Shift Work: Gut Health and Metabolic Disease

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Abstract

The number of people engaged in shift work continues to rise, and with it the research linking shift work to various diseases and conditions. Shift work changes the body's sleeping patterns and circadian rhythms which has an effect on all parts of the body including the heart, immunity, cancer development, and inflammatory processes. Altered sleeping patterns and circadian rhythms change the composition and anatomy of the gut and microbiome, which in turn affects the development of metabolic diseases. Shift work also changes one's eating patterns and habits. Altered eating habits similarly changes the composition and anatomy of the gut and microbiome. With the combined effects of sleep patterns and eating habits on the gut, it can be said shift work itself produces lasting and harmful effects in the gut and microbiome. These changes in the gut underlie many of the disease processes plaguing shift workers. With the gut having such widespread effects on the body, it should be the focus of research and treatment related to shift work associated disease processes.

Keywords: shift work, circadian rhythms, gut health, sleep patterns

Shift Work: Gut Health and Metabolic Disease

All of the research for this literature review was found through peer-reviewed journals through scholarly sources including Liberty University online databases and *UpToDate* medical databases. Inclusion criteria for these sources included peer-reviewed journals, original research with adequate sample sizes and methods or literature reviews containing studies with adequate sample sizes and methods. The methods for determining if a study was adequate as well as levels of research and evidence are included in the literature matrix in the appendix of this paper. Some key words that were used to locate research for this paper included shift work, circadian rhythms, gut health, sleep patterns, eating habits, metabolic disease, and cardiovascular disease. This allowed for a wide range of sources that could then be synthesized into one larger body review. A large volume of sources was located at first, and then the inclusion criteria as well as the literature matrix were used to determine which sources were appropriate for this paper and which could be eliminated. These sources were then synthesized to create the following literature review.

Shift work is a term that is becoming more widely used and prevalent in today's workforce. It is characterized by any routine of working outside the nine to five window (Reynolds et al., 2016b). The International Labor Office defines it as the organization of working so workers continue to succeed one another in shifts so the establishment can operate longer than the typical work hours of one individual (Faraut, Bayon, Leger, 2013). Today, it is estimated 20% of the Western workforce is engaged in shift work (Reynolds et al., 2016b). Common examples of shift workers are health care professionals who work up to twelve hour shifts succeeding one another so that the hospital is always in operation, and truck drivers who drive long hours at alternating times of the day. Shift work typically results in people working longer hours and working

through the night in any variety of flexible and variable shifts. Because of this, shift work is

associated with irregular life rhythms, sleep restriction, circadian desynchronization, and

psychical stress (Faraut, Bayon, Leger, 2013). The biological clock within is at a conflict with

these work rhythms. While some people can adapt to this altered rhythm of life, many struggle to

adapt resulting in anything from general fatigue to chronic exhaustion to serious pathological

conditions.

The body's circadian rhythms and sleep regulate many bodily processes, so the effects can be

widespread and severe. The most prevalent link exists between altered sleep and metabolic

disease. Metabolic diseases are a collection of health conditions that are defined by impaired

metabolic function – most common are obesity, type 2 diabetes, and metabolic syndrome

(Reynolds et al., 2016b). Links are also present between shift work and both cancer and

cardiovascular disease. With so many of today's population participating in shift work in some

form, the relationship between sleep loss and metabolic disease is vital to understand. As the

option does not exist to abolish shift work and nocturnal occupations, research must be done to

both determine and prevent the detrimental effects that are resulting from these disrupted life

patterns.

Recent developments and research have revealed a possible link between these in the area of

gut health. Gut health has been a growing term in both medicine and the food industry for the

past several years. It can be broadly defined as the effective digestion and absorption of food,

absence of GI illness, normal and stable intestinal microbiota, effective immunity, and overall

state of well-being (Bischoff, 2011). However, gut health and the true depths of its effect on the

body are still largely misunderstood and unclear. It is well-known the gastrointestinal tract has

widespread effects on health. Its functions are not purely related to the processing of food and

nutrients, but go deeper to the way it interacts with bacteria, effects epithelial and immune

functions, and communicates with the brain. This means gut health is not only related to the GI

tract, but also a person's behavior, mood, and overall health (Bischoff, 2011). The widespread

effects of gut health and the dangers inherent in its alteration may be key in understanding the

link between shift work and disease.

Shift Work and Sleeping Patterns

   The consequences of shift work have been evidenced to range from sleep loss and fatigue to

major effects on cardiovascular disease and cancer pathogenesis. Shift work has effects on the

quality and length of sleep as well as the desynchronization of circadian rhythms. Good quality

and duration of sleep effects many aspects of human functioning including stress regulation,

combating infectious disease, and emotional state. Shift work not only has physical effects, but

also has effects on social interaction and daily activities which may all contribute to the

development of chronic stress in shift workers. The biggest problem with shift work is not only

chronic sleep deprivation, but also poor sleep recovery, or hours slept the following day after a

night without sleep. Those who work night shift average about five to six hours of sleep recovery

the day following their night shift, which is one to four hours shorter than the average night sleep

one would typically get (Faraut, Bayon, Leger, 2013). This insufficient sleep recovery after night

shifts does not allow for full recovery of immune and endocrine function which further

predisposes for infection and disease.

   There has been an increase in evidence suggesting shorter sleep duration is associated with a

higher incidence of cardiovascular disease, diabetes, obesity, cancer, and ultimately mortality.

Shorter sleep duration has a direct effect on neuroendocrine stress, effecting mediators such as

cortisol and catecholamines that are released by the stress system. These mediators serve as

markers of stress that can be measured in the blood, saliva, and urine. Cortisol naturally follows a diurnal rhythm meaning it is released at scheduled times throughout the day – high levels early in the morning and low levels in the evening and at night. Circadian rhythms, the sleep/wake cycle, light conditions, and patterns of activity all contribute to regulating this scheduled release of cortisol. This is where shift work is likely to throw off the body's typical rhythms. Working overnight causes a desynchronization of biological rhythms, shifts the sleep/wake cycle, and flips activity periods and light exposure periods from the usual patterns. Similarly, catecholamines – epinephrine and norepinephrine – are typically released at highest concentrations during the day and minimum concentrations at night. Shift work and changes in activity patterns, light exposure, and circadian rhythms also effects their release times (Faraut, Bayon, Leger, 2013). Unfortunately, there are consequences to these changes in the secretion of cortisol and catecholamines.

There are several examples and studies that reveal how changes in sleep patterns effect the changes in release of cortisol and catecholamines. For instance, transportation industry drivers who worked extended hours and lacked sleep recovery in between shifts revealed not only increased cortisol excretion, but also increased urinary levels of norepinephrine (Faraut, Bayon, Leger, 2013). Another study looked at 10 male long-distance coach drivers during a 49 hour driving shift. Urine samples were collected every four hours and revealed mean urinary excretion rates of epinephrine and cortisol to be higher than baseline levels (Sluiter, van der Beek, Frings-Dresen, 1998). Other studies have been done on medical residents who worked at night with an average night's sleep of two hours. After a 30-hour work shift residents of various ages and genders showed increased blood levels of norepinephrine compared to residents who had not worked an extended shift (Zheng et al., 2006). Other studies showed that after disruption of

cortisol circadian rhythms by shift schedules, night shift workers required over one week of sleep recovery to return to normal rhythms as compared with those who worked day shifts (Faraut, Bayon, Leger, 2013).

All of these studies conclude that shift workers show higher levels of cortisol and catecholamines over time; so, what does this indicate? Because cortisol and catecholamines are stress markers in the body, elevated levels reveal an elevated stress response in these workers. This deregulation of the stress system and its effect on the body needs to be considered as a major contributing factor to the higher risk of developing cardiovascular disease in shift workers. Shorter sleep duration and disturbed sleep cycles also has a direct effect on immune and inflammatory biomarkers. Circadian sleep/wake rhythms regulate the activity and expression of several immune cells in the body. Some immune cells such as monocytes peak during the night, while others such as natural killer cells and neutrophils peak during the day. Several cytokines such as tumor necrosis factor follow diurnal rhythms with the highest levels during nighttime sleep. All of these release patterns are regulated by the bodies regularity of sleep patterns (Faraut, Bayon, Leger, 2013; Zheng et al., 2006; Sluiter, van der Beek, Frings-Dresen, 1998).

Several studies have been done to show this relationship between changes in the highs and lows of immune cell rhythms and sleep regulation. One study looked at shift work in nurses over time and the effect of fatigue on immune function. Following a long shift, natural killer cell activity was reduced compared to activity at the beginning of the shift. The decrease in natural killer cell activity was more pronounced in those with greater fatigue and drowsiness (Faraut, Bayon, Leger, 2013). Other studies have revealed that shift workers have higher leukocyte counts than typical day workers. One study involving 107 daytime workers and 101 shift workers – all of which had no history of inflammatory disease – revealed a higher rate of

subjective poor sleep directly correlated with an increase in leukocyte counts. A higher leukocyte count was correlated with shift work regardless of smoking, age, or physical activity (Faraut, Bayon, Leger, 2013). Blood counts of leukocytes has been shown to be a powerful predictor of restin levels, which is an adipokine that has direct effects on promotion of endothelial cell activation and is an inflammatory marker for atherosclerosis. Elevated leukocyte blood levels correlated to elevated restin levels in these rotating shift workers compared to day workers (Faraut, Bayon, Leger, 2013).

Another common inflammatory marker in the body is C-Reactive protein (CRP). Levels of CRP were evaluated in medical residents after a 30-hour extended shift compared to the same residents after a non-extended work day. Following the extended work shift, residents had five times higher CRP levels compared to after a non-extended shift (Zheng et al., 2006). These changes – increased leukocyte levels, increase in proinflammatory cytokines including CRP, and decreased natural killer cell activity – could be a defensive strategy of the immune system in response to circadian changes and sleep loss. The effects of these immune changes may have great clinical significance.

All of these neuroendocrine and immune changes, as well as circadian misalignment may ultimately reveal shift work as a possible carcinogen and cause of cardiovascular disease. The forced desynchronization of body rhythms that shift work causes could lead to increased oncogenesis. The alterations in circadian cell cycles may lead to uncontrolled cell division and growth. Changes in immunity may also be a large contributor to oncogenesis. Natural killer cells in the body typically exert cytotoxicity against cancer cells; however, shift workers have shown decreased natural killer cell activity following loss of sleep which is a huge consequence to the body's natural defense system against cancer development. The increase in pro-inflammatory

cytokines in shift workers which indicates a pro-inflammatory state in the body – that may progress to chronic inflammation – also increases the risk of oncogenesis, particularly in the colon and prostate. As stated, shift workers showed higher leukocyte counts as well as a pro-inflammatory state (Faraut, Bayon, Leger, 2013; Zheng et al., 2006; Puttonen, Viitasalo & Harma, 2011).

The longer employees work in night shift schedules, the more likely they are to develop heart disease. This is largely supported by the studies of neuroendocrine stress and immune responses just discussed. Endothelial dysfunction as a result of increased restin levels is a major cause for atherosclerosis in the body. Also, during typical body rhythms of nighttime sleeping, blood pressure decreases by 10-20% compared to daytime blood pressure (Faraut, Bayon, Leger, 2013). This is called "nocturnal dipping" and is mediated by a decrease in the sympathetic output at night. As night shift workers are shown to have high levels of cortisol and catecholamines which indicate a continued increase in sympathetic output and the stress repose, they are lacking this "nocturnal dipping". This is considered a strong risk factor for cardiovascular risks including hypertension (Faraut, Bayon, Leger, 2013 & Puttonen, Viitasalo & Harma, 2011).

Sleep loss causes significant increases in stress and immune markers, indicating sleep-dependent interactions between the central nervous and the neuroendocrine and immune systems. These changes occur in all subjects who are sleep-deprived, but occur to a lesser extent when sleep loss is counterbalanced with scheduled napping. During the early hours of slow-wave sleep (SWS), there is the minimum amount of cortisol release compared to the maximum amount of growth hormone release. This means the SWS period of sleep suppresses the release of the mediators of the stress response that cause so many harmful effects in the body. SWS sleep inhibits the hypothalamic-pituitary-adrenal (HPA) axis, thereby inhibiting cortisol and

catecholamine release from the sympathetic adrenal system, making this phase of sleep stress-relieving. Importantly, SWS can be achieved without having a full night's sleep, rather one can enter SWS during a short nap, and experience the same stress relieving effects. In a study of sleep-restricted intern residents who experienced only two hours of overnight sleep, a 30-min midday nap showed an improvement in alertness as well as normalizing leukocyte values during the following night of recovery sleep. This means simply taking a standard recovery night of eight hours after sleep restriction is less effective at normalizing leukocyte counts than when a midday nap is taken prior to the recovery night. So, napping does not just make one more alert, but it is stress-relieving by decreasing cortisol levels in the body and normalizing leukocyte levels after sleep (Faraut, Bayon, Leger, 2013).

Sleeping Patterns and Gut Health

The gut microbiota refers to the population of microbes living in the intestinal tract, with varying composition among every individual. The gut microbiota is mainly composed of Bacteriodetes and Firmicutes which encapsulate thousands of individual types of bacteria. At birth, humans are sterile with no bacteria in the gut, but the intestines are quickly populated with colonies from the mother and environment, and later from the diet (Vrieze et al., 2010). Gut dysbiosis is the term for when there is a disruption in the normal and healthy balance of bacteria in the gut, usually as a consequence of some type of stress. This may include pathobionts which are microbes in the intestines which have the potential to cause harm to the host (Reynolds et al., 2016b). Recent research has revealed circadian disruption and sleep loss – as in shift work – can cause dysbiosis in the gastrointestinal tract. Dysbiosis leads to problems in the integrity of the epithelial barrier of the intestines and is associated with an increased inflammatory response in the gut. Both of these are important factors in the onset of metabolic disease (Reynolds et al.,

2016a). There have been studies that have showed a connection between dysbiosis and circadian disruption, both in mice and human subjects, and this connection is vital for those who suffer chronic sleep loss and circadian disruption in the understanding of the onset of metabolic disease (Ley et al., 2005).

Individual bacterial species in the gut microbiome can impact disease related symptoms, so shifts in the bacterial colonies that are present in the gut can prompt specific disease-inducing activity (called "dysbiosis") or disease-protective activity (called "probiosis"). Some beneficial effects of gut microbiota include immune cell development and homeostasis, food digestion, support of fat metabolism, homeostasis of the epithelium, enteric nerve regulation, and promotion of angiogenesis. Inversely, a poorly adapted microbiome can impair these functions of homeostasis resulting in diseases ranging from allergies, inflammatory bowel disease, obesity, cancer, and diabetes. It is expected that gut microbiota would have an effect on intestinal disease due to the close proximity of the two; however, the effects of the gut microbiota have been shown to be more far reaching than just local effects, extending to other organ systems and even the brain. Dysbiosis has been linked to many diseases in the past including IBD, certain cancers, heart disease, and metabolic syndrome (Holmes, et. al. 2011).

While the overarching characteristics of the gut microbiota are the same in every human, there is large variability in the actual microbiota of each individual as it is affected by age, diet, and presence of disease. For example, the microbiota of mice (who share similar gut microbiome makeup to humans) who are obese show 50% less Bacteriodetes along with increased amounts of Firmicutes compared to non-obese humans. There are also increased amount of Lactobacillus in these obese subjects as well as an overall decrease in diversity of bacteria (Ley et al., 2005). Reynolds, et. al. (2016b) recounts two studies that looked at the impact of gut microbiota on

obesity. In one study, a fecal transplant from obese mice to non-obese mice resulted in onset of obesity of the originally non-obese mice independent of changes in diet (Reynolds et al., 2016b).

Taking this further, another study transplanted the gut microbiota of two human twins – one of whom was obese and one non-obese – into germ-free mice. These mice then took on the same body mass profile as the human from whom they received the gut microbiota – mice who received the microbiota from the obese twin showed greater body mass index than the other group of mice (Ridaura et al., 2013). This reveals an obvious relationship between bacteria in the gut and obesity. There is also strong evidence that supports a relationship between disruption of gut microbiota and type 2 diabetes. Upon examination, the gut environment of individuals with type 2 diabetes reflects gut microbial dysbiosis. These individuals have decreased amounts of butyrate-producing bacteria. Butyrate is associated with good health as it is an energy source for colonic epithelium, an important mediator of the inflammatory response in the colon, and a regulator of fat storing gene expression in adipocytes. The gut environment of people with type 2 diabetes also has an increased prevalence of opportunistic pathogens and increased oxidative stress which are indicative of metabolic disease. This all suggests a strong relationship between gut microbial dysbiosis and metabolic disease (Reynolds et al., 2016b).

Microbial resilience refers to the capacity of the gut microbiota to maintain a stable and balanced state despite disruptions and invasions. In diseases like obesity and diabetes, there is a loss of microbial resilience, possibly due to stress on the body (Kerr et al., 2015). Stress has been shown to disrupt the gut microbiota, which is revealed to contribute to poor health. As already discussed, those with disturbed sleep patterns and loss of sleep remain in a prolonged increased stress response identified by high cortisol levels in the body. This increase in physiological stress has a direct effect on the gut microbiota. A healthy gut environment is able to restrict the impact

of microbes on the body and support the action of anti-inflammatory bacteria. Stress disrupts this homeostasis of the gut environment by increasing gut permeability to harmful microbes as well as increasing the proliferation of these harmful bacteria. When the epithelial barrier in the gut is compromised this results in greater permeability, allowing more microbes to penetrate the epithelial barrier and enter the gut, which is a major contributor to pathological inflammation. This process is called bacterial translocation. Increased intestinal permeability is also called a "leaky gut," and this is heavily associated with metabolic disorders as well as other disorders such as liver diseases and autoimmune disorders. The leaky gut allows an increase in inflammatory microbial lipopolysaccharide and other bacteria to penetrate the body. This may be due to dysbiosis in the small intestines that causes an overgrowth of bacteria which promotes altered GI permeability. This ultimately disturbs the relationship between the microbiota and the immune system of the host body, causing an increase in secretion of proinflammatory cytokines which leads to a state of low-grade, continuous inflammation. This low-level chronic inflammation is hallmark of metabolic dysfunction (Kerr et al., 2015).

The increased inflammation due to intestinal permeability goes hand in hand with the increase in inflammatory cytokines due to sleep loss discussed previously, revealing that a relationship exists between inflammation, metabolic function, and gut microbiota (Zheng et al., 2006 & Kerr et al., 2015). Sleep loss causes the stress response which causes a disruption in gut microbiota which initiates the inflammatory process which is the basis for metabolic dysfunction (Reynolds et al., 2016b). Because of this, the GI barrier is vital in understanding the mechanisms that contribute to a healthy gut, as impairment of the GI barrier increases the risk for development of infectious, inflammatory, and functional gastrointestinal diseases. The effects are even more far reaching as disruption of the barrier can contribute to diseases that extend outside

of the gut, including metabolic disorder (Kerr et al., 2015 & Ley et al., 2005).

Inadequate sleep increases the risk for age-related cognitive decline, and research suggests a role of gut microbiota in this. Partial sleep deprivation that alters the human gut microbiome is also associated with cognitive changes, including learning and memory (Bruce-Keller et al., 2015). A study by Anderson, et. al. (2017) was done to determine the relationship between gut microbiome, sleep quality, and cognitive flexibility. In this study, stool samples from thirty-seven participants were provided for gut microbial sequencing. These participants also participated in a sleep quality index test as well as a cognitive function test. The results showed that better sleep quality was associated with better performance on the cognitive test as well as higher proportions of the gut microbial phyla Verrucomicrobia and Lentisphaerae. Cognitive function performance correlated with higher proportions of these two phyla. This means that lower proportions of Verrucomicrobia and Lentisphaerae are associated with poor sleep quality, and this may contribute to metabolic dysfunction and obesity. Lower proportions of Verrucomicrobia are seen in prediabetes and lower proportions of Lentisphaerae are associated with greater weight gain (Arble et al., 2015). The gut microbiota is implicated in several diseases including obesity, diabetes, and cardiovascular dysfunction which are all risk factors for the development of dementia. This and other recent studies have shown that increased incidence of sleep restriction alters the composition of the microbiome in healthy, young males, so this is not an issue that only effects the older adult population. These results emphasize the question of whether improving microbiome health may buffer against sleep-related cognitive decline, in part by decreasing the incidence of other metabolic diseases (Anderson, et. al. 2017 & Bruce-Keller et al., 2015).

Shift work and Eating Habits

Shift work has often been associated with abnormal eating behaviors that may, along with altered sleep, be linked to the prevalence of stress and diseases in night shift workers. These abnormal eating habits could be attributed to many things including time constraints, food availability, exhaustion, stress, and altered social patterns. Shift work disrupts the normal patterns of social life and eating habits. Many shift workers do not have a protected break time to eat, which can lead to snacking and grazing throughout the shift instead of consuming one full meal. Processed foods are often easy and fast which appeal to this population who do not get many breaks or have many food options to choose from (Wong et al., 2010). Foods high in sugar are easy and convenient to overcome cravings and exhaustion during long shifts. Past studies have shown that nurses on average consume more sweet food, high fat food, and fast snack food during night shifts to stay awake and have energy during longer shifts (Lancaster et al., 2001).

Wong et al. (2010) completed a study of 662 nurses working shift duties to show the positive association between shift work and abnormal eating behaviors. This study looked at emotional eating behaviors by evaluating individuals' self-perception of body weight changes, tendencies towards overeating, perceived organizational support (POS), and using the Dutch Eating Behavior Questionnaire (DEBQ). The DEBQ has three categories that were evaluated. The first was emotional eating in response to emotions like anxiety, stress, or fear. The second was external eating or eating in response to the sight or smell of food. The third was restrained eating or overeating after stopping a diet or a period of losing weight. The results showed 66.4% with abnormal emotional eating, 61.4% with abnormal external eating habits, and 64% with abnormal restraint eating. Many of these participants also perceived themselves to be overeating or gaining weight. This study concluded nurses and other shift workers need to be given healthy night snack options at greater convenience as well as education programs on healthy eating

habits (Wong et al., 2010).

Eating during abnormal circadian phases has been shown to also have an impact on cardiovascular risk. The increase in lipid, glucose, and protein levels after eating can lead to oxidative stress which is often associated with a higher risk for atherosclerosis. This means eating a meal high in lipids and carbohydrates and remaining in a state of hyperglycemia and hyperlipidemia is associated with increased oxidative damage that is linked to atherogenesis and cardiovascular risks as well as cancer pathogenesis (Faraut, Bayon, Leger, 2013). Lab studies have shown meals consumed during the night compared to during the day result in an impaired lipid and glucose tolerance which predisposes to longer periods of hyperglycemia and hyperlipidemia during the night (Faraut, Bayon, Leger, 2013). Studies have also shown night shift workers display significantly higher carbohydrate, specifically sweets, intake than day shift workers, as well as significantly lower intake of vegetables with high anti-oxidant capacities (Scheer et al., 2009). This shows night shift workers should be encouraged to eat fruits and vegetables rather than meals high in lipids and proteins because of the bodies altered nighttime metabolism.

Studies have also revealed sleep plays a role in the regulation of glucose metabolism, which is important here in its relationship to the development of type 2 diabetes. A balanced level of glucose in the body, or glucose homeostasis, depends on the balance between the liver's production of glucose and the tissue's use of glucose. This is largely dependent on the beta cells in the pancreas and their ability to release insulin both acutely and in a sustained manner. It is also dependent on insulin's ability to inhibit glucose production and promote the disposal of glucose by the tissues. Both the function of beta cells and insulin have been shown to be impacted by sleep. Periods of sleep disturbance or loss of adequate sleep have been linked to

insulin resistance and decreased glucose tolerance. Insulin resistance is when the body requires higher levels of insulin to reduce the same amount of blood glucose levels, or in other words, the body stops responding as well to insulin. Insulin resistance is a major risk factor for the development of type 2 diabetes. Glucose tolerance refers to how well the body's cells can absorb glucose, and impaired glucose tolerance means the body cannot regulate serum glucose as well (Spiegel et al., 2005).

One study evaluated eleven young, healthy males after six days of sleep restriction with only four hours of sleep per night followed by seven days of sleep recovery of twelve hours of sleep per night. The subjects revealed decreased glucose tolerance during the six days of sleep loss, mimicking a diagnosis of impaired glucose tolerance that is common in older adults. The subjects also revealed decreased insulin sensitivity in the morning after the six days of sleep restriction (Spiegel et al., 2005). Another study evaluated twelve healthy, young males after two consecutive nights of ten-hour sleep times compared to two consecutive nights of four-hour sleep times. After the two nights of short sleep times, the subjects showed higher glucose levels and lower insulin levels compared to the two days after long sleep times. They also showed an increased appetite for high carbohydrate content foods such as cakes, pastries, and bread following the sleep deprived nights (Spiegel et al., 2005).

Poroyko et. al. (2016) also performed a research study on mice to prove that sleep fragmentation causes coordinated changes in the microbiota which impacts its function, specifically in terms of insulin resistance. Sleep fragmentation can be related to the sleep loss characteristic of shift work. Evidence for increased insulin resistance was revealed in the study of adult male mice. They were randomly exposed to sleep fragmentation by employing intermittent tactile stimulation in the cage causing many episodes of arousal throughout the sleep

period. This prevented good and long-lasting sleep in the mice. Sleep fragmentation was

implemented for four weeks, and then recovery lasted for two weeks after that. The homeostasis

model assessment (HOMA-IR) was used to determine insulin resistance, which is represented by

(fasting insulin x fasting glucose/22.5. The fasting HOMA levels were higher in mice exposed to

sleep fragmentation than those who had normal sleep patterns, showing a relationship between

sleep fragmentation and increased insulin resistance (Poroyko et al. 2016).

Typically, in normal sleep patterns, the body has low cortisol levels at night. Low cortisol

levels cause an increase in insulin sensitivity. The pancreatic beta cells release of insulin is

stimulated by parasympathetic activation and is inhibited by sympathetic activation. Therefore,

any alteration in sympathovagal balance could disrupt the production of insulin. As stated

previously, sleep deprived individuals show higher serum cortisol levels, revealing increased

sympathetic stimulation. These elevated cortisol levels therefore result in reduced insulin

sensitivity, or insulin resistance. As sleep deprivation becomes more chronic, the body seems to

adapt as the initial impairment of glucose tolerance decreases and insulin resistance develops.

This is where the major risk for metabolic disease like type 2 diabetes is seen (Spiegel et al.,

2005).

Eating habits and Gut Health

Because research has shown night shift workers are more likely to consume high sugar,

carbohydrate, and fat content foods, it is important to consider the implications of these diet

choices on the gut. Kong et al. (2014) conducted a study of 45 overweight and obese but

otherwise healthy subjects, including six males and 39 females, where participants completed a

seven-day dietary record and bio-clinical and fecal bacterial data. These subjects had no

inflammatory or infectious diseases, cancer, cardiac diseases, or history of gastrointestinal

problems. Seventeen normal-weight subjects were also included in the study as a control group.

Dietary patterns, plasma and adipose tissue markers, and gut microbiota were evaluated. The

participants were placed into three clusters based on their seven-day food intake journals. Cluster

3 had a healthier dietary pattern based on the food journals, while Cluster 1 had the least healthy

dietary pattern. Healthier dietary patterns were characterized by higher consumption of fruits and

vegetables and lower consumption of sweets and sugary drinks. Unhealthy dietary patterns were

characterized by high consumption of potatoes, sweets, and sugary drinks (Kong et al., 2014).

Cluster 3 had the highest levels of anti-inflammatory cells and the lowest level of a

systemic inflammatory marker, while cluster 1 showed the worst metabolic profile including

higher levels of low density lipoproteins (LDL) cholesterol. Additionally, gut microbiota of

subjects in Cluster 3 showed higher gene richness than the other clusters, which was related to

lower levels of inflammatory markers. This gene richness was positively associated with

consumption levels of fruit. Comparatively, the members of cluster 1 showed a decrease in gene

richness of the intestinal microbiota. This low bacterial gene richness was associated with

impaired glucose homeostasis and higher low-grade inflammation. This study was looking to

draw the connection between dietary habits and changes in inflammation and metabolic markers

by looking at the role of gut microbiota. Gut microbiota has been shown to be involved in the

development of metabolic syndrome and low-grade inflammation associated with obesity. This is

linked to the research discussed earlier showing how increased cortisol levels caused sustained

low grade inflammation in the gut. This research reveals that not only disrupted sleep patterns,

but diet as well has an impact on inflammation in the gut which is a risk factor for several

metabolic diseases. Interestingly, there were no notable differences in BMI or weight loss

between the three clusters of differing eating habits in this study. While there is no evidence that

these healthier eating patterns have an impact on body weight, the evidence does suggest that a healthier eating pattern creates an environment in the gut microbiota that may protect against the development of metabolic disease and inflammation (Ahluwalia et al., 2013 & Kong et al., 2014).

Many of the body's peripheral appetite-regulating systems, such as gut hormones, are regulated and controlled by circadian rhythm and sleep cycles to achieve homeostasis. This is accomplished through sympathetic and parasympathetic activity and pituitary hormones controlled by the hypothalamus. Night shift work disrupts this homeostasis as the body is in prolonged sympathetic control and the stress response, which disrupts the activity of the regulating gut hormones. Two of these hormones important to regulation of appetite are leptin and ghrelin. Ghrelin is an orexigenic hormone, or an appetite stimulant, so excess amounts of ghrelin will stimulate hunger and in turn, excess consumption. Typically, ghrelin is stimulated by periods of fasting and levels fall following food consumption (Karra & Batterham, 2010). Sciavo-Cardozo et al, conducted a study on twenty-four overweight women, twelve of whom worked night shift and twelve worked day shift, to determine the effects of night work on appetite stimulating hormones. The gut hormone profile of the night shift workers showed a blunted post-prandial suppression of ghrelin compared to the day workers of the same age, gender, and weight. This results in a sustained increased appetite in these workers even after eating a full meal, which leads to over consumption of food. The night shift workers also showed increased total body and abdominal adiposity, lower insulin sensitivity, and alterations in lipids (Schiavo-Cardozo et al., 2013). These results go along with several other previous studies that found a blunted post-prandial suppression of ghrelin in those who were experiencing impaired sleep and night shift workers.

Leptin is produced in the adipose cells and its primary function is to inhibit hunger, which diminishes fat storage in the adipocytes. As leptin levels fall, appetite increases. Shea et al. (2005) reported a circadian rhythm in leptin concentration with levels increasing during the biological night and peaking in the morning. Studies have also shown leptin levels increase with the onset of sleep regardless of the time of day that the sleep takes place (Morris et al., (2012). This shows with circadian disruption and lack of sleep, levels of leptin will not rise and fall appropriately, and appetite will not be suppressed effectively overnight. This, combined with increased levels of ghrelin may stimulate overeating and subsequent weight gain.

In one study, when sleep was restricted mean leptin levels were 19% lower than compared to normal sleep pattern. This change in the regulation of leptin levels between the two sleeping patterns occurred despite similar diet, calorie intake, physical activity and body mass index (BMI) (Spiegel et al., 2005). Another study looked at twelve healthy young men first after two consecutive nights of ten hours of sleep, and then after two consecutive nights of four hours of sleep. There resulted a strong relationship between the increase in hunger during the periods of sleep restriction and the increase in the ratio of ghrelin to leptin (Spiegel et al., 2005). This all reveals the eating habits of night shift workers may not just be due to decreased availability of healthy foods or increased stress, but actual changes in gut hormone levels that stimulate appetite.

There has been a recent influx in research on probiotics, prebiotics, and synbiotics and their effect on overall gut health as well as disease prevention and symptom relief. A probiotic is defined as a live microbial food ingredient that is beneficial to health (Tuohy et al., 2003). The most common probiotics belong to the lactobacilli and bifidobacteria genera, as they are safe to

use in food. Probiotics have been researched to be effective against several gastrointestinal and other diseases. They have been used in subjects with inflammatory bowel disease (IBD) in which the gut is in a state of constant low-grade inflammation. Administration of probiotics to these patient's helps to regulate the inflammatory response as well as change the composition of gut microbiota. This is important to more than just inflammatory bowel disease as the previous research has shown that low-grade inflammation has greater effects on the body than just IBD. Probiotics could therefore be effective against the other metabolic diseases for which chronic inflammation is a risk factor (Tuohy et al., 2003).

A study by Chiang et al. (2000) looked at one strain of probiotics called *Bifidobacterium lactis* HN019 and its effect on immune function. This strain was said to be able to enhance nonspecific immunity including leukocyte proliferation, and enhance production of phagocytes and proinflammatory cytokines. Other studies showed that giving this probiotic to healthy elderly subjects initiated an increase in leukocyte counts and natural killer cells (Tuohy et al., 2003). This is vital because previous research has indicated sleep causes a drop in natural killer cells and leukocytes which contributes to both oncogenesis and cardiovascular risks. Probiotics may be able combat some of these risk factors in the gut.

Probiotics may also be able to support individuals who have a weakened GI barrier and are susceptible to pathogenic bacteria. They are able to prevent pathogenic bacteria from entering the gut through several mechanisms of action. Probiotics help to produce inhibitory compounds, reduce luminal pH, compete for nutrients and adhesion sites on the gut wall, and modulate the immune response, all of which protect the body from harmful pathogens entering the gut (Tuohy et al., 2003).

Prebiotics are "nondigestible food ingredients that beneficially affect the host by

selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon and thus improving host health" (Tuohy et al., 2003). Butyrate was previously discussed in relation to the deficit of butyrate-producing bacteria of those with type 2 diabetes. Butyrate promotes the proliferation of mucosal cells and accelerates the healing process in the colon. The use of prebiotics has been researched as a way of stimulating butyrate production in the colon of those with different inflammatory bowel conditions, thereby decreasing symptoms through the regulation of the inflammatory process and promotion of healing in the colon (Tuohy et al., 2003). This is vital research not only for those with inflammatory bowel conditions such as ulcerative colitis, but also those with type 2 diabetes as previously discussed.

A synbiotic is defined as a mixture of probiotics and prebiotics that produces beneficial effects in the host through the selective stimulation of the growth and activation of the metabolism of health-promoting bacteria. These work together to improve the gut health of the host through the combination of different mechanisms of action (Tuohy et al., 2003). Further research on probiotics, prebiotics, and synbiotics will be vital as research extends from solely intestinal disorders to inflammatory and metabolic disorders of the entire body. More studies will need to be conducted to determine if probiotics not only improve gut health, but also participate in the prevention of sleep-related cognitive dysfunction (Anderson et al., 2017). As more is learned about how the health of the gut effects the health of the entire body, there will be a greater focus on these and other microbially related drug targets.

Conclusion

This research reveals how shift work effects both sleeping and eating patterns and how altered sleeping and eating patterns effect gut health. Further, this research points to gut health as the link that puts shift workers at risk for cardiac and metabolic disease processes. All of the

alterations in the body which occur as a result of shift work have extensive effects on the human gut microbiome. Understanding the gut microbiome to be the link is only the first step. If the gut truly has such widespread effects on the body, research related to shift work and altered sleeping and eating needs to focus more on the gut microbiome of human subjects. Further, research will need to be done to understand how gut-focused treatments and interventions will change the negative effects of shift work being recorded. Shift work is only growing in today's society and there is no option to eliminate it due to negative health effects. Those working on night shift schedules – nurses, health care professionals, transportation employees – are vital to the wellbeing of society, and it should truly be unacceptable to see such deficits in overall health and quality of life.

If the cause cannot be removed, treatments will have to become more fine-tuned. Perhaps focusing on how the gut will affect the body will get to the underlying cause rather than merely treating the symptoms. First, there is a lack of knowledge about how eating and sleeping habits truly effect the body – mainly the gut microbiome – and this education needs to become more widespread. This includes education on the circadian rhythms of the body, risk factors, and behavioral triggers. Further, treatments that support gut health including prebiotics, probiotics, and intestinal-targeting drugs need to be researched and tested for use in these populations for both prevention and treatment. This also with behavioral and routine modification. According to the research, many of the negative health effects associated with shift work are reversible and preventable, but proactivity is vital. The gut serves as the underlying roots of the body – from it stems either one's health and well-being or one's sickness and decay. It is necessary today that the roots continue to be dug up and explored for the benefit of the body that stems from it.

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    randomized crossover trial. *Journal of American Medicine Association, 296*: 1049e50.

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
Ahluwalia, N., Andreeva, V.A., Kesse-Guyot, E., Hercberg, S. (2013). Dietary patterns, inflammation and the metabolic syndrome. Diabetes & Metabolism, 39: 99– 110.	To analyze the association between dietary patterns and inflammation and metabolic syndrome	N/A, various studies reviewed	systematic review of some RCTs, qaui-experimental, and non-experimental studies	Adhering to healthier diets can reduce inflammation and the metabolic syndrome	Level III: systematic review of some RCTs, qaui-experimental, andnon-experimental studies	No original research, bias from synthesis of various sources	Yes, gives good evidence for how diet effects inflammation.
Arble, D.M., Bass, J., Behn, C.D., et al. (2015). Impact of sleep and circadian disruption on energy balance and diabetes: a summary of workshop discussions. *Sleep, 38*(12):1849e60.	To translate findings from research related to the impact of sleep on diabetes into improving the health of the public.	N/A, various studies	Non-experimental	A relationship between sleep and diabetes was established along with the acknowledgement of the need for more research with human studies going beyond glucose and insulin studies.	Level IV, consensus panel based on scientific evidence	Bias, based largely on opinion r/t synthesis of research	Yes, gives a lot of good and varying evidence on circadian rhtyhms and diabetes.
Anderson, J., Carroll, I., Azcarate-Peril, M., Rochette, A.,	To establish a relationship between	37 particpants from ages 50-	An experimental study	Poor sleep quality was associated with poor	Level I: experimental	Conducted with a small	Yes, establishes evidence

Heinberg, L., Peat, C., Steffen, K., Manderino, L., Mitchell, J., & Gunstad, J. (2017). A preliminary examination of gut microbiota, sleep, and cognitive flexibility in healthy older adults. *Sleep Medicine, 38,* 104-107.	sleep, gut microbiome, and cognitive functioning in healthy adults.	85 excluding anyone with history of neurologic or psychiatric disorders, recent probiotic/ antibiotic use, or history of GI disorder.		cognitive performance and altered gut microbiota. There was a partial correlation between certain bacteria and cognitive performance.		smaple size	for a link between sleep, gut health and cognitive function
Benedict, C., Vogel, H., Jonas, W., Woting, A., Blaut, M., Schurmann, A., & Cedernaes, J. (2016). Gut microbiota and glucometabolic alterations in response to recurrent partial sleep deprivation in normal-weight young individuals. *Molecular Metabolism, 5,* 1175-1186.	How sleep loss causes changes in the gut that promote metabolic disturbances.	Randomized sample of nine healthy young men with no history of metabolic or psychiatric disorders.	An experimental study	After two days of sleep loss subjects showed alterations in the gut microbiome that have previously been associated with metabolic disorders. Also decreased insulin sensitivity.	Level I: experimental	Small sample size, short time frame	Yes, good evidence for sleep causing changes in gut
Bruce-Keller, A. J., Salbaum, J.M., Luo, M., et al. (2015). Obese-type gut microbiota induce neurobehavioral changes in the absence of obesity. *Biological Psychiatry,* 77(7):607e15.	To see if obesity-related changes in the gut microbiota are able to impair neurocognitive behavior in mice	Conventionally housed, nonobese, adult male C57BL/6 mice	Experimental study	There is a link between gut dysbiosis and neurological dysfunction related to obesity.	Level I: experimental	Mice subjects, no human comparison	Yes, good supporting evidence for the relationship between gut health and cognitive function

Faraut, B., Bayon, V., & Leger, D. (2013). Neuroendocrine, immune and oxidative stress in shift workers. *Sleep Medicine Review, 17,* 433-444.	Relationship beteween shift work and cardiovascular disease and cancer.	Various studies	Systematic review	Use of several lab studies to link circadian misalignment with neuroendocrine, immune, and oxidative stress systems in the shift work population	Level I: systematic review of RCTs	No original research	Yes, provides a lot of different research studies and evidence
Holmes, E., Li, J.V., Athanasiou, T., Ashrafian, H., & Nicholson, J.K. (2011). Understanding the role of gut microbiome–Host metabolic signal disruption in health and disease. *Trends in Microbiology, 19*(7).	To explore how the gut microbiome relates ot several metabolic diseases.	N/A, various studies	Systematic review	The gut has underlying effects on many disease processes in the body. This opens up doors for many new areas of treatment.	Level I: systematic review of RCTs	No original research	Yes, a synthesis of good studies to support the significance of gut health
Karra, E., Batterham, R. L. (2010). The role of gut hormones in the regulation of body weight and energy homeostasis. *Molecular and Cellular Endocrinology, 316,* 120-128.	Regulation of gut hormones as treatment for obesity and other metabolic disease	N/A, various studies	Nonexperimental, literature review	Gut hormones play a key role in regulation of body weight and treatments aimed at altering hormone levels will prove effective	Level V: literature review	No original research	Yes, provides good evidence and information on specific gut hormones
Kerr, C., Grice, D., Tran, C., Bauer, D., Li, D., Hendry, P., Hannan, G. (2015) Early life	Review how the devloping gut microbiota and	N/A; various studies	Nonexperimental, literature review	Research suggests that gut microbiome developme	Level V: literature review	No original research	Yes, provides good sources and evidence

events influence whole-of-life metabolic health via gut microflora and gut permeability. Critical Reviews in Microbiology, 41:3, 326-340, DOI: 10.3109/1040841X.2013.837863	intestinal barrier function in neonates will effect future microbial resilience			nt in early life will effect future resilience and adult metabolic health.			about how gut health effects development of disease.
Kong LC, Holmes BA, Cotillard A, Habi-Rachedi F, Brazeilles R, et al. (2014) Dietary Patterns Differently Associate with Inflammation and Gut Microbiota in Overweight and Obese Subjects. PLoS ONE 9(10): e109434. doi:10.1371/journal.pone.0109434	To understand how the dietary patterns of obese subjects relate to metabolic and inflammatory factors including gut health	45 overweight and obese subjects (6 men and 39 women) compared to 14 lean subjects as a reference group	Experimental study	Three clusters of dietary patterns were recognized in the obese subjects and these were related to inflammatory markers and gut microbiome diversity.	Level I: experimental	Limited number of subjects; high female to male ratio. Biases in analyzing dietary patterns	Yes, good framework for how diet effects inflammation and gut health.
Ley, R.E., Turnbaugh, P.J., Klein, S., Gordon, J.I. (2006). Microbial ecology: human gut microbes associated with obesity. *Nature;444*:1022e3.	To analyze the gene sequences from the intestinal microbiota and observe differences between lean and obese subjects.	C57BL/6J *ob*/+ mothers and their *ob/ob, ob*/+, and +/+ offspring	Experimental study	Obese mice showed 50% less bacteriodetes and an increase in firmicutes compared to lean counterparts	Level I: experimental	No human subjects, use of mice	Yes, this study uses a lot of data and gene sequences to emphasizes the microbiota changes in obesity.

Moon, S., Lee, B., Kim, S. & Kim, H. (2016). Relationship between thyroid stimulating hormone and night shift work. *Annals of Occupational and Environmental Medicine, 28:53.*	Looks at the relationship between night shift work and thyroid disease	967 female shift hospital workers from 2011-2015.	Quasi-experimental	Night shift workers had TSH levels that were 0.303 mlU/L higher than non-night shift workers indicating an increased risk for thyroid disease	Level II: quasi-experimental	Conducted in only one hospital/setting	Yes, good foundation for the relationship between shift work and hormone levels
Morris, C., Aeschbach, D., & Scheer, F. (2012). Circadian system, sleep, and endocrinology. *Molecular and Cellular Endocrinology, 349,* 91-104.	Looks at how circadian rhythms effect hormone secretion as well as circadian misalignment in night shift workers	N/A, various studies	Non-experimental, literature review	Alterations in sleep cycle and behavioral cycle (as in night shift) has adverse effects on many physiological processes related to hormone release	Level V: literature review	No original research	Yes, really good basis for how circadian misalignment affects the body
Poroyko, V., Carreras, A., Khalyfa, A., Khalyfa, A. A., Leone, V., Peris, E., Almendros, I., Gileles-Hillel, A. Qiao, Z., Hubert, N., Farre, R., Chang, E., & Gozal, D. (2016). Chronic sleep distribution alters gut microbiota, induces systemic and adipose tissue inflammation and insulin resistance in mice.	Looks at how chronic sleep fragmentation alters feeding bahviors and promotes obesity and insulin resistance	Adult male C57BL/6J mice from Jackson Laboratories. Mice were randomly assignes sleep control or sleep fragmentation	Experimental	Sleep fragmentation for four weeks increases food intake, insulin resistance, and inflammation without changes in body weight.	Level I: experimental	Research conducted with mice, no human subjects	Yes, even though it looks at mice it is a good basis for how sleep loss effects diet changes.

Scientific Reports, 6: 35405.							
Puttonen, S., Viitasalo, K., Härmä, M. (2011). Effect of shiftwork on systemic markers of inflammation. *Chronobiology International, 28*(6), 528-535.	To test is shift work is associated with high C-reactive protein and increased leukocyte count.	1877 airline company employees (1037 men, 840 women).	Experime ntal study	Shift work is associated with increased inflammati on seen in higher levels of CRP and leukocytes.	Level I: experime ntal	Possible bias in forming groups for the study, socioec onomic differen ces	Yes, gives specific evidence for increased inflamma tion related to shift work
Reynolds, A., Broussard, J., Paterson, J., Wright, K., & Feguson, S. (2016). Sleepy, circadian disrupted and sick: Could intestinal microbiota play an important role in shift worker health? *Molecular Metabolsim, 6,* 12-13.	Finding a link between sleep loss, circadian misalignm ent, and metabolic disease	N/A, various studies	literature review	Gives evidence for the need of human subject research on the gut microbiota of shift workers and the possible burden of these health effects.	Level V: literature review	No original research , personal bias	Yes, Gives a good overview to then dig deeper
Reynolds, A., Paterson, J., Ferguson, S., Stanley, D., Wright, K., & Dawson, D. (July, 2016). The shift work and health research agenda: Considering changes in gut microbiota as a pathway linking shift work, sleep loss and circadian misalignment, and metabolic disease. *Sleep Medicine*	To explore sleep and circadian disruption alters the gut microbiota and contributes to an inflammat ory state and metabolic disease associated with shift work.	N/A, various studies	Systemat ic review	There is evidence for a relationshi p between shift work associated sleep disruption and an inflammato ry state which promotes metabolic disease.	Level I: systemati c review of RCTs	No original research	Yes, gives a lot of evidence for how sleep loss leads to metabolic dysfuncti on

Reviews, 34, 3-9.							
Ridaura, V.K., Faith, J.J., Rey,F.E., Cheng, J., Duncan, A.E., Kau, A.L., etal. (2013). Gutmicrobiota from twins discordant for obesity modulate metabolism in mice. Science, 341:1241214.	To understand howthe gut microbiota influences the development of human obesity	2 human females and 2 germ free mice	Experimental	Environmental factors have a stronger influence on gut microbiota than genetics, and strongly influence obesity.	Level I: experimental	Small sample size, only female, use of mice	Yes, gives good supporting evidence for the overarching topic of obesity
Scheer, F.A., Hilton, M.F., Mantzoros, C.S., Shea, S.A. (2009). Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc Natl Acad Sci USA, 106*:4453e8.	To understand the underlying mechanisms of how shift work is associated with an increased risk for obesity, diabetes, and cardiovascular disease	10 adult subjects ranging from 19-41yrs (5 female); all healthy with no significant medical disorders	Experimental	Circadian misalignment altered the levels of several hormones and the research showed the cardiometabolic implications of shift work.	Level I: experimental	Small sample size.	Yes, despite small sample size, still gives very detailed analysis of how sleep loss and eating habits effect many parts of the body.
Sciavo-Cardozo, D., Lima, M., Pareja, J., & Geloneze, B. (2013). Appetite-regulating hormones from the upper gut: Disrupted control of Xenin and Ghrelin in night workers. *Clinical Endocrinology, 79*, 807-811.	To compare night workers with day workers regarding apetite-regulating hormones and other metabolic factors.	Twenty-four overweight women (12 night shift & 12 day shift)	Cross-sectional, observational study	Night shift workers compared to day shift had greater body fat mass percentage, greater energy intake, impaired sleep, lower insulin sensitivity, increased triglyceride	Level III	Small sample size, only female	Yes, good evidence for changes in ghrelin release among day and night shift workers

				s and increased C-reactive protein. Alos alterations in ghrelin and xenin release.			
Sluiter, J.K., van der Beek, A.J., Frings-Dresen, M.H. (1998). Work stress and recovery measured by urinary catecholamines and cortisol excretion in long distance coach drivers. *Occupational Environmental Medicine, 55*:407e13.	To determine how urinary excretion of cortisol and norepineprhine is related to sleep disturbance.	10 male long-distance coach drivers	Experimental	Those with periods of sleep loss show a greater urinary excretion of cortisol and norepinephrine than baseline.	Level I; experimental	Small sample size, only male	Yes, gives good detailed evidence about catecholamine and cortisol disruption
Spiegel, K., Knutson, K., Leproult, R., Tasali, E., Van Cauter, E. (2005). Sleep loss: a novel risk factor for insulin resistance and Type 2 diabetes. *Journal of Applied Physiology 99*. doi:10.1152/japplphysiol.00660.2005.	To understand the association between short sleep duration/ chronic sleep loss and obesity and diabetes.	N/A, various studies	Non-experimental; Literature review	In partial sleep restriction, there is altered glucose metabolism and appetite regulation assoiated with obesity and diabetes.	Level V: literature review	No original research	Yes, gives good insight into glucose tolerance and hormones related to appetite regulation.
Tuohy, K., Probert, H., Smejkal, C., Gibson, G. (2003). Using probiotics and prebiotics to improve gut	To understand how prebiotics, probiotics, and synbiotics affect the	N/A, various studies	Non-experimental; literature review	Prebiotics, probiotics, and synbiotics work through different mechanism	Level V: literature review	No orginal research	Yes, good look at treatemtns options for altered gut

health. *Drug Discovery Today* 8(15).	makeup of the gut microbiome			s to increase bifidobacteria and lactobacilli which could impact overall health of host in prevention of disease			microbiota
Vrieze, A., Holleman, F., Zoetendal, E., de Vos, W., Hoekstra, J., Nieuwdorp, M. (2010). The environment within: how gut microbiota may influence metabolism and body composition. *Diabetologia* 53:606-613.	To understand the pathophysiology behind how altered gut microbiome is associated with diabetes.	N/A, various studies	Non-experimental, literature review	The composition of gut microbiota, energy from diet, and synthesis of gut hormones all contribute to the pathopysiological development of diabetes.	Level V, literature review	No original research	Yes, provides a deeper understanding of the pathophysiological changes that occur and contribute to the gut r/t metabolic disease
Wong, H., Wong, M. C.S., Wong, S. Y.S., & Lee, A. (2010). The association between shift duty and abnormal eating behavior among nurses working in a major hospital: A cross-sectional study. *International Journal of Nursing Studies, 47,* 1021-1027.	To understand if shift duties were independent predictors of abnormal eating habits.	378 nurses who work on a full-time basis with the average age of 37.2yrs and 91.5% female.	Experimental	Shift duties were positively associated with abnormal eating behavior among registered nurses.	Level I: experimental	Sample size was mostly female, all in only one hospital. There could also be bias related to the use of surveys and questionnaires.	Yes, draws a good connection directly between shift work and eating habits with a large sample size.

Zheng, H., Patel, M., Hryniewicz, K., Katz, S.D. (2006). Association of extended work shifts, vascular function, and inflammatory markers in internal medicine residents: a randomized crossover trial. *Journal of American Medicine Association, 296*: 1049e50.	22 healthy Internal Medicine residents (15 men and 7 women); mean age 29yrs	To understand if sleep loss during extended shifts is associated with vascular inflammation and dysfunction.	Randomized control trial	Exteneded work shifts were associated with higher blood levels of IL-6, high-sensitivity CRP, and norepinephrine.	Level I: experimental	Small sample size, does not account for other factors including sleep history, stress, etc.	Yes, shows how sleep loss contributes to an increase in proinflammatory cytokines which causes inflammation and CV effects