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Literature review: The role of inflammatory biomarkers in the connections between sleep and chronic health conditions

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LITERATURE REVIEW: THE ROLE OF INFLAMMATORY BIOMARKERS IN THE CONNECTIONS BETWEEN SLEEP AND CHRONIC HEALTH CONDITIONS

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Introduction

Decades of research has shown that sleep plays a vital role in our health, and disruptions in sleep can have long term detrimental effects on our lives (Yoo, 2007). The recommended amount of sleep by the National Sleep Foundation (NSF) for adults is between 7-9 hours each night (NSF, 2020). It is common knowledge that too few hours of sleep are unhealthy, but scientists are only beginning to understand the mechanisms that explain the connections between sleep patterns and health outcomes (CDC, 2011). Additionally, recent research has shown that excess sleep can be just as detrimental, if not more, to health outcomes (Patel, 2009). One of the reasons that poor sleep can be a negative consequence for health is because sleep disruptions can lead to inflammation (Patel, 2009). Inflammation is often a positive event that is occurring in the body because it signifies that the body is healing. When a person gets a cut, the area around the wound becomes inflamed because inflammatory biomarkers are being called to the area to promote repair. However, too much inflammation can have negative consequences. If a person is consistently getting poor sleep, then their body believes that it is constantly needing repair. This activates the immune system and the previously mentioned inflammatory biomarkers are called to respond (Mullington, 2010). These biomarkers, which normally help to heal areas of damage, might cause the immune system to attack areas of healthy tissue, therefore causing damage rather than repairing damage. Therefore, it is important to understand how this affects chronic health. Chronic disease and inflammatory processes often coincide. When a patient has a chronic health condition, their immune system is activated and is sending inflammatory biomarkers to respond (Laveti, 2013). However, the question of whether the elevated levels of biomarkers are a side effect of the chronic disease or a cause of the disease is unknown. If it is a cause, then it is possible that poor sleep resulting in high levels of biomarkers could lead to chronic disease. In

the current review, research on the effects of inflammatory biomarkers that are elevated as a result of sleep is examined as well as the role that these biomarkers play in the increased risk for chronic health diseases.

Review of Literature

To begin this review, it is necessary to understand the process of inflammation and the role it plays in the body. The three biomarkers that will be discussed all have their own functions during the inflammatory response, and in order to evaluate the effect that they have on sleep and chronic disease, these jobs need to be fully understood. Once the biomarkers are discussed, the relationship that they have with sleep will be discussed. There are many aspects of sleep to examine including sleep duration, sleep efficiency, and sleep disorders. Research has shown that sleep impacts biomarker levels, but it needs to be further examined to determine how this can affect chronic disease (Patel, 2009). Chronic health issues are associated with inflammatory biomarkers, but this relationship will be discussed further in order to determine the process through which sleep predicts chronic health conditions via inflammatory biomarkers (Laveti, 2013). At the end of this review, the relationship between these three variables, sleep, inflammatory biomarkers, and chronic health disease, will be discussed.

Inflammatory Biomarkers

Inflammation is the body's reaction to invasion or infection. If either event occurs, the body signals the immune system to repair damaged tissue (Szalay, 2019). Cytokines are the actual components that signal the immune system to respond in a specific area of the body that is being invaded. They are involved in cell signaling and ultimately leave a chemical trail, leading the different molecules involved in healing to the area of injury (Black, 2004). When cytokines are elevated, this indicates that the body's immune system has been triggered, and there is

inflammation occurring somewhere in the body. Numerous cytokines are being studied regarding their relationship to chronic inflammation and sleep. The current review focuses on the inflammatory biomarkers, C-Reactive Protein (CRP), Interleukin-6 (IL-6), and Tumor Necrosis Factor-alpha (TNF-α) since prior literature has emphasized their connections with sleep issues and chronic health outcomes.

C-Reactive Protein

One crucial inflammatory biomarker is C-reactive protein. CRP is a plasma protein that is actively involved in the body's systemic response to inflammation. Many inflammatory biomarkers have multiple effects as a result of a single gene and this includes CRP because it has both proinflammatory and anti-inflammatory effects (Black, 2004). CRP affects inflammation through the role it plays in the complement system, which is a pathway that causes inflammation to occur (Black, 2004). CRP can mediate the pathway by binding to specific carbohydrates. This leads to the release of proinflammatory cytokines which as mentioned earlier, attract white blood cells to the area that requires healing. When CRP binds to the carbohydrate it causes opsonization of the target cell. Opsonization is the process by which a cell is coated so that macrophages, a type of white blood cell, can easily engulf and break down the cell through the process called phagocytosis. Phagocytosis is then upregulated meaning macrophages ingest foreign particles and remove them from the cell tissue (Black, 2004). This then causes an elevation in serum levels, therefore indicating the occurrence of an inflammatory response.

With each acute inflammation stimulus, the plasma level of CRP may rise as much as 1000-fold and more (Black, 2004). These CRP levels are used as a test by medical professionals in order to predict a patient's risk of developing cardiovascular disease in the future. According to the American Heart Association, CRP tests are beneficial in predicting the risk of patients who

have a 5-10% chance of having a heart attack in the next ten years (Mayo Clinic, 2017). This test is also used to predict risk of having a second heart attack in patients who have already experienced their first heart attack. Studies have found that CRP levels also have a strong positive correlation with body mass index (BMI) a common risk factor for cardiovascular disease(Pepys & Hirschfield, 2003). Regarding its relationship to other relevant cytokines, CRP production in the liver is regulated by IL-6 (Black, 2004). An increase in CRP leads to an increase in other biomarkers as well, such as IL-6 and TNF-α levels.

Interleukin-6

A second cytokine that plays a significant role in the inflammatory process is interleukin-6, or IL-6. IL-6 attracts white blood cells to the area that needs healing during inflammation and promotes accumulation of these cells (Barnes, 2011). White blood cells are agents of the immune system that respond to and fight off infection in order to protect the body. IL-6 also promotes B-cell activity meaning that additional antibodies are produced in the body to help fight off foreign invaders (Barnes, 2011). B-cells are a specific branch of white blood cells that are created to produce antibodies. IL-6 not only affects B-cells, but it affects T-cells, another type of white blood cell. T-cells target and destroy abnormal cells in the body and typically require strict regulation in order to limit the number of cells they kill. However, IL-6 rescues T-cells from cell death, or apoptosis (Barnes, 2011). If T-cells are not being readily destroyed, then they can turn to healthy cells to attack. Therefore, it is suspected that IL-6 is involved in autoimmune diseases because they increase the number of T-cells in our bodies (Barnes, 2011). IL-6 is also considered one of the “chief stimulators” in the production of acute-phase proteins, which are the plasma proteins whose concentrations vary during acute inflammatory responses (Gabay, 2006). Acute inflammation is inflammation that is temporary, for example when a person falls and scrapes

their knee. Chronic inflammation, on the other hand, is inflammation that is long term and present throughout a person's life. The main switch from acute inflammation to chronic inflammation is the recruitment of monocytes, a type of white blood cell, to the area of injury (Gabay, 2006). The recruitment of monocytes is one of the functions of IL-6 and therefore, IL-6 is thought to be the key player in the transition from acute inflammation to chronic inflammation. During chronic inflammation, IL-6 then induces an innate immune response to affected cells and an adaptive immune response directed against reinfection (Gabay, 2006). Innate immune responses are the responses that every person has at birth (NCBI, 2016). It is our natural response to foreign invaders. Adaptive immune response is the response that is saved after the initial exposure, so that our body knows how best to fight off infection when re-exposed at a later point in life (NCBI, 2016). Overall, IL-6 has been shown to be positively associated with inflammation in the body, and its serum levels could be used to indicate related chronic diseases. As mentioned previously, the other type of inflammatory biomarker affected by CRP is TNF-α.

Tumor Necrosis Factor-alpha

Tumor Necrosis Factor-alpha (TNF-α) is another biomarker that plays a vital role in the process of inflammation. It was initially discovered for its antitumor activity but is now known to be an inflammatory mediator (Sethi & Aggarwal, 2008). It is a protein that is produced by white blood cells and eventually leads to the activation of other inflammatory genes (Popa, 2007). It is considered the most abundant early mediator at the site of injury and is the "master regulator" in pro-inflammatory cytokine production (Parameswaran & Patial, 2010). TNF-α is produced by both monocytes and macrophages, and as it is produced, it activates other macrophages (Parameswaran & Patial, 2010). If there are high levels of TNF-α, then it is known that there has been an activation of inflammation. Other studies report that TNF-α induces changes in both

lipid and glucose metabolism. It has inhibitory effects on insulin receptors, which can lead to diabetes, a risk factor for heart disease (Popa, 2007). It has also been shown to contribute to atherosclerosis for numerous reasons including recruitment and activation of white blood cells and other inflammatory molecules, promoting the expression of different adhesion molecules in vessel walls, and causing an inflammatory cascade inside arterial walls (Popa, 2007). TNF-α clearly plays a major role in the activation and regulation of inflammation, and several factors point to the suspicion that it can indicate cardiovascular risk factors and disease.

Each of these three inflammatory biomarkers are a result of chronic inflammation. If the biomarkers are elevated in the body, then this means that the body's defense mechanism, white blood cells, are being called to an area to destroy infection or invaders. If there are no obvious foreigners, then it is thought that the white blood cells turn to healthy cell tissue and work to destroy it (Szalay, 2019). Sleep deprivation is thought to be one of the inducers of these biomarkers, therefore attracting of white blood cells over long periods of time (Trott et. al., 2012). This ultimately affects the overall health of an individual and can increase the risk of chronic diseases.

Sleep Duration, Quality, and Disorders and the Relationship to Inflammatory Biomarkers

Sleep disruptions are examined in terms of sleep duration, quality, and disorders. Recent research suggests that both acute and ongoing sleep disruptions have a negative impact on one's health in the short term and in terms of long term outcomes as indicated by increased risk for obesity, coronary artery disease, diabetes, and mortality (Patel, 2009). One commonly used method is polysomnography, which assess brain electrical activity, airflow, respiratory effort, and other physiological measures to determine sleep patterns. Commonly used indicators of sleep quality from polysomnography recordings include sleep onset latency (or the amount of

time it takes a person to fall asleep), the number of wake episodes a person experiences throughout the night, and how long those wake episodes are. These can impact the efficiency of a person's sleep each night. Sleep efficiency is defined as the ratio of total sleep time to total time in bed (Reed & Sacco, 2016). Total sleep time is the time spent sleeping as opposed to the time spent watching TV, looking on one's phone, reading, etc. (Reed & Sacco, 2016). Another way that sleep duration is commonly assessed is by using self-reported habitual sleep time (Reed & Sacco, 2016). This method is less reliable than a polysomnography due to the influence of social desirability bias and fallibility of human memory. Additionally, people may overestimate or underestimate their self-reported sleep patterns (Lauderdale, 2008). While many people may experience a low sleep efficiency or poor duration of sleep on its own, sleep disorders can also cause issues in these two areas.

Duration and quality of sleep are disrupted by sleep disorders which is defined as any condition that changes the way you sleep and has an overall negative impact on your health (Mayo Clinic, 2019). Insomnia is one of the most common sleeping disorders (Basta, 2007). Statistics show that 25-33% of the population complains of difficulty falling asleep or difficulty staying asleep and around 10% complain of this being a chronic issue. Insomnia is often not discussed in society today and it is found that somewhere around 60% of all insomniacs do not seek medical assistance (Basta, 2007). Because of the lack of treatment, insomnia has large implications on public health.

Another sleeping disorder that may be associated with cardiovascular disease and mortality risk and is obstructive sleep apnea (Motamedi et.al., 2009). Sleep apnea is when a person's sleep is disturbed multiple times during the night due to an obstruction in respiration often due to the collapse of the nasal passageway. It is estimated that 20% of all adults have a

mild form of sleep apnea and 7% of the population have moderate or severe symptoms (Motamedi et.al., 2009). When sleep apnea occurs, it interrupts the sleep cycle leading to fragmented sleep wherein the patient may experience apnea (complete cessation of breathing) or hypopnea (partial cessation of breathing) for more than 30 times an hour in cases of severe apnea (Ruehland, 2009).

Restless Leg Syndrome is another sleep disorder that may be related to chronic disease. Patients with restless leg syndrome experience an urge to move their legs while at rest, particularly at night (Trott et. al., 2012). This disrupts sleep patterns and is suspected to be associated with elevated inflammatory markers. The final sleep disorder that will be discussed is nightmare disorder which is defined as the repeated occurrence of nightmares that cause distress and cannot be attributed to another mental health disorder or substance use (American Psychiatric Association, 2017). Nightmares occur during REM sleep and are generally associated with symptoms of physical arousal. Nightmares often lead to awakenings, but this is not required to be diagnosed with a nightmare disorder. A nightmare sleep disorder is recognized as having one or more episodes per week lasting one to six months (Gieselmann et.al., 2019). It is suggested that these sleep disorders indicate a higher risk for future chronic conditions due to the disruption of sleep and the effect it has on inflammatory biomarkers such as C-reactive protein, Interleukin-6, and Tumor Necrosis Factor-α.

Several studies involving sleep duration, sleep quality, and sleep disorders, many of which resulted in elevated CRP, IL-6, and TNF- α and are summarized in Table 1. In studies looking at sleep duration, whether it be above or below the recommended amount of sleep, it was often found that there was elevated CRP (See Table 1). One study noted a U-shaped curve in results with CRP spiking at greater than 9 hours of sleep and less than 5 hours of sleep

(Grandner, 2013). However, one interesting finding in this study was that women tended to have elevated CRP with greater than 9 hours of sleep and men tended to have elevated CRP with less than 5 hours of sleep. Averaging these results among the overall population resulted in the U-shaped curve but splitting by gender resulted in only one end of the spectrum showing elevation in CRP levels. Patel's study (2009) found similar results with elevated CRP secondary to sleep that was greater than 9 hours. They also found elevations in IL-6 with long durations of sleep while TNF-α in participants who had shortened sleep duration (Patel, 2009). Shearer and colleagues (2001) studied participants' levels of IL-6 and TNF-α and found increased levels with sleep loss. Similar to this, another study showed elevated CRP levels with sleep loss (Meier-Ewert, 2004). Overall, most studies generally agree with the findings that any amount of sleep outside the usual 6-9 hours can lead to increased cytokine levels in the blood (see Table 1). However, there have been a couple of studies that have found contradicting results as well. Frey's results showed that there were decreased levels of CRP and IL-6 when participants suffered from sleep deprivation, however they did note several other inflammatory biomarkers were elevated instead (2007).

Sleep quality may also be a factor that is associated with increased inflammatory biomarker levels as shown in Table 1One study examined social connections and sleep efficiency and how that impacted levels of IL-6 (Friedman, 2005). Social connections and sleep efficiency were measured using a self-report survey and the participants were also given a health assessment by a professional (Friedman, 2005). This study found that women with good social connections and good sleep efficiency had relatively low levels of IL-6 whereas women with poor social connections and poor sleep efficiency had noticeably higher levels of IL-6 (Friedman, 2005). Women with some combination of the two options had similarly low levels of

IL-6 as those who had both good social connections and good sleep efficiency (Friedman, 2005). Additionally, studies observed sleep quality using an electroencephalogram to measure brain waves and determine which stages of sleep the participant was experiencing (Hong, 2005). Poor sleep included several episodes of disrupted sleep and complaints of fatigue the following morning. They found that patients with lower sleep efficiency had higher levels of IL-6 the following morning than those patients with higher sleep efficiency (Hong, 2005). Both studies found elevated levels with decreased sleep efficiency. Although one would expect that Friedman's study would find elevated levels with those participants with poor sleep efficiency and good social connections rather than only those who were rated as poor in both categories. This could be unreliable information, meaning that the results are not scientifically correct, as it is very difficult to measure one's own sleep quality. Hong's study (2005) was able to measure sleep efficiency using an EEG as well as self-report.

Most research on the associations between sleep and inflammatory biomarkers focuses on several sleeping disorders including sleep apnea, insomnia, restless leg syndrome, and more. Razhegi (2011) conducted a broader study that focused on insomnia, restless leg syndrome, nightmares, narcolepsy, sleep apnea, and sleepwalking in dialysis patients. They used dialysis patients because they had noticed a pattern of sleep disorders among that group. When comparing CRP levels to those of a control group, the researchers found a notable elevation (Razhegi, 2011). One study with a particular focus on sleep apnea found that CRP levels were elevated in children who struggle with sleep apnea, and it was particularly high in those that complained of sleepiness and fatigue the following morning (Tauman, 2004). Another similar study found elevated levels of IL-6 and TNF-α in adult males with obstructive sleep apnea as compared to the control and they concluded that this could provide evidence that there is a

correlation to cardiovascular comorbidities (Ciftci, 2004). Other disorders besides sleep apnea have also been studied such as insomnia. Burgos and colleagues in 2005 used polysomnography to study patients with primary insomnia several days in a row. They measured serum levels of IL-6 during the evening and late at night and compared these serum levels to patients without any sleeping disorders. Their results showed a noticeable elevation of IL-6 levels in patients with primary insomnia (Burgos, 2005). On the other hand, patients with restless leg syndrome were found to have no correlating IL-6 or TNF-α levels, but elevated CRP levels were observed (Trotti et. al., 2012). Elevated cytokine levels were found in many research studies, not just those that were mentioned. Most provide support towards the theory that sleep does affect inflammation and poor sleep patterns could lead to a rise in inflammatory biomarkers (see Table 1). Several studies have shown that factors such as sleep duration, sleep quality, and various sleep disorders can all lead to this elevation. The question at hand is whether this elevation in biomarker levels can further lead to things such as chronic diseases.

Chronic Health Outcomes

Disease can be classified into two main categories, acute versus chronic. The current review focuses primarily on chronic disease and how it relates to increased inflammatory markers. Chronic disease is any disease or illness that is long developing and ongoing whereas acute disease is a sudden onset episode. Frequently, in case of chronic disease, patients will experience an acute exacerbation of symptoms that can be life-threatening. Patients with chronic diseases tend to have elevated inflammatory markers over extended periods because the body is undergoing stress from their disease, and their immune system is on constant overdrive (Pahwa, 2019). This elevation of inflammatory biomarkers can have severe consequences on a person's overall health and may lead to health problems such as cardiovascular disease and strokes.

Cardiovascular Disease (CVD)

The leading cause of death in the United States today is cardiovascular disease. Cardiovascular disease includes any issues with the heart such as heart attacks, coronary artery disease, congestive heart failure, arrhythmias, and heart valve problems (American Heart Association, 2014). Cardiovascular disease leads to damage to the heart which in turn triggers an immune response causing white blood cells to attack cardiac muscle (Ludwig-Maximilians-Universität München, 2017). One factor linked to cardiovascular disease is an increased level of cytokines such as IL-6, TNF-α, and CRP. These inflammatory biomarkers have proinflammatory, procoagulant (promotion of blood clotting), and growth promoting effects. They are produced directly in the arterial wall when elevated due to factors such as smoking and alcohol consumption (Mendall, 1997). TNF-α has been found to be associated with body mass index (BMI) which is also a common cardiac risk factor (Mendall, 1997). Another study suggested that CRP may be a more significant biological risk factor of heart disease than cholesterol as previously believed (Notarangelo, 2017). In order to develop heart disease, cholesterol first must be modified before it leads to plaque formation on the arterial walls. The plaque is recognized as a "foreign body" and the immune system is then triggered, sending out inflammatory biomarkers such as CRP to respond to the attack (Notarangelo, 2017). Elevation of these inflammatory biomarkers can destroy the cell wall as it attacks the plaque and cholesterol, and this causes damage to the blood vessels creating an increased risk for heart attacks (Notarangelo, 2017). This implies a positive correlation between elevated inflammatory biomarkers and cardiovascular disease.

When looking deeper into studies, the correlation becomes more apparent, particularly with CRP. Table 2 summarizes trends of several studies that found relationships between

elevated CRP levels in patients either before or after experiencing a stroke or a cardiovascular issue such as coronary artery disease, acute coronary syndrome, myocardial infarction, or angina. Biasucci (2004) noted in their study of patients at the time of admission to the coronary unit in the hospital that there was a relationship between elevated IL-6 and elevated CRP, thus confirming the relevance of cytokine influence on the prognosis of unstable angina. They also reported that medications used to treat acute coronary syndrome were found to be most effective for lowering cardiac risk in patients who initially had high CRP levels (Biasucci, 2004). Another study analyzed a larger pool of patients who have already had experiences with CVD and noted that CRP blood levels showed consistent associations in those patients, although it was unclear as to the exact relationship between CVD and CRP elevation (Kaptoge, 2010).

Similar studies also found elevations in IL-6 and TNF-α to patients who have experienced a cardiovascular event (See Table 2). IL-6 was associated with increased atherosclerosis, which occurs when fatty plaque is deposited inside the artery walls (Kato, 2002). This is consistent with the discussion of the effect that IL-6 has on the development of CVD since atherosclerosis causes vessel diameter to decrease and eventually leads to CVD (Mayo Clinic, 2018). Because IL-6 increases as plaque buildup increases in the vessel walls, IL-6 could be an indicator of oncoming cardiac disease. As for TNF-α, studies have shown that the presence it has in cardiac tissue suggests that it plays a role in the pathogenesis of cardiomyopathy, thus possibly being another indicator of CVD (Habib, 1996). Because these studies generally follow up on patients after a CVD event has occurred, it is difficult to conclude that these mentioned biomarkers affect the body which eventually leads to CVD or whether they are just signs that the body has had damage from the disease. In other words, do the elevated biomarkers cause the

disease or does CVD cause the elevated biomarkers due to the amount of stress and repair it is undergoing?

While these particular reports studied patients only after they have experienced CVD, longitudinal studies have also been done in order to examine change over time. One group of researchers performed a longitudinal study over the course of 17 years on high risk, but healthy patients with follow-ups to look for death or myocardial infarctions (Kuller, 1996). They found a significant correlation between those patients with both elevated CRP and later developing CVD (Kuller, 1996). This study stood out since they focused on outcomes over an extended period and for following CRP levels prior to a heart attack or cardiovascular problem leading to death. Other factors were also accounted for in order to rule out the risk factors as being the only cause. For example, they found that CRP was notably elevated in smokers, even after accounting for the different factors that could affect their risk, such as the number of cigarettes per day or how long they have been a smoker (Kuller, 1996). This was again shown in another pre-CVD study as well as involving IL-6. This study was broad and observed the interleukin levels in over 14,000 men who were considered healthy. The patients who eventually had myocardial infarctions were observed to have increased IL-6 (Ridker, 2000). In addition to CVD, another health problem that is affected by chronic inflammation is a cerebrovascular accident.

Strokes

A cerebrovascular accident, commonly known as a stroke, occurs when there is a lack of blood flow to the brain which causes active ischemia to cranial tissue. This is typically caused by a blocked vessel that supplies blood to the brain or by bleeding in the brain. Sleep is commonly believed to be a predictor of stroke risk. Studies have shown that short amounts of sleep increased risk by 18% while extended amounts of sleep increased the risk of stroke by 46% after

accounting for cardiovascular risk factors and comorbidities (Leng 2018). This risk is nearly twice the risk of a patient receiving the proper amount of sleep each night. In addition to these findings, there is also an association between patients who experience chronic inflammatory diseases such as systemic lupus erythematosus and rheumatoid arthritis, and those who experience strokes (Kamel & Iadecola, 2017). Patients who have these inflammatory illnesses have a significantly increased risk of having a stroke as compared to those with the common risk factors (Kamel & Iadecola, 2017). This raises the question of whether elevated inflammatory biomarkers such as CRP, IL-6, and TNF-α have implications for increased risk for having a stroke.

After analyzing several studies, a similar pattern was found between cytokine levels and strokes as was found with CVD (see Table 2). For example, Tancin Lambert and colleagues (2020) studied stroke patients with atrial fibrillation. This condition is a major risk factor for having a stroke, and they found that there were numerous cytokines that were associated with atrial fibrillation. They determined that there was a strong possibility that IL-6 could be very useful in identifying atrial fibrillation in patients which relates to strokes since almost a quarter of all strokes are related to atrial fibrillation (American Heart Association, 2017). Reports that studied TNF-α also examined risk factors of strokes and the TNF-α showing a positive association with typical risk factors such as cholesterol, blood pressure, age, smoking, and BMI (Cui, 2012). In demonstrating the relationship between these biomarkers and common risk factors, it becomes more evident that there could be an association between elevated biomarkers and the prognosis of strokes. However, risk factors were not the only aspect examined; patients with strokes were studied as well. Whiteley completed a three-year study from 2002-2005 involving follow-ups with patients post-stroke in order to test for CRP and IL-6 levels in the

blood as well as the outcomes of the cases. It was found that elevated levels were associated with poor outcomes later in life, although they could not determine a model to predict recurrent strokes or outcomes (Whiteley, 2005). Several other studies showed results consistent with these outcomes, as seen in Table 1.

Overall, it is clear that there is an association between inflammatory biomarkers and chronic health outcomes, but a definite relationship cannot be established for several reasons. Multiple studies addressed their limitations, but in many cases the limitations impede the findings. Many studies had very small sample sizes due to the availability of patients or difficulty recruiting patients. Without larger sample sizes, results may be affected due to increased margin of error and decreased representation of the population. Even in those studies that had large sample sizes, problems with causation versus correlation were apparent. Many studies only included patients after they have experienced an acute health crisis. By that point most of them already had elevated biomarker levels, and it cannot be determined whether the biomarkers were elevated prior to the event or after the event. This is due to not being able to accurately predict the who, what, or when of a health crisis. When you are unsure if someone will eventually have a stroke, it is difficult to collect data. Some research addressed both issues and included large sample sizes as well as using longitudinal studies of high-risk patients who may or may not develop CVD or stroke. However, even with these studies it can be challenging to show that the inflammatory biomarkers are elevated because the patient is about to have an acute crisis or if they are elevated for some other reason in the body such as hypertension or high cholesterol which are risk factors of many chronic health problems. There is a positive correlation between inflammation and chronic disease, although determining whether there is a causal effect would require more research to be done. Also, due to ethical concerns with conducting experiments for

high risk factors, the effect of inflammation on chronic disease cannot be easily examined since researchers cannot experimentally manipulate these variables. This correlation can be related back to the discussion of sleep and its impact on inflammation. Poor sleep can lead to an elevation of inflammatory biomarkers in the body and having these biomarkers being elevated chronically may lead to the development of chronic health disease.

Conclusion

Based on prior research on the relationship between sleep and inflammatory biomarker levels as well as between chronic health disease and inflammatory biomarker levels, several conclusions may be drawn. When first examining the effects of sleep on inflammation, it can be concluded that several factors leading to an unusual amount of sleep, or to disturbed sleep, causing the body to respond by signaling the release of inflammatory markers. Studies have consistently found elevations in CRP, IL-6, and TNF-α when sleep duration was altered, sleep quality was decreased, or in patients with several different sleep disorders. If a person is consistently experiencing these different effects, then the body will also continuously be experiencing an inflammatory response. As mentioned earlier, the release of these biomarkers can be beneficial when there is a need for repair and healing in the body. However, when there is no need for inflammation, these biomarkers have no specific location to go to, and they will spread out and begin attacking healthy tissue, which will have negative consequences on the body.

When looking at the effects of inflammation on chronic disease, it becomes more challenging to make a definitive conclusion. While many studies point towards an association between the two, most are unable to establish a clear causal connection due to ethical reasons since inflammation cannot be experimental manipulated in experimental settings. In many

studies, it is undetermined whether the inflammation levels came first and caused the chronic disease or worsened chronic disease or whether the chronic health disease is causing inflammation to increase inside the body. In order to determine this, more experimental longitudinal studies need to be conducted. If researchers can begin by looking at inflammatory biomarker levels in patients throughout their lifetime, they will be able to see how these levels are affected before and after they develop chronic disease and compare these results to patients experiencing similar problems. The challenge with this is that not only does it take time to conduct longitudinal studies, but it is also difficult to control factors that may cause different reactions in patients, such as stress levels, careers, living locations, etc. Without being able to control these factors, it may never be known definitively whether the elevated cytokine levels are increasing the risk of chronic diseases or if other factors that lead to chronic disease.

Although it can be established that sleep does impact levels of inflammatory biomarkers in the body, it is difficult to say whether those elevated biomarkers do lead to chronic diseases. There is still a lack of clarity that this very well could be the case due to the handful of longitudinal studies done regarding chronic disease and biomarker levels. These studies, as mentioned earlier, have found that there is a positive association between the two variables, and this could potentially indicate that chronically elevated biomarkers may increase the risk of developing chronic disease later in life. Because the biomarkers are elevated, this means that the body's immune system is active. However, when there is no apparent reason for it to be active, the body is attacking cells that do not need to be destroyed. As a result, this attack can lead to the destruction of vessels and tissue that is vital to keep intact in order to stay in good health. Sleep changes may predict an increase in inflammatory biomarker levels, but the question at hand is whether this, in turn, increases the risk of developing chronic diseases. While this does seem to

be the cause, more research needs to be conducted about the causal effect between inflammatory biomarkers and chronic health problems to confidently come to this conclusion. Until there is extensive research in this area, it cannot be confirmed that the lack of quality sleep can lead to chronic diseases. Although a definitive relationship cannot yet be fully established, these results show significant promise regarding the future of sleep studies and health. By understanding how inflammation impacts chronic health disease, other issues that affect inflammation can also be studied and identified as causes of chronic health disease. This research also highlights the importance of studying sleep and how adjusting one's sleep is a simple way to live a healthier life and decrease the risk of poor health in the future. These findings could be used to emphasize sleep disorder interventions as a method to reduce inflammation in patients who suffer from chronic disease. Overall, these studies could change the way health professionals talk about sleep and other causes of inflammation and emphasize the long-term impact that it can have on a person's body and health.

References

American Heart Association. (2014, March 27). Strokes in atrial fibrillation patients on the rise, despite improved treatments. Retrieved from https://newsarchive.heart.org/strokes-atrial -fibrillation-patients-rise-despite-improved-treatments/

American Heart Association. (2017, May 31). What is Cardiovascular Disease? Retrieved from https://www.heart.org/en/health-topics/consumer-healthcare/what-is-cardiovascular -disease/

American Psychiatric Association. (2017). *Diagnostic and statistical manual of mental disorders: Dsm-5*. Arlington, VA

Barnes, T. C., Anderson, M. E., & Moots, R. J. (2011). The Many Faces of Interleukin-6: The Role of IL-6 in Inflammation, Vasculopathy, and Fibrosis in Systemic Sclerosis. *International Journal of Rheumatology*, *2011*, 1–6. doi: 10.1155/2011/721608

Basta, M., Chrousos, G. P., Vela-Bueno, A., & Vgontzas, A. N. (2007). Chronic Insomnia and the Stress System. *Sleep Medicine Clinics*, *2*(2), 279–291. doi: 10.1016/j.jsmc.2007.04.002

Benamer, H., Steg, P. G., Benessiano, J., Vicaut, E., Gaultier, C. J., Boccara, A., Aubry, P., Nicaise, P., Brochet, E., Juliard, J.M., Himbert, D., & Assayag, P. (1998). Comparison of the prognostic value of C-Reactive protein and troponin I in patients with unstable angina pectoris. *The American Journal of Cardiology*, *82*(7), 845–850. doi: 10.1016/s0002-9149(98)00490-1

Biasucci, L. M. (2004). CDC/AHA Workshop on Markers of Inflammation and Cardiovascular Disease. *Circulation*, *110*(25), 560–567. doi: 10.1161/01.cir.0000148983.88334.80

Black, S., Kushner, I., & Samols, D. (2004). C-Reactive Protein. *The Journal of Biological Chemistry*, *279*(47), 48487–48490. doi: 10.1074/jbc.R400025200

Bokhari, Shakoori, & Ghafoor. (2014). TNF-alpha: a risk factor for ischemic stroke. *NCBI*, 111–114. doi: https://www.ncbi.nlm.nih.gov/pubmed/25603656

Burgos, I., Richter, L., Klein, T., Fiebich, B., Feige, B., & Voderholzer, U. (2005). Increased nocturnal interleukin-6 excretion in patients with primary insomnia: A pilot study. *Brain, Behavior, and Immunity*, *20*(3), 246–253. Retrieved from https://www.sciencedirect.com/science/article/pii/S0889159105001108?via=ihub

Centers for Disease Control and Prevention (CDC). (2011, March 4). Effect of short sleep duration on daily activities--United States, 2005-2008. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21368739.

Ciftci, T. U., Kokturk, O., Bukan, N., & Bilgihan, A. (2004). The relationship between serum cytokine levels with obesity and obstructive sleep apnea syndrome. *Cytokine, 28*(2), 87–91. doi: 10.1016/j.cyto.2004.07.003

Cui, G., Wang, H., Li, R., Zhang, L., Li, Z., Wang, Y., Hui, R., & Wang, D. W. (2012). Polymorphism of tumor necrosis factor alpha (TNF-alpha) gene promoter, circulating TNF-alpha level, and cardiovascular risk factor for ischemic stroke. *Journal of Neuroinflammation*, *9*(1). doi: 10.1186/1742-2094-9-235

Eshaghi, F. S., Ghazizadeh, H., Kazami-Nooreini, S., Timar, A., Esmaeily, H., Mehramiz, M., Avan, A., & Ghayour-Mobarhan, M. (2019). Association of a genetic variant in AKT1 gene with features of the metabolic syndrome. *Genes & Diseases*, *6*(3), 290–295. doi: 10.1016/j.gendis.2019.03.002

Firat Guven, S., Hamidullah Turkkani, M., Ciftci, B., Ulukavak Ciftci, T., & Erdogan, Y. (2012). The relationship between high-sensitivity C-reactive protein levels and the severity of

obstructive sleep apnea. *Sleep and Breathing*, *16*, 217–221. Retrieved from https://link.springer.com/article/10.1007/s11325-011-0492-2

Frey, D. J., Fleshner, M., & Wright, K. P. (2007). The effects of 40 hours of total sleep deprivation on inflammatory markers in healthy young adults. *Brain, Behavior, and Immunology*, *21*(8), 1050–1057. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17524614

Friedman, E. M., Hayney, M. S., Love, G. D., Urry, H. L., Rosenkranz, M. A., Davidson, R. J., Singer, B.H., & Ryff, C. D. (2005). Social relationships, sleep quality, and interleukin-6 in aging women. *Proceedings of the National Academy of Sciences*, *102*(51), 18757–18762. doi: 10.1073/pnas.0509281102

Gabay, C. (2006). Interleukin-6 and chronic inflammation. *Arthritis Research and Therapy*, *8*(2). doi: 10.1186/ar1917

Gieselmann, A., Aoudia, M. A., Carr, M., Germain, A., Gorzka, R., Holzinger, B., Kleim, B., Krakow, B., Kunze, A.E., Lancee, J., Nadorff, M.R., Nielsen, T., Riemann, D., Sandahl, H., Schlarb, A.A., Schmid, C., Schredl, M., Spoormaker, V.I., Steil, R., … Pietrowsky, R. (2019). Aetiology and treatment of nightmare disorder: State of the art and future perspectives. *Journal of Sleep Research*, *28*(4). doi: 10.1111/jsr.12820

Grandner, M. A., Buxton, O. M., Jackson, N., Sands-Lincoln, M., Pandey, A., & Jean-Louis, G. (2013). Extreme Sleep Durations and Increased C-Reactive Protein: Effects of Sex and Ethnoracial Group. Sleep, 36(5), 769–779. doi: 10.5665/sleep.2646

Guilleminault, C., Kirisoglu, C., & Ohayon, M. M. (2004). C-Reactive Protein and Sleep-Disordered Breathing. *Sleep*, *27*(8), 1507–1517. doi: 10.1093/sleep/27.8.1507

Habib, F., Springall, D., Davies, G., Oakley, C., Polak, J., & Yacoub, M. (1996). Tumour necrosis factor and inducible nitric oxide synthase in dilated cardiomyopathy. *The Lancet*, *347*(9009), 1151–1155. doi: 10.1016/s0140-6736(96)90610-8

Hong, S., Mills, P. J., Loredo, J. S., Adler, K. A., & Dimsdale, J. E. (2005). The association between interleukin-6, sleep, and demographic characteristics. *Brain, Behavior, and Immunity*, *19*(2), 165–172. doi: 10.1016/j.bbi.2004.07.008

"How Much Sleep Do We Really Need?" *National Sleep Foundation*, 2020, www.sleepfoundation.org/articles/how-much-sleep-do-we-really-need.

Jenny, N. S., Tracy, R. P., Ogg, M. S., Luong, L. A., Kuller, L. H., Arnold, A. M., Sharrett, A.R., & Humphries, S. E. (2002). In the Elderly, Interleukin-6 Plasma Levels and the −174G>C Polymorphism Are Associated With the Development of Cardiovascular Disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *22*(12), 2066–2071. doi: 10.1161/01.atv.0000040224.49362.60

Kaditis, A. G., Alexopoulos, E. I., Kalampouka, E., Kostadima, E., Germenis, A., Zintzaras, E., & Gourgoulianis, K. (2005). Morning Levels of C-Reactive Protein in Children with Obstructive Sleep-disordered Breathing. *American Journal of Respiratory and Critical Care Medicine*, *171*(3), 282–286. doi: 10.1164/rccm.200407-928oc

Kamel, H., & Iadecola, C. (2012). Brain-Immune Interactions and Ischemic Stroke Clinical Implications. *Neurological Review*, 576–581. Retrieved from https://jamanetwork.com/journals/jamaneurology/fullarticle/1149695

Kaptoge, Di Angelantonio, Lowe, Pepys, Thompson, Collins, & Danesh. (2010). C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet*. doi: 10.1016/S0140-6736(09)61717-7

Kato, A., Odamaki, M., Takita, T., Maruyama, Y., Kumagai, H., & Hishida, A. (2002). Association between interleukin-6 and carotid atherosclerosis in hemodialysis patients. *Kidney International*, *61*(3), 1143–1152. doi: 10.1046/j.1523-1755.2002.00215.xrochfor

Kokturk, O., Ciftci, T. U., Mollarecep, E., & Ciftci, B. (2005). Elevated C-Reactive Protein Levels and Increased Cardiovascular Risk in Patients With Obstructive Sleep Apnea Syndrome. *International Heart Journal*, *46*(5), 801–809. doi: 10.1536/ihj.46.801

Kuller, L. H., Tracy, R. P., Shaten, J., & Meilahn, E. N. (1996). Relation of C-Reactive Protein and Coronary Heart Disease in the MRFIT Nested Case-Control Study. *American Journal of Epidemiology*, *144*(6), 537–547. doi: 10.1093/oxfordjournals.aje.a008963

Larkin, E. K., Rosen, C. L., Kirchner, H. L., Storfer-Isser, A., Emancipator, J. L., Johnson, N. L., Zambito, A.V., Tracy, R.P., Jenny, N.S. & Redline, S. (2005). Variation of C-Reactive Protein Levels in Adolescents. *Circulation*, *111*(15), 1978–1984. doi: 10.1161/01.cir.0000161819.76138.5e

Latini, R., Bianchi, M., Correale, E., Dinarello, C. A., Fantuzzi, G., Fresco, C., Maggioni, A.P., Mengozzi, M., Romano, S., Shapiro, L., & Ghezzi, P. (1994). Cytokines in Acute Myocardial Infarction. *Journal of Cardiovascular Pharmacology*, *23*(1), 1. doi: 10.1097/00005344-199401000-00026

Lauderdale, D. S., Knutson, K. L., Yan, L. L., Liu, K., & Rathouz, P. J. (2008). Self-Reported and Measured Sleep Duration. *Epidemiology*, *19*(6), 838–845. doi: 10.1097/ede.0b013e318187a7b0

Laveti, D., Kumar, M., Hemalatha, R., Sistla, R., Naidu, V.G., Talla, V., Verma, V., Kaur, N., & Nagpal, R. (2013). Anti-Inflammatory Treatments for Chronic Diseases: A Review. *Inflammation Allergy Drug Targets, 12*(5), 349-361. doi: 10.2174/18715281113129990053

Leng, Y., Cappuccio, F., Wainwright, N., Surtees, P., Luben, R., Brayne, C., & Khaw, K.-tee. (2015). Sleep duration and risk of fatal and nonfatal stroke. *American Academy of Neurology, 84*, 1066–1078. doi: 10.1212/WNL.0000000000001371

Lindmark, E., Diderholm, E., Wallentin, L., & Siegbahn, A. (2001). Relationship Between Interleukin 6 and Mortality in Patients With Unstable Coronary Artery Disease. *Jama, 286*(17), 2107. doi: 10.1001/jama.286.17.2107

Liuzzo, G., Biasucci, L. M., Gallimore, J. R., Grillo, R. L., Rebuzzi, A. G., Pepys, M. B., & Maseri, A. (1994). The Prognostic Value of C-Reactive Protein and Serum Amyloid A Protein in Severe Unstable Angina. *New England Journal of Medicine, 331*(7), 417–424. doi: 10.1056/nejm199408183310701

Ludwig-Maximilians-Universität München. (2017, November 28). Cardiovascular disease: The immune response to heart attacks. *ScienceDaily*. Retrieved February 21, 2020 from www.sciencedaily.com/releases/2017/11/171128120147.htm

Ma, Z., Yue, Y., Luo, Y., Wang, W., Cao, Y., & Fang, Q. (2020). Clinical Utility of the Inflammatory Factors Combined With Lipid Markers in the Diagnostic and Prognostic Assessment of Ischemic Stroke: Based on Logistic Regression Models. *Journal of Stroke and Cerebrovascular Diseases, 29*(4), 104653. doi: 10.1016/j.jstrokecerebrovasdis.2020.104653

Mayo Clinic. (2017, November 21). C-reactive protein test. Retrieved from https://www.mayoclinic.org/tests-procedures/c-reactive-protein-test/about/pac-20385228

Mayo Clinic. (2018, April 24). Arteriosclerosis / atherosclerosis. Retrieved from https://www.mayoclinic.org/diseases-conditions/arteriosclerosis-atherosclerosis/symptoms-causes/syc-20350569

Mayo Clinic. (2019, August 10). *ClinicSleep disorders*.Retrieved from https://www.mayoclinic.org/diseases-conditions/sleep-disorders/symptoms-causes/syc-20354018

Meier-Ewert, H. K., Ridker, P. M., Rifai, N., Regan, M. M., Price, N. J., Dinges, D. F., & Mullington, J. M. (2004). Effect of sleep loss on C-Reactive protein, an inflammatory marker of cardiovascular risk. *Journal of the American College of Cardiology*, *43*(4), 678–683. doi: 10.1016/j.jacc.2003.07.050

Mendall, M. A., Patel, P., Asante, M., Ballam, L., Morris, J., Strachan, D. P., Camm, J., & Northfield, T. C. (1997). Relation of serum cytokine concentrations to cardiovascular risk factors and coronary heart disease. *Heart*, *78*, 273–277. doi: 10.1136/hrt.78.3.273

Motamedi, K., McClary, A., & Amedee, R. G. (2009). Obstructive Sleep Apnea: A Growing Problem. *The Ochsner Journal*, *9*, 149–153. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3096276/

Napoli, M. D., Papa, F., & Bocola, V. (2001). C-Reactive Protein in Ischemic Stroke. *Stroke*, *32*(4), 917–924. doi: 10.1161/01.str.32.4.917

NCBI. (2016, August 4). The innate and adaptive immune systems. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK279396/.

Notarangelo, G. (2017, November 10). How Our Immune System Causes Heart Attacks (and Cancer). Retrieved from http://sitn.hms.harvard.edu/flash/2017/immune-system-causes-heart-attacks-cancer/

Pahwa, R., Goyal, A., Bansal, P., & Jialal, I. (2020). Chronic Inflammation. *NCBI*. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK493173/

Parameswaran, N., & Patial, S. (2010). Tumor Necrosis Factor-α Signaling in Macrophages. *Critical Reviews™ in Eukaryotic Gene Expression*, *20*(2), 87–103. doi: 10.1615/critreveukargeneexpr.v20.i2.10

Patel, S. R., Zhu, X., Storfer-Isser, A., Mehra, R., Jenny, N. S., Tracy, R., & Redline, S. (2009). Sleep Duration and Biomarkers of Inflammation. *Sleep*, *32*(2), 200–204. doi: 10.1093/sleep/32.2.200

Pepys, M., & Hirschfield, G. (2003). C-reactive protein: a critical update. *The Journal of Clinical Investigation*, *111*(12), 1805–1812. Retrieved from https://www.jci.org/articles/view/18921/pdf

Popa, C., Netea, M. G., Van Riel, P. L. C. M., Van Der Meer, J. W. M., & Stalenhoef, A. F. H. (2007). The role of TNF-α in chronic inflammatory conditions, intermediary metabolism, and cardiovascular risk. *Journal of Lipid Research*, *48*(4), 751–762. doi: 10.1194/jlr.r600021-jlr200

Razeghi, E., Sahraian, M. A., Heidari, R., & Bagherzadeh, M. (2012). Association of inflammatory biomarkers with sleep disorders in hemodialysis patients. *Acta Neurologica Belgica*, *112*(1), 45–49. doi: 10.1007/s13760-012-0003-7

Reed, D. L., & Sacco, W. P. (2016). Measuring Sleep Efficiency: What Should the Denominator Be? *Journal of Clinical Sleep Medicine*, *12*(02), 263–266. doi: 10.5664/jcsm.5498

Ridker, P. M., Rifai, N., Stampfer, M. J., & Hennekens, C. H. (2000). Plasma Concentration of Interleukin-6 and the Risk of Future Myocardial Infarction Among Apparently Healthy Men. *Circulation*, *101*(15), 1767–1772. doi: 10.1161/01.cir.101.15.1767

Ruehland, W.R., Rochford, P.D., O'Donoghue, F.J., Pierce, R.J., Singh, P., & Thornton, A.T. (2009). The New Aasm Criteria for Scoring Hypopneas: Impact on the Apnea Hypopnea Index. *Sleep*, *32*(2). doi: 10.5665/sleep/32.2.150

Schiza, S. E., Mermigkis, C., Panagiotis, P., Bouloukaki, I., Kallergis, E., Tzanakis, N., Tzortzaki, E., Vlachaki, E., & Siafakas, N. M. (2010). C-reactive protein evolution in obstructive sleep apnoea patients under CPAP therapy. *European Journal of Clinical Investigation*, *40*(11), 968–975. doi: 10.1111/j.1365-2362.2010.02348.x

Sethi, G., Sung, B., & Aggarwal, B. (2008). TNF: A master switch for inflammation to cancer. *Frontiers in Bioscience, Volume*(13), 5094–5107. doi: 10.2741/3066

Shearer, W. T., Reuben, J. M., Mullington, J. M., Price, N. J., Lee, B.-N., Smith, E. B., Szuba, M.P., Van Dongen, H.P., & Dinges, D. F. (2001). Soluble TNF-α receptor 1 and IL-6 plasma levels in humans subjected to the sleep deprivation model of spaceflight. *Journal of Allergy and Clinical Immunology*, *107*(1), 165–170. doi: 10.1067/mai.2001.112270

Smith, S. C., & Allen, P. M. (1992). Neutralization of endogenous tumor necrosis factor ameliorates the severity of myosin-induced myocarditis. *Circulation Research*, *70*(4), 856–863. doi: 10.1161/01.res.70.4.856

Song, C., Lin, A., Bonaccorso, S., Heide, C., Verkerk, R., Kenis, G., Bosmans, E., Scharpe, S., Whelan, A., Cosyns, P., de Jongh, R., & Maes, M. (1998). The inflammatory response system and the availability of plasma tryptophan in patients with primary sleep disorders and major depression. *Journal of Affective Disorders*, *49*(3), 211–219. doi: 10.1016/s0165-0327(98)00025-1

Szalay, J. (2018, October 19). *What Is Inflammation?* https://www.livescience.com/52344-inflammation.html

Tancin Lambert, A., Kong, X. Y., Ratajczak-Tretel, B., Atar, D., Russell, D., Skjelland, M., Bjerkeli, V., Skagen, K., Coq, M., Schordan, E., Firat, H., Halvorsen, B., & Aamodt, A. H. (2020). Biomarkers Associated with Atrial Fibrillation in Patients with Ischemic Stroke: A Pilot Study from the NOR-FIB Study. *Cerebrovascular Diseases Extra*, 11–20. doi: 10.1159/000504529

Tauman, R., Ivanenko, A., Obrien, L. M., & Gozal, D. (2004). Plasma C-Reactive Protein Levels Among Children With Sleep-Disordered Breathing. *Pediatrics*, *113*(6). doi: 10.1542/peds.113.6.e564

Trotti, L. M., Rye, D. B., Staercke, C. D., Hooper, W. C., Quyyumi, A., & Bliwise, D. L. (2012). Elevated C-reactive protein is associated with severe periodic leg movements of sleep in patients with restless legs syndrome. *Brain, Behavior, and Immunity*, *26*(8), 1239–1243. doi: 10.1016/j.bbi.2012.06.003

Vgontzas, A. N., Zoumakis, E., Bixler, E. O., Lin, H.-M., Follett, H., Kales, A., & Chrousos, G. P. (2004). Adverse Effects of Modest Sleep Restriction on Sleepiness, Performance, and Inflammatory Cytokines. *The Journal of Clinical Endocrinology & Metabolism*, *89*(5), 2119–2126. doi: 10.1210/jc.2003-031562

Vgontzas, A. N., Papanicolaou, D. A., Bixler, E. O., Kales, A., Tyson, K., & Chrousos, G. P. (1997). Elevation of Plasma Cytokines in Disorders of Excessive Daytime Sleepiness: Role of Sleep Disturbance and Obesity. *The Journal of Clinical Endocrinology & Metabolism*, *82*(5), 1313–1316. doi: 10.1210/jcem.82.5.3950

Volpato, S., Guralnik, J. M., Ferrucci, L., Balfour, J., Chaves, P., Fried, L. P., & Harris, T. B. (2001). Cardiovascular Disease, Interleukin-6, and Risk of Mortality in Older Women. *Circulation*, *103*(7), 947–953. doi: 10.1161/01.cir.103.7.947

Yoo, S., Gujar, N., Hu, P., Jolesz, F.A., &Walker, M.P. (2007).The Human Emotional Brain without Sleep — a Prefrontal Amygdala Disconnect. *Current Biology, 17*(20). doi:10.1016/j.cub.2007.08.007.

Whiteley, W., Jackson, C., Lewis, S., Lowe, G., Rumley, A., Sandercock, P., Wardlaw, J., Dennis, M., & Sudlow, C. (2009). Inflammatory Markers and Poor Outcome after Stroke: A Prospective Cohort Study and Systematic Review of Interleukin-6. *PLoS Medicine*, *6*(9). doi: 10.1371/journal.pmed.1000145

Woodward, M., Rumley, A., Tunstall-Pedoe, H., & Lowe, G. D. O. (1999). Associations of blood rheology and interleukin-6 with cardiovascular risk factors and prevalent cardiovascular disease. *British Journal of Haematology*, *104*(2), 246–257. doi: 10.1046/j.1365-2141.1999.01158.x

Zampelas, A., Panagiotakos, D. B., Pitsavos, C., Das, U. N., Chrysohoou, C., Skoumas, Y., & Stefanadis, C. (2005). Fish Consumption Among Healthy Adults Is Associated With Decreased Levels of Inflammatory Markers Related to Cardiovascular Disease. *Journal of the American College of Cardiology*, *46*(1), 120–124. doi: 10.1016/j.jacc.2005.03.048

Zimmermann, J., Herrlinger, S., Pruy, A., Metzger, T., & Wanner, C. (1999). Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney International*, *55*(2), 648–658. doi: 10.1046/j.1523-1755.1999.00273.x

Appendix

Table 1

Studies Focused on Sleep and Inflammatory Biomarkers

Study	Year	Sample Size	Sleep Disorder	CRP	IL-6	TNF-α
Burgos	2005	22	Insomnia	N/A	Elevated	N/A
Firat Guven	2012	76	Sleep Apnea	Elevated	N/A	N/A
Frey	2007	19	Sleep Deprivation	Decrease	Decrease	N/A
Friedman	2005	74	Sleep Efficiency	N/A	Elevated	N/A
Grandner	2013	5587	Sleep Duration	Elevated	N/A	N/A
Guilleminault	2004	239	Sleep Apnea	Elevated	N/A	N/A
Hong	2005	70	Sleep Quality	N/A	Elevated	N/A
Kaditis	2005	141	Sleep Apnea	No relationship	N/A	N/A
Kokturk	2005	173	Sleep Apnea	Elevated	N/A	N/A
Larkin	2005	143	Sleep Apnea	Elevated	N/A	N/A
Meier-Ewert	2004	20	Sleep Loss	Elevated	N/A	N/A
Patel	2009	614	Sleep Duration	Elevated with long duration	Elevated with long duration	Elevated with short duration
Razeghi	2012	108	Sleep Disorders	Elevated	N/A	N/A
Schiza	2010	528	Sleep Apnea	Reduced with CPAP	N/A	N/A
Shearer	2001	42	Sleep Loss	N/A	Elevated	Elevated
Song	1998	30	Sleep Disorders	N/A	Elevated	N/A
Tauman	2004	81	Sleep Apnea	Elevated	N/A	N/A
Trotti	2012	137	Restless Leg Syndrome	Elevated	No correlation	No correlation
Ciftci	2004	43	Sleep Apnea	N/A	Elevated	Elevated
Vgontzas	2004	25	Sleep Restriction	N/A	Elevated	Elevated in men
Vgontzas	1997	41	Sleep Disorders	N/A	Elevated	Elevated

Table 2:

Studies Focused on Chronic Health and Disease and Inflammatory Biomarkers

Study	Year	Sample Size	CVD or Stroke	CRP	IL-6	TNF-α
Biasucci et al.	2004	67 patients	CVD	Elevated	Elevated	N/A
Bokhari et al.	2014	131 patients	Stroke	N/A	N/A	Elevated
Ma et al.	2020	588 patients	Stroke	Elevated	Elevated	Elevated
Benamer et al.	1998	195 patients	CVD	No correlation	N/A	N/A
Eshaghi et al.	2019	618 Patients	CVD	Elevated	N/A	N/A
Jenny et al.	2002	5201 patients	CVD	n/a	Elevated- 5%	N/A
Kuller et al.	1996	737 patients	CVD	Elevated	N/A	N/A
Kaptoge et al.	2010	160,309 patients	CVD and Stroke	Elevated	N/A	N/A
Liuzzo et al.	1994	92 patients	CVD	Elevated	N/A	N/A
Mendall et al.	1997	198 Patients	CVD	N/A	Elevated	Elevated
Napoli et al.	2001	193 Patients	Stroke	Elevated	N/A	N/A
Ridker et al.	2000	14,916 patients	CVD	Elevated	Elevated	N/A
Lindmark et al.	2001	3489 patients	CVD	N/A	Elevated	N/A
Kato et al.	2002	156 patients	CVD	N/A	Elevated	N/A
Tancin Lambert et al.	2020	26 patients	stroke	N/A	Elevated	N/A
Volpato et al.	2001	620 patients	CVD	N/A	Elevated	N/A
Whiteley et al.	2009	844 patients	stroke	Elevated	Elevated	N/A
Woodward et al.	1999	1574 patients	CVD	N/A	Correlation	N/A
Zimmermann et al.	1998	280 patients	CVD	Elevated	N/A	N/A
Zempelas et al.	2005	1514 patients	CVD	33% lower CRP	33% lower	21% lower
Smith and Allen	1992	Mice, unknown	CVD	N/A	N/A	Elevated
Habib et al.	1996	40 patients	CVD	N/A	N/A	Elevated
Latini et al.	1994	18 patients	CVD	N/A	N/A	Elevated
Cui et al.	2012	2415 patients	Stroke	N/A	N/A	Elevated