50-79</td>
<td>17</td>
<td>Questionnaire</td>
<td>Death certificate or self-reporting</td>
<td>Age, race, socio-economic status, depression, smoking, exercise, hormone replacement, previous CVD, diabetes, hypertension, BMI, high cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ikehara</td>
<td>2009</td>
<td>Japan</td>
<td>JACC study</td>
<td>1988-91</td>
<td>--/--723</td>
<td>40-79</td>
<td>18</td>
<td>Questionnaire</td>
<td>Death certificate</td>
<td>Age, BMI, PH of hypertension, diabetes, alcohol, smoking, education, exercise, employment, mental stress, depression, fresh fish intake</td>
<td></td>
</tr>
<tr>
<td>Stone</td>
<td>2009</td>
<td>USA</td>
<td>SOF study</td>
<td>1993-94</td>
<td>--/--/723</td>
<td>69+</td>
<td>18</td>
<td>Questionnaire</td>
<td>Death certificate</td>
<td>Age, BMI, PH diabetes, Parkinson’s, dementia, COPD, non-skin cancer, osteoarthritis, CVD, hypertension, walks, alcohol use, smoking, depression, cognitive status, estrogen and hypnotic use</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Location</td>
<td>Study Name</td>
<td>Year Range</td>
<td>Hours</td>
<td>Sample Size</td>
<td>Method</td>
<td>Age, Sex, Smoking, Alcohol Consumption, BMI, Physical Activity, SES, Mental Status, Hypertension, Diabetes</td>
<td>BMI, Physical Activity, SES, Mental Status, Hypertension, Diabetes</td>
<td></td>
<td></td>
</tr>
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<td>--------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suzuki</td>
<td>2009</td>
<td>Japan</td>
<td>Shizuoka study</td>
<td>1999</td>
<td>≤5h</td>
<td>--/--184</td>
<td>Questionnaire</td>
<td>National Vital Statistics Database</td>
<td>Addendum: BMI, physical activity, SES, mental status, hypertension, diabetes</td>
<td></td>
<td></td>
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<tr>
<td>Chien</td>
<td>2010</td>
<td>Taiwan</td>
<td>Chin-Shan Community Cardiovascular Cohort Study</td>
<td>1990-95</td>
<td>≤6h</td>
<td>--/--127</td>
<td>Questionnaire</td>
<td>Death certificate, verified by house-to-house visits</td>
<td>Addendum: BMI, smoking, alcohol consumption, marital status, education, occupation, regular exercise, family history of CHD, hypertension, diabetes, cholesterol, HDL, triglyceride, glucose, uric acid</td>
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<td></td>
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<tr>
<td>Sabanayagan</td>
<td>2010</td>
<td>USA</td>
<td>National Health Interview Study (NHIS)</td>
<td>2005</td>
<td>≤5h</td>
<td>--/111/304</td>
<td>Questionnaire</td>
<td>Physician diagnosis (self-report)</td>
<td>Addendum: BMI, smoking, alcohol, physical activity, BMI, diabetes, hypertension, depression</td>
<td></td>
<td></td>
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<tr>
<td>Kronholm</td>
<td>2011</td>
<td>Finland</td>
<td>FINRISK</td>
<td>1972,77</td>
<td>≤5h</td>
<td>--/--748</td>
<td>Questionnaire</td>
<td>National Causes-of-Death register, Hospital Discharge Register</td>
<td>Addendum: Age, marital status, income, social activity, BMI, smoking, total cholesterol, triglycerides, systolic blood pressure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Men and women combined.

bWomen only.

*Quality was not assessed in studies not included in the original publication.

Note: Studies presented after the bolded line were not included in the original publication by Cappuccio (2011) and have been published since June 2009.

Note: BMI = Body Mass Index; SBP = systolic blood pressure; HRT = hormone replacement therapy; MI = myocardial infarction; CHD = coronary heart disease; HDL = high density lipoprotein cholesterol; CVD = cardiovascular disease; GHQ = General Health Questionnaire; FH = family history; PH = patient history; COPD = chronic obstructive pulmonary disease; SES = socio-economic status.
### Table 2

**Examples of Risk Factors’ Relationship with cIMT**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biological</strong></td>
<td>(Spearman’s rank r)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.11</td>
<td>0.11</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>0.16</td>
<td>0.16</td>
</tr>
<tr>
<td>Weight</td>
<td>0.14</td>
<td>0.17</td>
</tr>
<tr>
<td>Waist-to-Hip Ratio</td>
<td>0.14</td>
<td>0.18</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>0.24</td>
<td>0.23</td>
</tr>
<tr>
<td>Low Density Lipoprotein Cholesterol</td>
<td>0.21</td>
<td>0.22</td>
</tr>
<tr>
<td>High Density Lipoprotein Cholesterol</td>
<td>-0.13</td>
<td>-0.11</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.14</td>
<td>0.18</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>0.19</td>
<td>0.19</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>0.23</td>
<td>0.14</td>
</tr>
<tr>
<td>Fasting Insulin</td>
<td>0.16</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Behavioral</strong></td>
<td>(Odds ratio)</td>
<td></td>
</tr>
<tr>
<td>Smoking (Never vs. Current)</td>
<td>2.4</td>
<td>3.7</td>
</tr>
<tr>
<td>Alcohol Use (None vs. Daily)</td>
<td>1.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Exercise (None vs. Frequent)</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Psychosocial</strong></td>
<td>(β)</td>
<td></td>
</tr>
<tr>
<td>Depression*</td>
<td>0.16</td>
<td>0.16</td>
</tr>
</tbody>
</table>

*Sutton-Tyrrell, & Kamarck, 2007; ns = not significant; *indicates data for men and women was not analyzed separately*
Table 3

Characteristics of studies examining relationship between sleep duration and cIMT

| Author      | Year | N    | Sample            | M Age | Gender | Sleep Duration Measure | cIMT Measure                                                                 | Covariates                                                                 | Results                                                                 | Effect size (adjusted) |
|-------------|------|------|-------------------|-------|--------|------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------------------------|------------------------|
| Abe         | 2011 | 2214 | Japanese community | 64.2  | 51.9%  | survey of duration; ordinal response choices | Most severely affected site on R or L side; ≥1.2mm = disease | age, sex, LDL, HDL, TG, FPG, HbA1c, SBP, DBP, BMI, alcohol, smoking | cIMT sig. greater in those with TST >7h; no sig. differences between 5h and 6h. | β: -- | OR: 1.087 | AMD: -- |
| Wolff       | 2008 | 2383 | community         | 61.9  | 48.9  | survey of bedtime, wake time, and nap time | mean far-wall IMT; cIMT > 1.0mm + plaque in ≥2 locations on 1 side or stenosis >50% in 1 side CCA = disease | Age, sex, smoking status, alcohol consumption, physical activity, shift work, socioeconomic factors, body mass index, HDL and LDL cholesterol ratio, previous myocardial infarction, HT | 7-8 hours sleep duration related to sig. lower mean values of cIMT 4-5 hours sleep duration. | β: -- | OR: -- | AMD: 0.038 |
| Nakazaki    | 2012 | 81   | elderly           | 73.6  | 70.9  | Actigraphy; categorized by hour | Mean maximum CCA and ICA IMT | age, gender, race/ethnicity, abdominal height, SBP, anti-HT medications, glucose, LDL and HDL cholesterol, lipid-lowering medication, sleep quality, perceived stress score, depressive symptoms, physical activity, smoking, shift work, second job | U-shaped relationship with <5 or >8h related to higher cIMT. Only for actigraphy, not survey. | β: -0.32 | OR: -- | AMD: -- |
| Ma          | 2013 | 257  | American police officers | 42.2  | 26.1  | Actigraphy; survey of duration; categorized by hour | Mean cIMT and mean maximum cIMT | age, gender, education, BMI, physical activity, smoking, hypertension, dyslipidemia, diabetes, history of CVD, role overload and depression | Nighttime sleep duration not sig. related to cIMT. <7h nighttime sleep duration and <30m napping had higher levels of cIMT compared to people with higher sleep duration, more napping, or both. | β: -- | OR: -- | AMD: 0.022 |
| Schwartz    | 2012 | 126  | American caregivers | 74    | 71.0  | Actigraphy           | Mean far-wall cIMT | age, gender, education, BMI, physical activity, smoking, hypertension, dyslipidemia, diabetes, history of CVD, role overload and depression | Analyses stratified by gender. cIMT sig. greater in men but not women for both mean and maximum cIMT. | β: -0.01 | OR: -- | AMD: -- |
| Sands       | 2012 | 617  | healthy           | 43.4  | 58.0  | Actigraphy           | Mean IMT, mean maximum IMT, segment-specific associations | age, sex, race, BMI, depression, smoking, waist circumference, LDL, HDL, diabetes, SBP, DBP | cIMT. Sig. in bulb, not cIMT. Sig. in bulb, not | β: -0.026 | OR: -- | AMD: 0.001 |

Note: cIMT = carotid intima-media thickness; AMD = adjusted mean difference; LDL = low density lipoprotein cholesterol; HDL = high density lipoprotein cholesterol; TG = triglycerides; FPG = fasting plasma glucose; SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index; PSQI = Pittsburgh Sleep Quality Index; AHI = apnea-hypopnea index; SpO2 = oxygen saturation; SE = sleep efficiency; TST = total sleep time; HT = hypertension; CVD = cardiovascular disease
Table 4

*Characteristics of a Sample of 300 Community Members*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>150 (50.00)</td>
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<tr>
<td>Age, mean (SD)</td>
<td>42.44 (12.76)</td>
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<tr>
<td>Race/Ethnicity, n (%)</td>
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</tr>
<tr>
<td>Non-Hispanic White</td>
<td>180 (60.00)</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>46 (15.30)</td>
</tr>
<tr>
<td>Non-Hispanic Other</td>
<td>17 (5.70)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>57 (19.00)</td>
</tr>
<tr>
<td>Sleep duration (hours), mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Single point retrospective estimate</td>
<td>7.05 (1.44)</td>
</tr>
<tr>
<td>Sleep diary</td>
<td>6.87 (1.60)</td>
</tr>
<tr>
<td>Actigraphy</td>
<td>6.70 (1.13)</td>
</tr>
<tr>
<td>Sleep insufficiency (minutes), mean (SD)</td>
<td>46.90 (81.48)</td>
</tr>
<tr>
<td>Carotid intima media thickness (mm), mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Mean Maximum Far Common Carotid Artery</td>
<td>0.78 (0.14)</td>
</tr>
<tr>
<td>Mean Maximum Bifuraction (BIF)</td>
<td>0.92 (0.20)</td>
</tr>
<tr>
<td>Mean Maximum Internal Carotid Artery (ICA)</td>
<td>0.72 (0.15)</td>
</tr>
<tr>
<td>Mean Maximum BIF/ICA</td>
<td>0.84 (0.17)</td>
</tr>
</tbody>
</table>

*Note: CCA = mean maximum far common carotid artery; BIF = mean maximum bifurcation; ICA = mean maximum internal carotid artery; BIF/ICA = mean maximum bifurcation/internal carotid artery*
Table 5

*Partial Correlations of Potential Covariates with CCA cIMT, Controlling for Sleep Duration*

<table>
<thead>
<tr>
<th>Potential Covariate</th>
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<td><strong>Demographics</strong></td>
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<td>Age</td>
<td>.48**</td>
</tr>
<tr>
<td>Gender</td>
<td>.02</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>.17*</td>
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<tr>
<td><strong>Biological Risk Factors</strong></td>
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<tr>
<td>BMI</td>
<td>.05</td>
</tr>
<tr>
<td>Hypertension</td>
<td>.20*</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>.05</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>.01</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>.21*</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
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</tr>
<tr>
<td>TNF-α</td>
<td>-.01</td>
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<tr>
<td>C-reactive protein</td>
<td>-.07</td>
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<tr>
<td>Interleukin-6</td>
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<tr>
<td><strong>Behavioral</strong></td>
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<tr>
<td>Smoking</td>
<td>-.19*</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>.06</td>
</tr>
<tr>
<td>Alcohol Use</td>
<td>-.13*</td>
</tr>
<tr>
<td><strong>Sleep</strong></td>
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</tr>
<tr>
<td>Sleep Apnea Risk</td>
<td>.06</td>
</tr>
<tr>
<td>Sleep Medication Use</td>
<td>.06</td>
</tr>
<tr>
<td>Insomnia Symptoms</td>
<td>-.10</td>
</tr>
</tbody>
</table>

Note: cIMT = carotid intima-media thickness; CCA = common carotid artery; BMI = body mass index; BP = blood pressure; LDL = low density lipoprotein cholesterol; TNF-α = tumor necrosis factor alpha.

Note: *$p < .05$; **$p < .001$
### Table 6

*Results of Hierarchical Linear Regression to Test Relationship between Sleep Duration and Covariates with Carotid Intima-Media Thickness*

<table>
<thead>
<tr>
<th></th>
<th>CCA</th>
<th></th>
<th>BIF</th>
<th></th>
<th>ICA</th>
<th></th>
<th>BIF/ICA</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE B</td>
<td>β</td>
<td>B</td>
<td>SE B</td>
<td>β</td>
<td>B</td>
<td>SE B</td>
</tr>
<tr>
<td>Model 1</td>
<td>0.00</td>
<td>0.00</td>
<td>0.19*</td>
<td>0.00</td>
<td>0.00</td>
<td>0.13</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.00</td>
<td>0.00</td>
<td>0.11</td>
<td>0.00</td>
<td>0.00</td>
<td>0.02</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Model 1 – Unadjusted.  
Model 2 – Adjusted for age, gender, and race/ethnicity.  
*Note: * $p < .05$  
*Note: CCA = mean maximum far common carotid artery; BIF = mean maximum bifurcation; ICA = mean maximum internal carotid artery; BIF/ICA = mean maximum bifurcation/internal carotid artery*
Table 7

*Results of Hierarchical Linear Regression to Test Relationship between Sleep Duration, Insufficient Sleep, the Interaction, and Covariates with Carotid Intima-Media Thickness*

<table>
<thead>
<tr>
<th></th>
<th>CCA</th>
<th>BIF</th>
<th>ICA</th>
<th>BIF/ICA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE B</td>
<td>β</td>
<td>B</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Duration</td>
<td>0.00</td>
<td>0.00</td>
<td>0.12</td>
<td>0.00</td>
</tr>
<tr>
<td>Insufficient Sleep</td>
<td>0.00</td>
<td>0.00</td>
<td>0.10</td>
<td>0.00</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Duration</td>
<td>0.00</td>
<td>0.00</td>
<td>0.12</td>
<td>0.00</td>
</tr>
<tr>
<td>Insufficient Sleep</td>
<td>0.00</td>
<td>0.00</td>
<td>0.07</td>
<td>0.00</td>
</tr>
<tr>
<td>Interaction</td>
<td>0.00</td>
<td>0.00</td>
<td>0.15*</td>
<td>0.00</td>
</tr>
<tr>
<td>Model 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep Duration</td>
<td>0.00</td>
<td>0.00</td>
<td>0.08</td>
<td>0.00</td>
</tr>
<tr>
<td>Insufficient Sleep</td>
<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
<td>0.00</td>
</tr>
<tr>
<td>Interaction</td>
<td>0.00</td>
<td>0.00</td>
<td>0.10</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Model 1 – Sleep duration and insufficient sleep (unadjusted).
Model 2 – Adjusted for interaction between sleep duration and insufficient sleep.
Model 3 – Adjusted for covariate added in Model 2 and age, gender, and race/ethnicity.
Note: CCA = mean maximum far common carotid artery; BIF = mean maximum bifurcation; ICA = mean maximum internal carotid artery; BIF/ICA = mean maximum bifurcation/internal carotid artery
*Note: *p < .05, **p < .001
Table 8

*Correlations of Sleep Duration Assessed by Survey, Sleep Diary, and Actigraphy with cIMT*

<table>
<thead>
<tr>
<th></th>
<th>CCA</th>
<th>BIF</th>
<th>ICA</th>
<th>BIF/ICA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survey</td>
<td>0.04</td>
<td>-0.02</td>
<td>0.09</td>
<td>0.01</td>
</tr>
<tr>
<td>Sleep Diary</td>
<td>0.05</td>
<td>-0.14*</td>
<td>-0.03</td>
<td>-0.12</td>
</tr>
<tr>
<td>Actigraphy</td>
<td>0.19**</td>
<td>0.13</td>
<td>0.10</td>
<td>0.14</td>
</tr>
</tbody>
</table>

*Note: *p < .05; **p < .001

*Note: CCA = mean maximum far common carotid artery; BIF = mean maximum bifurcation; ICA = mean maximum internal carotid artery; BIF/ICA = mean maximum bifurcation/internal carotid artery*
Table 9

*Comparisons between Magnitude of Sleep Duration Assessment Methods’ Relationships with cIMT*

<table>
<thead>
<tr>
<th></th>
<th>CCA</th>
<th>BIF</th>
<th>ICA</th>
<th>BIF/ICA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Z</td>
<td>p</td>
<td>Z</td>
<td>p</td>
</tr>
<tr>
<td>Actigraphy and Survey</td>
<td>-1.96</td>
<td>.050</td>
<td>-1.88</td>
<td>.061</td>
</tr>
<tr>
<td>Sleep Diary and Survey</td>
<td>-0.12</td>
<td>.903</td>
<td>1.42</td>
<td>.156</td>
</tr>
<tr>
<td>Actigraphy and Sleep Diary</td>
<td>-2.03</td>
<td>.042</td>
<td>-3.80</td>
<td>.000</td>
</tr>
</tbody>
</table>

*Note: CCA = mean maximum far common carotid artery; BIF = mean maximum bifurcation; ICA = mean maximum internal carotid artery; BIF/ICA = mean maximum bifurcation/internal carotid artery*
Figure 1. Diagram of carotid artery.

Note: CCA = mean maximum far common carotid artery; BIF = mean maximum bifurcation; ICA = mean maximum internal carotid artery
Figure 2. Relationship between age and carotid intima media thickness for each segment.
Figure 3. Differences in mean maximum carotid intima media thickness in the common carotid artery by race/ethnicity.
Figure 4. Interactions between sleep duration, sleep insufficiency, and cIMT in two segments.
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