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I. Introduction:

1.1 Background information on smoking, sleep quality, and cognitive function

Different domains of life require deep reasoning, good decision-making, solid memory and highly selective attention. Many sectors in life require mental critical skills including deep reasoning, good decision-making, solid memory, and high selective attention which is known as social cognition and is highly recommended for individuals inside society. Age is among the top risk factors for cognitive impairment (2); (3), nevertheless, there are other factors, including genetic background, education level, brain damage, a lack of physical activity, chronic diseases, exposure to toxins or pesticides, and substance abuse (4) such as cigarette (5). Several research papers prove the effects of smoking on sleep quality (6). Other studies demonstrate the impact of smoking on cognitive functions (7). However, Sleep disorders related to cognitive dysfunction in smokers have been given less attention in the medical literature. This thesis meta-analysis study along with a systematic review might provide an accurate understanding of smoking's impact on sleep and cognitive functions in smokers.

Smoking's influence on sleep quality and cognitive function is yet unknown. Pathophysiological research has revealed a relationship between cholinergic neurotransmitters and memory, learning, and attention problems (8). Scopolamine, an anticholinergic medication, inhibits the function of cholinergic muscarinic receptors, which causes learning impairment (9). According to the same author, injecting physostigmine improves acetylcholine release and hence cognitive skills in Alzheimer's patients. Attention, memory, and executive functioning have been proven to be affected by smoking. In clinical research about Brain-Derived Neurotrophic Factor, it has been found in the hippocampus, cortex, and basal forebrain. BDNF has an important role in memory and mental processes. The research of Yamada and his fellows has shown that the increase in BDNF mRNA expression is associated with long-term memory and learning. Activation of TrkB/phosphatidylinositol-3 kinase (PI3-K) in the hippocampus was associated with spatial memory (10). Genetic knockdown of BDNF or its receptor known as tyrosine receptor kinase B (TrkB) causes the severity of memory and learning ability in mice, chicks, and rats (11). In 2000 participants over 50, tobacco measures were measured in patients with subclinical atherosclerosis. The relationship between life expectancy, smoking and cognitive deterioration have been observed in men but not in women (12).

In the assessment of cognitive performance on nicotine intake, 20 smokers were subjected to a Questionnaire on Smoking Urges (QSU) and 2 cognitive tests before and after puffing two cigarettes during two sessions of 90 minutes each. In every session, the subjects had to be deprived of smoking for 18 hours after smoking two cigarettes. The findings of these tests did not show any significance in reasoning items, while the response was slow and the score of QSU increased. The result emphasizes that tobacco obstination enhances cognitive performance (13). A future meta-analysis study could offer a more precise evaluation of how smoking affects cognitive processes.

According to earlier studies, smoking increases the chance of developing different sleep problems including insomnia and sleep apnea and reduces the duration and sleep quality. In a cohort study 958 participants out of 30,097 had possible sleep disorder related to smoking

(pack-years odds ratio 1.01) (14). A group of 50 smokers had more problems falling asleep than a group of 50 non-smokers when they were matched by age and gender. Also, when a group of eight chronic smokers stopped smoking, their sleep patterns improved dramatically. These results agree with studies that discuss nicotine's stimulating properties (15). From 2005–2006, the National Health and Nutrition Examination Survey found that sleep disruptions in people aged 20 and over were assessed among smokers who were currently smoking, had recently stopped smoking, and never smoked (NS). When compared to non-smokers (NS), current smokers (CS) reported considerably shorter total sleep time, greater sleep start latency, increased difficulties falling asleep, sustaining sleep, and waking up earlier than intended. Ex-smokers who reported disruptions comparable to NS and CS slept less well than non-smokers (16).

Despite extensive research on shift work adaptation, little is known about how individual and environmental variables interact to impact sleep among shift workers. In this study, age, smoking, and a negative affect (NA) were investigated as indicators of sleep length and quality throughout three work phases (day shifts, NS, and leave periods, LP). Data were collected from personnel working 12-hour shifts onshore (n= 330) or offshore (n = 456). Onshore, the work phase interacted with smoking, age, and other variables to predict sleep length, whereas NA interacted with other factors to predict sleep quality. Offshore, individual factors did not predict patterns of sleep measurements throughout the DS, NS, and LP phases. Shiftwork adaptability is considered in the offshore environment (17).

Moreover, smoking has been proven to lead to severe damage to cognitive processes including speed processes, memory, and attention through several neurotransmitters. Neurotransmitter modulation by nicotine intake is well documented (18,19). Dopamine involves many brain functions such as sleep, reward and high cognitive functions (20). Abnormalities in dopamine release have been documented in the pathologies of many behavioural and neurological disorders. A common cause of several neurogenerative diseases goes back to the destruction of dopaminergic neurons in the substantia nigra. In a positron emission tomography study, dopamine has been screened in synaptic clefts of patients with neurogenerative disorders. In a study where CSF and plasma concentrations of dopamine homovanillic acid were measured in cigarette smokers, PTSD and HIV patients (21), smokers had significantly reduced HVA levels in their CSF but not in their plasma. The average HVA concentration in their CSF was only 54% of that found in nonsmokers (22). Moreover, a rodent study showed the effects of nicotine on the rat brain's ability to absorb dopamine.

Glutamatergic neurotransmissions are essential systems for memory, learning and cognition (27). GABA is well-documented to be involved in perceptual and attentional functions. To prove the link between GABA concentration and normal mental processes a study applied Mescher-Garwood point-resolved spectroscopy (MEGA-PRESS) 1H-MRS approach on 94 healthy adults. The cognitive abilities of subject was measured using Montreal Cognitive Assessment Battery. The results showed that a high concentration of GABA in the frontal and posterior midline is related to high cognitive performance in the subjects (28). The cerebral cortex has a high concentration of GABA-A. Nicotine's impact on the GABA inhibitory neurotransmitters was found to determine the levels of effect on male and female smokers. Nuclear magnetic resonance spectroscopy was applied to measure the concentration of GABA in the brain cortex of 10 healthy male and 6 female smokers. The subjects were asked to abstain from nicotine intake for 48 pre-experiment and after the experiment for men. The same procedure was applied to the group of females during and after their ovulation phase. The group control included 7 males and 13 non-smoker females. The results reveal significant differences

in cortical GABA levels between the male and female groups. The cortical GABA levels of smoking females have significantly dropped during the ovulation period, while male smokers and non-smokers have shown no changes in the cortical GABA concentration (29).

The earlier investigations of the neuropharmacology of smoking found that nicotinic AChRs are the main targets of nicotine in the cholinergic system. Acetylcholine receptors consist of α4 and β2 subunits. Investigation found that receptors β2 and Ach α4 involved in reward, cognition, mood and many neurological disorders (30). The findings of a positron emission tomography (PET) study have revealed that a single drag of tobacco leads to the activation of α4β2-receptors for 3 hours in many brain regions. Another study reported that the brain switches off 90 % of these receptors for 3,5 hours after each cigarette (31). A defect occurs in smokers who puff 20 cigarettes a day and leads to the destruction of α4β2-receptors. A longitudinal study lasted five years and aimed to investigate the effects of smoking on the cognitive functions of 791 elderly patients without dementia proved that most cognitive functions decline over time in current smokers faster than the non-smokers of age less than 75 years old. This study demonstrated that the decline in smokers without an APOE-ε4 allele has been more pronounced (32).

The goal of this meta-analysis study is to provide a profound knowledge of the mechanisms that link smoking, sleep quality, and cognitive processes. By identifying the specific pathways in which smoking impacts these areas, neuroscientists and psychiatrists may have better knowledge to develop targeted interventions and support for smokers and individuals experiencing sleep and cognitive difficulties.

1.2 Purpose and significance of the study

Since smoking is a public health issue adopted as a spread behavior by a large number of people in our communities, smoking should have an invisible effect on the health of smokers and their surrounding people, like passive smokers. This effect can be statistically measured to determine the level of impact cigarettes have on sleep and cognitive quality of smokers. The primary objective of this study is to test the effects of smoking on sleep quality and cognitive functions in smokers. This study tries to test whether smoking has effects on sleep quality and cognitive functions of smokers more than non-smokers. Based on the previous literature, we hypothesize that smoking affects negatively the sleep quality of smokers more than non-smokers. We also hypothesize that smoking may have an impact on different cognitive functions of smokers more than non-smokers.

Based on the previous literature review, smoking has effects on sleep quality and also cognitive functions. Many studies have failed to study the impact of smoking on both sleep quality and cognitive functions. Furthermore, no study has investigated this effect by measuring different sleep tests and also investigating other areas of cognition. This study is the first to cover research on the effects of smoking on sleep quality and cognitive functions, collecting data from most of the published studies that cover smoking effects on sleep qualities and different domains of cognitive functions, including attention, concentration, memory, and language.

1.3 Interdisciplinarity

The threat of human errors on public safety due to lack of sleep is oversimplified in many fields of research. Thanks to interdisciplinarity, this investigation links between disciplines and

covers the gaps between specialties regarding sleep disorders, cognitive functions, and the effects of smoking on both functions. This strategy will improve many areas of life. One noteworthy example is the everyday occurrence of human mistake in many areas of life. Because they don't get enough sleep, human mistakes made by transportation workers, for example, have a clear and direct impact on public health globally. Due to fatigued driving, the National Highway Traffic Safety Administration recorded 91,000 collision incidents that resulted in 800 fatalities and 50,000 injuries. The Federal Aviation Administration documented 4 to 7 business aviation accidents occurred because of lack of sleep and fatigue. Lack of sleep leads to low concentration, confusion, and low attention, as reported in the study of W. Price and D. C. Holley, which happened on 182 flights in September 1978. In this crash, 135 people died, besides 9 civilians on the ground. According to the National Transportation Safety Board, 85% of accidents happen due to “human errors” (403). The human errors of rail transport are not much better than aviation transportation since the Federal Railroad Administration reported that railway employees working night shifts are at higher risks of fatigue leading to fatal errors.

This meta-analysis is going to provide quantitative proof of the medical reasons behind sleep disorders and cognitive impairment in patients who use exogenous stimulants like cigarettes. The thesis explains also the underlying mechanisms that contribute to both cognitive functions and sleep pathophysiology. The findings of this research are expected to advance the theoretical understanding in the fields of psychiatry, neuroscience, cognitive therapy epidemiology, and many other sectors of life. In light of these results, researchers will be considering the effects of smoking on sleep quality and also cognitive functions during interventions leading to effective strategies across various disciplines.

1.4 Statement of the Research Problem

There are 5000 thousands of pharmacological components in tobacco that have been documented (41) and 9600 components based on 7000 references, as documented in the book of Rodgman and Perfetti (42). Every single component of these chemicals is known to contribute not only to carcinogenic, mutagenic, and toxicological effects but also induce several pulmonary, cardiovascular, and neurological diseases that affect sleep quality and cognitive functions. Consequently, questions have been raised about the importance of investigations into the effects and aetiology of tobacco on the sleep structure and cognitive functions of smokers.

Over many years, several studies suggested a great association between sleep disturbances and tobacco (43); (44); (45); (46); (47); (48); and cognitive dysfunctions and smoking (49) (50); (51); (52); while a large number of other studies have surprisingly shown no significance of the effects of smoking on the sleep architecture (53) and cognitive functions of smokers compared to non-smokers (54); (55). According to the findings of Foley, there was an instantaneous association between sleep complaints and other chronic diseases in the sleep structure of smokers among the cohorts of 9000 mature individuals (56). Unlike the results of Foley, Janson and his colleagues reported in their research, which aimed to investigate the actual causes of sleep disturbances in the population of 2202, a strong correlation between the increase of sleep latency and the incline of nighttime arousing (57). In a rodent study, nicotine as well as anabasine and anatabine, tobacco constituents, have been reported to improve the work of cognitive functions in rodents. Specifically, anabasine and anatabine have shown different significant improvements in memory and attention (58).

1.5 Research questions and hypotheses

Research questions:

1. How does smoking generally affect sleep quality?
2. Could smoking affect the general cognitive functions?
3. Which area of cognition-memory, attention, focus, reasoning, and executive function is affected most than others?

Research hypotheses:

1. Smoking decreases the sleep quality of smokers more than non-smokers.

2. Smoking may have negative impact on the cognitive functions of smokers compared to non-smokers.

3. Many areas of cognitive functions may be influenced by smoking including attention, memory, and executive function experiencing the most significant negative effects.

1.6 Theoretical and methodological concepts

The theoretical and methodological concepts relevant to this thesis about the effects of smoking on sleep and cognitive function are:

- **Cognitive neuroscience:** to understand the neural processes underlying cognitive functions and how smoking can impact them, particularly in the areas of attention, memory, and executive function.
- **Cognitive load theory:** to investigate the amount of mental effort required for a task and how it affects performance, which may be relevant for understanding the impact of smoking on cognitive function.
- **Neurocognitive theory:** to propose how smoking affects the brain's neurocognitive processes, leading to impairments in attention, memory, and other cognitive functions.
- **Bio-psycho-social model:** there is a connection between smoking (external stimulant), sleep patterns (physiological system), cognitive functions (neuro-psychological function) and social factors. Interaction between these systems demands understanding the underlying mechanisms of each. Applying this model to this thesis may help to identify the complex interaction between smoking behaviour, individual differences, and social context.
- **Psychophysiology model:** to examine the interaction between the mind's motives for smoking and the body and how smoking can affect physiological responses, such as heart rate and brain activity, that are related to both sleep and cognitive function.
- **Addiction theory:** The thesis covers the significant theories that explain the underlying psycho-neurological-pharmacological mechanisms of addiction to decipher the mechanisms of smoking's impact on smoking on cognitive functions and sleep patterns in smokers.

II. Literature Review:

2.1 Aetiology of Addiction

The phenomenon of addiction has been for decades considered a debate for researchers and clinicians. Addiction is a heterogeneous phenomenon characterized by compulsive and even destructive behaviors. This chapter intends to study the concept of addiction by emphasizing certain opinions of early addiction specialists in the light of the worldwide classification "bible" codes, namely the International Classification of Diseases, Eleventh Revision (72) and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (73).

Gurus in addiction research have approached addiction behaviours from different perspectives. Before diving into the categorization systems' criteria, it is important to consider the perspectives of early pioneers in the field of addiction research who have made a substantial contribution to our understanding of this complex behavior.

2.1.1 Definition of Addiction

According to the National Institute on Drug Abuse's (NIDA) director, Dr. Nora Volkow, who investigates in the neuroscience of addiction and represents the neurobiological perspective, Dr. Volkow's research has shown how drug use affects the reward system of the brain and how these changes are linked to the compulsive character of addiction. Dr. Volkow identified addiction as a brain disorder, highlighting the complex link between brain chemistry and addiction susceptibility (74).

Dr. Herbert D. Kleber is a neuroscientist who has made an important contribution to our understanding of the phenomenon of addiction and has interest about the impact of drugs on the brain's reward system. In addition, Dr. Kleber has consistently supported medication-assisted therapy (MAT) as an important procedure of addiction rehabilitation. His work emphasizes the significance of using behavioral therapy in combination with pharmaceutical treatments to deal with the complexity of addiction (75).

In the Harvard Grant Study, one of the longitudinal-running studies in the field of psychology and psychiatry that began in 1938 and was conducted by Dr. George Vaillant and E. Vaillant, the findings provided essential data on addiction and recovery over the course of an addict's life. Interestingly their results questioned the concept that addiction is only controlled by genetics. Dr. Vaillant emphasizes the impact of heterogeneous factors, including social-psychological factors, on the risk of addiction (101). The same perspective more or less has been adopted by the addiction expert Dr. Stanton Peele (76).

Addiction has been seen by Dr. Stanton Peele as an influence by psychological and environmental elements in combination with dependence on drugs. Dr. Stanton Peele denies the classical model of diagnosis tackling addiction, with more emphasis on the need to consider the environmental and psychological factors combined with drug abuse in the diagnosis of addiction (77).

In addition to the perspectives discussed by these addiction aetiology pioneers, I find it essential to shed light on how addiction is classified under the DSM-5 and ICD-11 categorization systems. According to the ICD-11, the widely accepted categorization code used

to classify illnesses and medical disorders issued by the World Health Organization (WHO), this code index sees addictive behaviors as a range of behaviors associated with drug use and addictive behaviors. Based on ICD-11, “addictive behaviors”, “hazardous use”, and “dependence syndrome” are the major symptoms of addiction. The “Addictive Behaviors" item in the ICD-11 is categorized as "Mental, Behavioral, or Neurodevelopment Disorders." This category includes substance use diseases, such as "Dependence Syndrome" and "Hazardous Use of Psychoactive Substances”. The “hazardous use" category refers to drug use behaviors that increase the possibility of negative outcomes but may not always imply dependency. Dependency syndrome, based on the criteria outlined in ICD-11, characteristics of both psychological and physiological substance dependence are included. These characteristics include a strong need to use, struggle with abstaining, signs of withdrawal, tolerance, and disinterest in other hobbies and interests.

The American Psychiatric Association's DSM-5 is the main used index in the US for diagnosing mental health diseases. According to the DSM-5, the definitions of "substance addiction" and "dependence" have been modified by using a new term so called "substance use disorder" (SUD). The new diagnosis "Substance Use Disorder (SUD)" consists of three severity subcategories, namely mild, moderate, and severe. These subcategories require the use based on association with drugs like alcohol, cannabis, and opioids. An individual has to meet several characteristics to be diagnosed with a drug use disorder. These characteristics should meet certain aspects like lack of control over the use of the substances, social difficulties, dangerous use, tolerance, withdrawal, and cravings, as well as other issues that will be discussed in the coming chapters.

The DSM-5 proposes a dimensional assessment method that calculates the total severity of the condition by taking into consideration the severity of each criterion. The DSM-5 includes disorders unrelated to substances as well as disorders associated with substances, including gambling disorders, under the heading of "Substance-Related and Addictive Disorders."
In summary, the phenomenon of addiction is complex, continuously shifting and developing from the perspectives of many specialists, and codified in categorization systems like DSM-5 and ICD-11. Nora Volkow's neurobiological viewpoint emphasizes the significant influence addiction has on the reward system in the brain

2.1.2. The Lesch Aetiology of Addiction

The Lesch aetiology of addiction depends on many complex factors explained by the interaction of social, psychological, and biological paradigms. Regarding the psychological approach presented by Lesch, the paths of addiction involve individual experiences, taught behaviours, cognitive processes, and early relationships inside society. Epidemiological studies have shown a deep connection between social circumstances and addictive drugs, which confirms the social approach that emphasizes the influence of the family, culture, and the role of social factors in addiction aetiology. The lesch biological approach provides proof about alcohol and tobacco that stresses the role of the neurotransmitter system, neural models, as well as the genetic predisposition of individuals in heterogeneity of addiction. Moreover, the psychiatric perspective presented by Lesch about the underlying mechanisms of addiction meets the clarification of Damasio and others that explain the relationship between neurological processes and emotional dynamics. According to Lesch, the dynamic nature of addiction demands considering multidimensional approaches in designing successful prevention for addiction (79).

These factors stay fundamentally behind the craving and the withdrawal in some typologies of smoking, like in types 3 and 4. However, it is worth mentioning that Lesch classifies tobacco addiction based on the level of nicotine consumption. Lesch has 4 types of smokers according to their level of severity. Type I and type 2 are light smokers, while type III and type IV are heavy smokers. These latest types are also more complex than what was previously suspected due to several clinical factors, on top of their comorbidities, which are linked to insomnia (80). The previous code of ICSD-II has several characteristics for insomnia disorder, among which are attention deficiency, memory disorders, lack of energy, and motivation, besides continued panic (63).

The psychiatric comorbidity was confirmed in more than one study, which stressed the relationships between smoking and psychiatric disorders and proved the positive relationship between nicotine addiction and some mental disorders like depression and stress (64), (65). In a longitudinal epidemiological study run by The Medical School of Johns Hopkins, insomnia in 1053 medical students was reported to have a strong correlation with other psychiatric disorders and was considered an earlier sign, which is followed by stress and depression (70). Moreover, insomnia is not only linked to psychiatric comorbidities but also to other substances like alcohol. According to Lesch, dependent smokers who drink alcohol show the symptomatology of sleep disturbance and depression in contrast to non-alcoholic smokers who aim for stress relief after drinking (71).

In light of the latest findings of Lesch, type 1, which is scored according to Fägerstrom at 5 points, and type 2, which is scored by Fägerstrom at ≤ 4 points, are still free from psychiatric co-morbidities and behavioural disorders that are present in type 3 and type 4 dependent smokers (80). Up to this date, no data refers to the relationship between psychiatric comorbidity or behavioural disorders and sleep disturbances in types 1 and 2. The therapeutic efficacy of the drugs used for withdrawal therapy and relapse prophylaxis in type 1 like Varenicline and MAOIs (moclobemide) (80) is undeniable; however, insomnia was produced as a side effect in type 1 nicotine addiction (81). While in type 2, less serious insomnia has been produced as a result of drugs used like acamprosate (82) bupropion (83), and moclobemide (84) for the treatment of type 2. This observation may raise the importance of knowing whether insomnia in type 1 and type 2 is produced as a result of side effects of the drugs used for therapeutics or due to adverse effects of tobacco addiction. Furthermore, there is no guarantee proving that comorbidity (like stress or depression), but not the interaction between sleep promoters (like prostaglandin D2, delta sleep-inducing peptide, muramyl, dipeptide 1, fatty acid primary amides, and melatonin) and smoking components that lead to insomnia disorder in type 3 and type 4 and leads to the same effect in type 1 and type 2 just as well. The Lesch typology provides great support for any future studies that aim to measure the level of addiction related to the level of severity in sleep quality and cognitive functions of smokers.

2.1.3 Factors Contributing to Nicotine Addiction

Addiction is a compound compulsive behaviour, whereas drug abuse is considered a complex disorder that demends medical attention. Long-term use of external substances like tobacco leads to tremendous changes in the brain chemistry, brain circuits and impacts brain functions like memory, decision-making, attention, and personal judgment. Tobacco addiction is a complex health issue that requires shedding light on trigging factors that contribute to the perseverance of smoking abuse.

2.1.3.1 Genetic Factors

Genetic factors play a major key factor in tobacco addiction aetiology. Research on twins has revealed 50% of genetic effects on cigarette abuse. Specific genes in several types of receptors believed to be linked to smoking addiction, like GABA receptors, dopamine receptors, transporters of dopamine, and nicotine receptors, have been investigated (85).

The α5/α3/β4 nicotinic cholinergic receptor gene complex on chromosome 15 has been the main genetic factor that determines nicotine addiction, according to a recent investigation in genomic studies. Surprisingly, many factors like the quantity of nicotine intake, cotinine level, and related disorders to smoking are linked to nicotine dependence and the α5/α3/β4 gene area (86); (87).

Other eight twin meta-analysis studies about the link between genetics and person's tendency of addiction showed the following results: abuse tendency for cocaine intake ranged between 42% and 79%. Addiction to opioids has been examined in two studies, namely the study of Kendler et al. (88) and Tsuang et al. (89), who announced 23% and 54% genetic attribution factors, respectively.

Different genes were identified for each type of substance or behavioural addiction. Certain genes have been linked in many studies with alcohol abuse, like ADH1B and ALDH2. Investigations have shown that polymorphisms in ADH1C specifically (rs698 and rs1693482) were found to be involved in alcohol consumption. In chromosome 15, different versions of specific genes, specifically CHRNA5/CHRNA3/CHRNB4, are connected to nicotine abuse (90). Variations within the CHRNA4 gene have shown a great impact on the consumption behaviour of smoking in participants within 24 hours (91). Some other studies have shown the link between the DRD2/ANKK1 Taq1A allele and the high nicotine addiction tendencies (92).

2.1.3.2 Environmental Factors

Animal models provided by Caprioli and colleagues (2007) prove that the environment has an impact on drug addiction (93). As reported in Caprioli and colleagues' studies, seeking drugs can be due to maternal separation during infancy, as reported in many rodent studies that make individuals more susceptible to addiction than others (94); (95); (96); (97); (98). Similar findings of neonatal isolation experience on rodents showed that isolation of small rats increased the level of dopamine in the accumbens when they got cocaine compared to non-isolated small rats (99).

In studies about the self-administration of morphine and heroin comparison between single-housed (SH) and group housing environment (GH) rats, increased self-administration has been shown in SH rats compared to GH rats (100), (101). In another modified study that added to SH and GH another group of rats with an enriched housing (EH) designed model with toys, wheels, and exercise equipment that tended to increase mental and physical stimulation in rats, amphetamine consumption has still been found to be higher in the SH group of rats and lowest in the EH, while the GH group of rats has fallen in between (102). These results suggested that drug-seeking behavior is linked to the social interaction and variety of objects available in the environment of individuals.

Social stress has been linked to the self-administration of cocaine in rats. Compared to non-pressured rats, socially pressured rats by the same sex or the opposite sex have shown higher consumption of cocaine (103); (104); (105); (106). Some studies have shown the connection between sledge administration to cocaine and social defeat in rats. After the rats of these studies have been exposed to continuous social stress, their brain areas—the prelimbic area and infralimbic cortex, NAc, amygdala, and ventral tegmental area (VTA)—have shown changes in the levels of the mRNAs Fos and zif268 (107); (108); (109).

In the same context, two groups of monkeys, dominant and subordinate monkeys, have shown different reactions to the self-administration of cocaine. Having been injected with cocaine and saline, the subordinate group of monkeys showed great responses to cocaine but not to saline compared to the dominant group of monkeys, who showed no differences in response to cocaine and saline. This study concluded that there is a significant correlation between drug intake and social hierarchy (110). The study of Ramsey and Van Ree in 1993 about rats who just witnessed other rats being exposed to electrical shocks and forced to position on a hot plate showed higher cocaine administration than the control groups. This group of studies confirms the association between the effects of social stress and cocaine intake (111).

Physical stressors have been another factor that plays a big role in the drug-seeking behavior of individuals. Foot shock experiments have been proven to encourage drug self-administration of cocaine (112), morphine (113), and alcohol (114), while tail pinch has shown facilitation of amphetamine self-administration (115), and immobilization has shown self-administration of alcohol.

Food restriction effects on self-administration of cocaine, ketamine, amphetamine, and phencyclidine have been proven in many studies done by Carroll and colleagues. (116); (117); (118); (119). They have experimented with free-feeding vs. food-restricted models on rats and monkeys. The results obtained have shown the great effects of the food restriction group of rats on all types of drugs compared to free food restriction. Surprisingly, when the group of restricted foods were refed, the results showed less self-administration of drug intake in this group (118).

Talking about environmental factors' effects on drug intake requires shedding light on the role of family in drug addiction. In the study of Jêdrzejczak, M., done in 2005 about the family connection to an individual’s addiction, 559 recruited persons have shown that addicts come from unstable families. Moreover, families suffer a lack of connection because of divorce, the death of some parents, members of the family with continuous conflicts, an electrified negative home atmosphere, and animosity among family members. All these social factors play a significant role in addiction vulnerability. The research proves the positive effects of family stability in drug prevention (120).

In a meta-analysis study by Hunter and Schmidt, 16 out of 32 studies were investigated to test whether individual or environmental factors influence people’s addiction tendencies. The results showed that environmental factors of people's tendency to drug addiction were 0.61 ($P \leq 0.00001$), while the effect size of individuals tendencies to drug addiction was 0.45 ($P \leq 0.03$) (121).

2.1.3.3 Behavioral Factors

Numerous behavioural factors play a significant role in individual vulnerability to substance addiction. The reinforcement factor has been since ages the center of interest of many behaviorists and researchers. Reinforcement has been defined as positive reinforcement and negative one. The positive use of a substance as a reward for reinforcement of repeated behaviour. Reinforcement can also be misused to reward a negative behaviour based on harmful substances to relief pain or negative emotions which lead to addiction (122).

Throughout repetition of any surrounding stimulus, like light, smell, places or activities, association to specific response due to drug addiction becomes as strong as the substance of addiction. Smokers, for example, prefer certain places like coffee shops, certain times of smoking during the day, or specific smells which build significant associations with the pleasurable effects of nicotine and these cues in their brains. Childress and colleagues (1984) demonstrated the efficiency of environmental cues in triggering addiction and craving in addicts despite the absence of a substance. Studies have proven similar effects and pathways in the brain triggered by cues (123). This activation causes the release of the same neurotransmitters, namely dopamine during pleasure and reward. This explains the level of challenge addicts confront during contacting any cues involved in the process of reward and substance which stresses the importance of controlling environmental cues to control any undesirable behaviour leading to addiction.

The influence applied by the social environment on addicts has been a major factor in seeking addiction. As explained in the environmental factors behind addiction previously, peer pressure encourages each other, and family situations as well as social influences have a strong impact on the addictive behaviours of individuals. (124).

The social network represented by media has a strong influence on the perception of individuals towards the use of addictive substances. Social media and cultural norms contribute drastically to facilitating the use of substances. Adults specifically have a strong tendency to mimic any adult behaviours regardless of the harmful results.

The impact of stress and the coping strategy with stress has a strong association with addiction. Addictive behaviours to reduce stress and to cope with daily stressful situations lead many individuals to be susceptible to addiction (125).

2.1.4 Summary of Addiction Concepts

This section of the aetiology of addiction covered multiple dimensions believed to be involved in addiction, presenting different perspectives and contributions of early pioneers. It highlighted each of the reliable indexes, DSM-5's, and ICD perspectives on both the definition and classification of tobacco addiction. By emphasizing the relationship between social cues, psychological factors, and biological factors and categorizing smokers according to their severities and comorbidities, Lesch's aetiology has served to further explain the complexities of addiction. This chapter also covered the genetic investigations that specify the link between heritability and addiction and emphasized the impact of the environment, including social stress, family stability, and physical stressors, on the-seeking behavior of addiction. Furthermore, reinforcement and environmental cues are believed to be the behavioral factors that significantly contribute to addiction. Understanding the complex nature of addiction and its various factors may offer a deep foundation for demystifying its impact on the sleep structure and cognitive abilities of smokers.

2.2 The effects of smoking on cognitive function

Most experts have always seen smoking behaviour as an effect of pharmacological abuse, which leads to cardiological, pulmonary, and immunological damage in smokers. These physical damages can be only rectified by quitting the habit of smoking. Oversimplification of the complexity of systems behind smoking behavior is similar to the analogy of focusing on the iceberg surface without recognizing the real size of the iceberg beneath the water. This superficial diagnosis is what leads most smokers to fail to quit smoking regardless of the huge efforts and financial support invested in the rehab centres. This chapter sheds a glimpse of attention to other systems that may explain how smoking behaviour can be affected by other dimensions rather than the pharmacological side of tobacco.

2.2.1 Cognitive Theories of Smoking

Several cognitive theories have been developed to understand the complexities of smoking behaviours. These theories explain how the psychological and cognitive processes interfere with smoking and addiction. This chapter identifies the cognitive theories believed to drive smokers to smoking behaviours or reinforce their habits of smoking.

2.2.1.1 Theory 1: Cognitive -Behavioral Theory

In light of cognitive theories of smoking, cognitive-behavioral theory suggests an exhaustive Framework for investigating the complicated relationship between beliefs, actions, and smoking habits (127).

Cognitive-behavior theory stresses the connection between thoughts, emotions, and behaviours (128). According to CBT, persons' thoughts, feelings, and beliefs towards smoking have a major impact on their smoking behaviour. If an individual, for instance, thinks that smoking releases stress, this kind of belief can provide feelings of comfort during stressful situations (129).

Recognition and modification of the thought patterns that associate smoking with good feelings and successful handling of social situations can be a significant step in the prevention process. The harmful thinking patterns that deceive smokers into being dependent on smoking in certain situations can be altered once these patterns are modified (130).

Cognitive-behaviour theory emphasizes the role of craving and triggers as crucial mechanisms in seeking smoking behaviours. The theory assumes altering smokers' attitudes and actions towards cigarette stimuli can control these triggers. Cognitive behavioural therapy suggests techniques that enable smokers to control the urge to smoke behaviour by recognizing smoking triggers, applying substitute behaviours, and learning coping mechanisms (131).

Cognitive-behavior theory stresses the importance of coping strategy development. These coping strategies cover withdrawal symptoms, stress management, and urging resistance by modifying the construction of cognitive and behavioural patterns (132).

The cognitive behavioural theory provides the behavioural change and maintenance model as an intervention strategy model. This model emphasizes the modification of smoking

behaviours such as setting clear visions, tracking the process, and adopting reinforcement of new positive behaviours for individuals to stop smoking behaviours (133).

In conclusion, cognitive behavioural theory acknowledges the effects of thoughts and beliefs on smoking behaviours. CBT provides a structured approach including coping strategies, modified thought patterns, and coping techniques as a cessation model for smoking behaviour.

2.2.1.2 Theory 2: Expectancy Theory

The potential decision-making processes as well as how various cognitive biases and cognitive processes may influence smokers' decision-making. The fact that smokers choose to smoke does not, however, preclude the possibility that they could choose to stop. Whereas most people seem to find it hard to escape the cycle of dependence on short-term reinforcement contingencies; to resist giving in to their present wants, cravings, or fears; and to start working toward a long-term objective with little expectation of success.

According to the expectation theory, one's willingness to engage in action depends on their expectation that it will result in positive results. Furthermore, according to Bandura's Social-Learning Theory, a person's behavior is more predicated on what they assume than on what is factually true (134). According to research on substance use, an individual's opinions about the advantages of using drugs are strong indicators of future usage. Smokers were more likely to give up smoking, for instance, if they had lower hopes that smoking would relieve bad emotions or boredom. The expectation of pleasant consequences and the desire to avoid undesirable outcomes have also been linked positively to nicotine dependency in regular smokers.

For instance, the subjective expected utility (SEU) hypothesis proposes that people choose between competing behaviors based on a perceptive parameter in which the behavior with the highest subjective value is chosen to provide the greatest benefit regardless of the alternative behavior’s objective value (or cost). This theory claims that smokers hold more favorable opinions about the advantages of continuing to smoke than they do about the advantages of quitting. For instance, even if a smoker is aware of the advantages of quitting, he or she will continue to smoke if they feel that doing so will maximize the benefits of smoking for one aspect of smoking's role in their lives (like social benefits, avoiding physiological withdrawal) (135).

2.2.1.3 Theory 3: The Social Learning Theory (SLT)

The Social Learning Theory (SLT) offers an extensive model for comprehending how people learn smoking habits from interaction with society, mimicking, and observations. SLT theory stresses the significant role of mates, family, and mass media in adopting smoking habits by serving as significant role models and motivating factors (136; 137).

The social learning theory attributes smoking behaviours to the observational learning of individuals. Smokers learn the behaviour of smoking by observing and then imitating other smokers, specifically those influential role models in society. In 1977, Bandura’s notion of modelling emphasizes the strong impact of observed behaviours on individuals' behaviours (136).

Adopted Smoking behaviour has been assigned to the influence of role models in society. Smokers, especially teens, have a strong tendency to mimic adults’ behaviours inside the

family and admire members of society, specifically role models and influential figures. Literature has shown that adolescent smokers are influenced by peer pressure to adopt smoking behaviours. Bandura (1986) stressed in his research that the perception of individuals towards showing attraction and acceptance of smoking behaviours is strongly influenced by family members and peers (138).

Smoking behaviour is influenced by the power of media and social networks. Media representations like social media, movies, and advertisements have a strong impact on adopting smoking behaviour as an acceptable behaviour in society. Smokers' perceptions have been strongly shaped by the media, which normalizes the behaviour of smoking via a tremendous amount of exposure, especially for young audiences. According to Bandura (2001), media is a powerful source for modelling of smoking behaviour (139).

The Social Learning Theory (SLT) suggests the significant role of reinforcement and conditioning in maintaining smoking behaviour. Smoking behaviour is positively reinforced by the social acceptance towards smoking and the pleasure obtained from smoking. Furthermore, the conditioning process associated with smoking behaviour in certain contexts reinforced the habit of smoking, as reported by (140).

Thus, social learning theory explains how individuals adopt smoking behaviour from society and peers through observation and imitation. The social learning theory also stresses the role of mass media in shaping the subconsciousness of smokers, especially teenagers who find smoking via the continuous amount of repetition of socially accepted behaviour.

2.2.1.4 Theory 4: Cognitive Dissonance Theory

According to cognitive dissonance theory, people experience discontent when their beliefs contradict their behaviour. Cognitive dissonance theory highlights the inner struggle individuals undergo when their attitudes and convictions contradict their behaviours and activities. In the case of smokers, for example, they know perfectly the hazardous effects of smoking and they probably have watched a vivid example of a friend or family member who met a tragic end due to extended consumption of tobacco, yet they do not mind smoking without thinking about the bad implications. This behaviour is unquestionably defined by smokers as improper behaviour, which they may prevent their children from doing, but they nevertheless do it anyhow. such behaviour can induce a sense of a mental discomfort known as cognitive dissonance (141).

According to Cooper j 2007 individuals under the feeling of pain due to contradictory behaviour with their beliefs try to create an inner balance as a natural reaction towards cognitive dissonance this balance is a natural psychological defence mechanism known as cognitive consistency to minimize the pressure created as a cognitive dissonance justifying the need for smoking to reduce the stressful situation for instance support the smokers behaviour why they smoke (142),,(143).

Harmon-jones and colleagues propose that to reduce the annoyance of contradiction in their perspectives and behaviours people tend to adopt new convictions and attitudes either by quitting smoking or by underestimating the risk of tobacco to regain cognitive stability (144)

Finally, cognitive dissonance theory explains the number of psychological tensions smokers face when their smoking behaviours contradict their convictions about smoking this notion

highlights how this conflict encourages smokers to develop their smoking behaviours to reduce cognitive dissonance.

2.2.2 Psychological Theories of Addiction

2.2.2.1 Theory 1: Psychodynamic Theory

According to depth psychology, Zingerle (1994) highlighted three main functions of addiction: first, addiction serves as a means of satisfaction; second, it serves as a form of defensive strategy (as in the case of depression and anxiety); and third, it serves as a means of reward, such as for a feeling of being worthless (145).

Addiction can be seen as a tendency in the oral development stage, as Strotzka H. proposed in 1982. (Strotzka 1982). Freud emphasized the oral-erotic aspects and justified them with early emotional derangements and a lack of affection, with both the delay in maturity as a key factor. According to Freud, changes in emotional experience result in an alteration in how we deal with the derived emotions, which are always found in unconscious insecurity. Anxiety is a major factor in the development of addiction. Adults regress when they are inebriated because inhibitions and protective behaviour disappear, making previously repressed sources of pleasure available once again. According to Strotzka, a patient with severe depression is an oral-dependent person who is denied essential supplies (146).

2.2.2.2 Theory 2: Ego-Psychological Approaches

Abnormalities in self-image formation result in abnormality in perception, which leads to an absence of distinction of emotions and their interpretation; structural abnormalities in interpersonal interactions, which are generally linked to primitive survival mechanisms; disappointment prejudice; emotional and impulsive behavior disorders; judgment disorder, particularly in predicting the influence of one's behavior on others; and dependent conflicts between symbiotic and autonomic requirements.

2.2.2.3 Behavioral Approach

Within the behavioural approach, specifically within the framework of operant conditioning proposed by Skinner, any behaviour is learned by reward or punishment. This theory explains how tobacco dependence behaviours are acquired through reward. Over time, smokers may need high doses of nicotine to reach the same stress relief effects, leading to an increase in tobacco consumption. This cycle is used to explain how addictions develop to maintain addiction. Positive and negative stimuli can enhance or decrease the consuming behaviour, according to Skinner's concept of operant conditioning (Skinner 1938).

2.2.3 Cognitive Bias in Smokers: Influence of Smoking on Attention and Attitude

Smoking has been documented to have influence on the cognitive judgment of smokers.
In a study by Bradley, Brendan P., et al. (2008) tend to investigate how smokers react to smoking-related images, researchers wandered whether smokers focused more on how important these images were to their smoking habit or on how much they liked them. They

used a mix of happy and sad smoking scenes and interestingly, the findings revealed that smokers paid more attention to both types of images when they were shown for a longer time, but not for a shorter duration, compared to nonsmokers. While there wasn’t a big difference in how both groups approached the pleasant smoking images, smokers had a stronger reaction to the negative ones. Interestingly, smokers rated both happy and sad smoking images more positively than nonsmokers, suggesting they have a more favorable view of smoking-related cues overall.

2.2.4 Attentional Bias in Substance Abuse: Smokers' Alertness for Nicotine Signals

Utilizing visual probe tasks, two studies were conducted to evaluate attentional biases towards smoking-related stimuli in smokers and nonsmokers. Smokers who had made several efforts to quit smoking demonstrated an attentional preference for smoking-related scenarios when images were shown to them for 500 milliseconds in Experiment 1. Experiment 2 confirmed this conclusion, revealing that when images were given for 2,000 ms, smokers as a whole showed attentiveness for smoking-related signals, while nonsmokers did not. The results of the 500-ms exposure condition imply that among smokers, early focusing of attention to smoking signals is related to recurrent failed efforts at cessation. The findings are explored concerning reward theories of addiction and selective attention component processes such as initial orientation vs. maintenance (149).

2.2.5 Smokers' Selective Processing of Smoking-Related Stimuli

This study set out to understand how smokers, ex-smokers, and people who have never smoked react to smoking-related cues like seeing words related to cigarettes. The researchers wanted to see if abstinence (staying without cigarettes for 24 hours) or someone's smoking history would affect how quickly they could identify the colour of smoking-related words compared to neutral words (like "chair" or "table"). The researchers adjusted the Stroop task to fit the purpose of the investigation. The research included 95 subjects, 43 smokers, 22 ex-smokers, and 30 non-smokers. Smoke smokers were asked to abstain for 24 hours, while others were left to smoke as normally. The main aim of the test was to test if the obstinate smokers found it hard to ignore smoking-related words influenced by craving for smoking. The results were surprising for 24-hour abstinence smokers who did not show any different tendency to process smoking-related words more than other free smokers. The second interesting fact was regarding the ex-smokers who did not have to struggle with any nostalgic feeling of missing smoking by not showing different reactions to smoking-related words exactly similar to never smokers. The group of current smokers took longer to identify the colours of smoking-related words compared to neutral ones, indicating that smoking cues continue to capture their attention. This effect was especially pronounced in smokers who are more sensitive to the rewards of pleasure and satisfaction. In summary, one has learned from this study that current smokers have higher attention bias toward smoking-related cues which did not appear with smokers who quit. The study proves that abstaining from smoking for 24 hours does not change the attention bias indicating that just long-term quitting is more significant for restructuring the brain reaction to smoking triggers. (150).

2.2.6 Relationship to reward theories of addiction and selective attention processes

The interaction between addiction and selective attention according to reward theories provides a clear interpretation of the underlying complex mechanisms of the cognitive system. Reward theories demystify the brain system's response during the addictive behaviours of smokers. The external stimulus requires the involvement of certain neurotransmitters in the brain, like dopamine, which is necessary for processing information during human interaction with the environment. The loop of repetition due to addiction depends on the strength of the response after the stimulus. In-depth, the neural correlation of craving, reward, and reinforcement demands understanding how selective attention as a fundamental element in cognitive processing links to compulsive addictive behaviour. The limited attention capacity we have led our brain to naturally limit the stimuli for the possibility of memory processing and decision-making (151). This attentional priority has been defined by scientists to have two forms: voluntarily directed towards stimuli (152), (153), and involuntarily attracted by physical stimuli (154), (155). The mechanisms involved in the voluntarily directed attentional stimuli are a dorsal frontal-parietal network (156, 157), while the involuntarily driven attentional stimuli are controlled by the ventral temporal-parietal connection of the brain (158, 157, 159).

Interestingly, research in this sense revealed the fact that the natural survival instinct gives priority to any stimulus to provide information for the survival process. (160, 161, 162, 163, 164, 165). However, it has been scientifically challenging to know whether the reward or the goal is what drives attention when it comes to studying attention linked to reward (166). Some scientists provide evidence that even the non-oriented rewarding stimuli can involuntarily shift the attention of oriented task stimuli. To illustrate, imagine the scenario of a smoker who is engrossed in the process of reading and can be automatically diverted by capturing the involuntary attention of the stimulus of cigarette smoke despite the voluntarily directed attentional stimuli of reading (167, 168, 161).

2.2.7 Imaging studies on the effects of smoking on cognitive functions

Tobacco has been proven to lead to a sequence of chemical changes in the functions of the brain of smokers. In the dorsal lateral prefrontal cortex (DLPFC), which is involved in problem-solving, attention, and working memory in the human brain, nicotine has been screened to increase the functions of this region in the brain of smokers. Conversely, as can be seen in (figure 1) of the following image, nicotine has been shown to lower smokers' anterior cingular cortex (ACC) activity. The ACC is in charge of mistake detection and conflict monitoring in the human brain.

Imaging techniques on effects of nicotine on cognitive functions in the brain

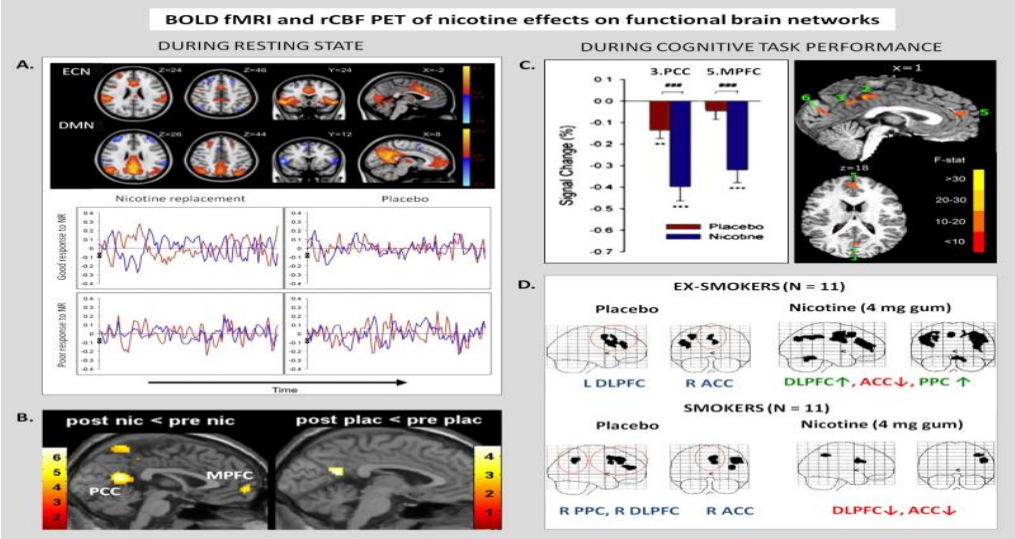

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Figure 1: The graphs represent different cases of blood oxygenation levels dependent on imaging techniques: regional cerebral blood flow (rCBF) in PET and (BOLD) fMRI to measure the effects of smoking on cognitive functions in many brain regions. A. represents studies on executive control networks (ECN) and default mode networks (DMN). B. represents studies on the effects of nicotine on DMN. C represents the studies on nicotine impact on DMN (MPFC and PCC) in spatial attention in smoking and placebo. D. graph measures nicotine effects on the dorsolateral prefrontal cortex during the working memory task in former vs. current smokers.

The study includes investigating the effects of nicotine on two essential anatomical regions of the human brain, the medial prefrontal cortex (MPFC) and posterior cingulate cortex (PCC). The main functions of MPFC involve highly complex cognitive processing like decision-making, planning, problem-solving, and emotional responses. Unlike the MPFC, the posterior cingulate cortex (PCC) is more responsible for self-reflection, special navigation, and the internal world than the external world. These two regions in DMN are supposed to be active during rest and passive during high-performance activity. These regions have been screened, confronting changes in their activities during exposure to nicotine. Nicotine further reduced the activities of these regions in DMN (406).

2.3 Smoking and Sleep Quality

Sleep disorders has increasingly driven the attention of scientists in the last decades. When scientists search the causing factors, nicotine has appeared to be on the top list of scientists radar. Given the fact that tobacco has been proven to lead to hazardous pathologies and tremendous internal damages, sleep architectures and patterns are required to investigate to understand how smoking affects the sleep patterns and lead to sleep disorders in smokers.

2.3.1 The Molecular Biology of the Circadian System

The human circadian rhythm is a body's internal clocks subjected to physiological and behavioral rhythms (169). Interference between time and structure, as determined by homeostatic and circadian mechanisms, is a characteristic of sleep regulation (170).

The processes that determine sleep regulation are the ultradian system, the circadian system, and homeostasis. The sleep ultradian rhythm refers to the biological rhythm that occurs in less than 24 hours a day and includes 90 to 120 minutes of sleep cycles within the four sleep stages of humans. The inner clock is built of behavioral, physical, and psychological systems that are

subjected to the day cycle, respond to light and darkness, and are adjusted by homeostatic hormones. 171).

The underlying molecular mechanisms of the circadian system have received considerable attention in the recent decade. In 2017, a Nobel Prize in medicine was awarded for the research discoveries of the molecular mechanisms controlling the circadian system (172). The biological rhythm of animals and humans is synchronized with the earth's rotation. Isolating the gene that controls the internal clock system in drosophila, a fruit fly, enabled three laureate pioneers, Jeffrey C. Hall, Michael Rosbash, and Michael W. Young, to discover the proteins responsible for the human circadian system (173).

In 1984, Michael W. Young and his fellows found a technique to restore the circadian rhythm of arithmetic drosophila by a period gene segment using the P-element transformation technique (174, 175). The level of the protein PER was recognized as a factor involved in the circadian rhythm mechanisms. However, Sehgal et. al., published in 1991, showed that the protein is not necessarily run by the exogenous system, like light and darkness, but rather by changes in the endogenous system (176). To demystify the underlying mechanisms influencing the PER protein levels during the day and night in Drosophila, Hall and Roshbash tested mRNA and PER levels of Per in mutated drosophila. Surprisingly, their results showed that the levels of mRNA influence the levels of protein PER, and reciprocally, the levels of protein PER affect the mRNA level. This loop regularly occurs via per mRNA transcription in the nucleus and is transported into the cytoplasm to synthesize PER protein. PER protein is programmed to turn to block the transcription of more mRNA in the nucleus. This process decreases the levels of PER synthesis. Hall and Roshbash concluded that in a precise cyclic rhythm, the protein PER regulates itself in a feedback loop (177).

In 1994, Sehgal and his fellows discovered a gene called timeless (Tim) that causes the rhythmicity of the circadian system of drosophila to inhibit per mRNA transcription (178) and also inhibits PER protein synthesis (179). In light of Voshall's results about Tim, Young investigated Tim to find out that protein PER needs to bind protein TIM to enter the nuclei to cause circadian rhythm. Tim protein is discovered to gradually degrade under the effect of light (180). This process can be described by TIM-PER proteins building up in the cells at night, and TIM starts to be demolished by the light of the day. A few years later, Young discovered another gene called double-time (dbt), which affects the PER protein and the circadian rhythm. In the meantime, Hall and Rosbah found that new genes called clock (Clk) and cycle (Cyc) influence the circadian system by affecting Per and Tim (181). The Cry gene produces a protein called CRY, which binds to TIM to reset the circadian system under the light effect. The binding of CRY helps TIM to start degrading so as not to enable TIM to bind to PER protein to access the nucleus. Regardless of the findings of this research about the effect of cry, period, timeless, double-time, clock, and cycle on the circadian system, many other pathological variants have a huge influence on the sleep rhythm of the human sleep behavior phenotype (182).

2.3.1.1 Circadian Rhythms and Sleep patterns

According to sleep physiology, there are two types of sleep rhythms: REM and NREM sleep frequency. During REM sleep, the brain is functioning in the cortex and the eye can still move. Furthermore, a variety of physiological changes occur during this condition, including changes in blood pressure, breathing, and muscle twitches. While in NREM sleep, three stages of waves were screened: N1, N2, and N3.

Approximately 75 % of sleep is spent on these phases. Slow-wave sleep is another phase which is considered the deepest sleep phase described by the presence of delta waves and many studies have proven the importance of delta waves for memory consolidation. Every stage of these has characteristics and different brain waves. The sleep state occurs in one cycle which last for 90 min and during which 4 stages are repeated for 4 to 5 sleep cycles. (Patel, Aakash K., et al., 2022).

Alpha Rhythm is recognized in sleep literature as the onset of electroencephalogram EEG. Alpha activity is characterized by frequency between 8 and 13 cycles per second. Alpha frequency occurs over the brain and specifically in the occipital, posterior region. It is triggered by the brain during closed eyes and can be relinquished once the eye is open or as a result of mental visual stimuli even if the eye is closed. This wave is inhibited in the brain by other EEG forms during sleep (184).

Research has found a correlation between sleep NREM and the decreased activity of the Ascending Reticular Activating System (ARAS), which is an important part of the brainstem that is responsible for wakefulness, attention, and consciousness. Further studies have shown the parallel activation of VLOP, anterior hypothalamus, as well as basal forebrain once the ARAS activity is dropped (185).

Sleep rapid eye movements (REM) are raised in the brain as a result of chemical activities. Cholinergic neurons induce acetylcholine in the region of the pedunculopontine and laterodorsal tegmental nuclei. Studies have shown how the decrease of aminergic neurotransmitters such as dopamine, serotonin, and norepinephrine synchronizes the elevation of cholinergic neurons (186).

Studies have shown that acetylcholine levels decreased by one-third during wave slow-wave sleep and increased over the baseline during REM sleep (187; 188). The locus coeruleus recordings have shown that noradrenergic neurons are less active during sleep-wave sleep and not working during the REM sleep phase. During REM sleep, serotonin levels in the frontal cortex decreased (189). Various stages of altered waking behaviour have also been documented. In animal studies, acetylcholine levels have been increased in the hippocampus by 175% than in wakeful active cats (188).

Most research about memory theories done by Chrobak and Buzsaki in 1994 and Wilson and McNaughton in 1994 proposes that memory consolidation occurs during two active periods causing changes in the level of acetylcholine (190; 191). During wakefulness, information in our hippocampus is quickly processed and stored by existing cortical representations in a transitional temporal memory. Interestingly, the neocortex has a significant feedback effect on the development of the hippocampus, though there is less feedforward for continuous memory recall during waking hours. During slow-wave sleep and tranquil awake periods, the hippocampus and neocortex feedback loop are more influential. In this stage, the stored memory representation is spontaneously reactivated even in the absence of external stimuli. Memory consolidation (neocortex-based long-term semantic or episodic memory) is enhanced by the process that transfers from the hippocampus to the neocortex (192).

2.3.2 The effects of smoking on sleep patterns

In a cohort study of 958 (3.2%) participants out of 30,097 participants, had possible REM sleep behaviour disorder related to smoking (pack-years odds ratio 1.01) (193).

When matched by age and sex, a group of 50 smokers had more trouble falling asleep than a group of 50 non-smokers. Personality traits and substance use did not differ between the two groups. Also, when a group of eight chronic smokers stopped smoking, their sleep patterns improved dramatically. These results agree with studies that discuss nicotine's stimulating properties (194).

Inadequate sleep caused by sleep disruptions is related to unfavourable physical, cognitive, and public health effects. The goal of this research was to identify sleep disorders linked to smoking status. From the 2005–2006 National Health and Nutrition Examination Survey, sleep disruptions in people aged 20 and over were assessed among smokers who were currently smoking, had recently stopped smoking, and never smoked (NS). When compared to nonsmokers (NS), current smokers (CS) reported considerably shorter total sleep time, greater sleep start latency, increased difficulties falling asleep, sustaining sleep, and waking up earlier than intended. Ex-smokers who reported disruptions comparable to NS and CS slept less well than nonsmokers (195).
Despite extensive research on shiftwork adaptation, little is known about how individual and environmental variables interact to impact sleep among shift workers. Age, smoking, and negative affectivity (NA) were investigated as predictors of sleep length and quality over three work phases in this study (day shifts, DS; night shifts, NS; and leave periods, LP). Data were obtained from employees working 12-hour shifts onshore (n = 330) or offshore (n = 456). Onshore, the work phase interacted with smoking, age, and other variables to predict sleep length, whereas NA interacted with other factors to predict sleep quality. Offshore, individual factors did not predict patterns of sleep measurements throughout the DS, NS, and LP phases. Shiftwork adaptability is considered in the offshore environment (196).

Despite evidence suggesting a link, there is little epidemiological or clinical information on the association between smoking and sleep disruption. A study investigated the assumption that cigarette smoking is linked to sleep disruption. A longitudinal epidemiologic investigation of sleep-disordered breathing included the collection of survey data from 3,516 participants. Insomnia, hypersomnia, and parasomnia symptoms were evaluated using the Diagnostic and Statistical Manual of Mental Disorders criteria (3rd ed., revised). Smoking was connected with problems falling asleep and waking up in both males and females. Only women who smoked were found to have excessive daytime drowsiness, whereas only men who smoked were found to experience nightmares and unsettling dreams (197).

2.3.2.1 Impact of Smoking on Circadian Rhythms

The internal circadian clock sited in the suprachiasmatic nucleus (SCN) regulates the secretion of melatonin, produced by the pineal gland, and is believed to be among the neurohormones responsible for sleep rhythm (198). Misalignment in the mechanism system of SCN (199), the hypothalamic-pituitary adrenal axis (HPA) (200), or the hypothalamus, leads to sleep disorders. The acetylcholine neurotransmitter, as well as the monoamines, namely serotonin, dopamine, histamine, and norepinephrine, are neurotransmitters involved in the wakefulness system in the brain (201; 202). The ventrolateral preoptic nucleus (VLPO) is known to secrete GABA and galanin, inhibitory neurotransmitters that have an important role in suppressing the wake system in TMN, LC, dorsal raphe, locus coeruleus, and LDT (202). Many sleep types of research have shown the impact of lesions in the VLPO neurons, which represent the sleep system, on both NREM (203) and REM sleep patterns by decreasing the sleep quality by more than 50% (202). Nicotine influences the circadian system by stimulating the nicotinic

acetylcholine receptors (nAChRs) in the SCN of the hypothalamus (204). Accidentally, nicotine produces the same effects that acetylcholine induces in the nAChRs (205). Moreover, nicotine causes disturbances in the regulation of HPA (206), (207). Vgontzas showed that insomnia is linked to the rise of ACTH and cortisol levels in the plasma (208). This may raise the importance of doing clinical investigations about the hazardous effects of nicotine on the sleep aetiology of addicted patients.

2.4 The relationship between sleep patterns and cognitive function

There is a reciprocal relationship between sleep disorders and cognitive dysfunction. Several studies have appeared in recent years documenting the link between sleep disorders and cognitive dysfunction in many neurodegenerative diseases. Numerous studies have revealed that sleep disorders do not just impair cognition functions but also cause malfunction in the gastrointestinal, metabolic, immune, and circulatory systems (209; 210; 211; 212; 213; 214; 215).

Some studies have linked sleep deprivation to fatal health problems (216; 217), and many results showed that sleep loss causes premature death in fruit drosophila, rodents, dogs, and cockroaches without a clear explanation about the mechanisms of death (218; 219; 220; 221).

Oxidative stress is assumed to be among the reasons for the premature death of animals exposed to sleep deprivation. To test the validity of this assumption, scientists checked the endogenous antioxidant defense in rodents, and liver weakness proves high oxidation related to sleep loss in these rodents (222; 223; 224). However, these investigations could not confirm whether the high oxidative stress in the brain is a cause or consequence of death in sleep-deprived animals.

To determine the underlying mechanisms of premature death occurring in sleep-deprived animals, a recent study done by the Department of Neurobiology of the University of Harvard in 2020 found that sleep loss leads to death through the accumulation of reactive oxygen species (ROS) in the gut. In this study, they tried three different methods to measure the effect. After applying various markers to damage cells in multiple tissues of flies, the results showed asymmetrical, short-lived, high reactions of ROS during sleep deprivation in the flies. According to clinical literature, excessive generation of ROS is known to lead to the spread of oxidation, which surpasses the capacity of cellular antioxidant systems (225; 226).

In a study on drosophila, the result showed that a lack of sleep causes impairments in memory consolidation (227). In response to concerns raised about sleep loss and whether all the cognitive capacities are defective due to sleep loss or just specific ones, Killgore and his fellows provided neuroimaging evidence to prove that the prefrontal cortex is the most susceptible part of the brain to be affected by sleep disorders. It is surprising that sleep loss does not affect creative or inventive thinking, but it does affect decision-making, planning activities, and reasoning (228).

2.4.1 Sleep disorders and cognitive dysfunctions in psychiatric and neurodegenerative diseases

Twenty-seven studies that included 69216 population showed that persons with sleep disorders have higher risks of cognitive dysfunctions and Alzheimer's disease than those without sleep problems by 1.55 and 1.65 (229), respectfully.

Sleep disorders are associated with cognitive dysfunction in Parkinson's disease. In advanced PD patients, clinical research has found through different assessment tools that aim to measure the level of cognitive impairment related to sleep patterns that there is a strong association between neuropsychological functions and sleep disorders in PD. This cohort study was conducted on 181 Parkinson's advanced patients. The study adopted the Parkinson's disease Sleep Scale (PDSS-2) and Epworth Sleepiness Scale (ESS). The PDSS-2 consists of 15 sleep-evaluating items regarding disturbed sleep, motor symptoms, and PD symptoms at night. The Epworth Sleepiness Scale consists of home activities like lying, watching TV, reading, and drinking alcohol items. This study used a comprehensive neuropsychological battery to evaluate the cognitive faculties of PD patients, like the executive functions applying Trail Making Test B (TMB) and Frontal Assessment Battery (FAB). For reasoning assessment, the study used the Raven Color Progressive Matrices Test (RCPMT), the memory Corsi Black Tapping Test (CBT), and the attention Digit Cancellation Test (DCT). For assessing the language faculty, the study used phonemic verbal fluency (PVF) and category verbal fluency (CVF). The findings of this study showed a strong association between neurophysiological factors and sleep disorders in the Parkinson's Diseases Sleep Scale (PDSS-2) except for memories. The results showed high scores in PDSS-2 that refer to strong sleep disorder and poor reasoning (RCPTM: ß = -0.214; p = 0.002) and poor attention (DCT: ß = -0.194; p = 0.007). The executive functions in this assessment showed that (TMB: ß = 0.156, while the p-value = 0.031, and FAB: ß = -0.139, with a p-value = 0.049). However, no significant correlation was found between ESS and cognitive skills in PD patients. Hence the study concludes that impairment in mental faculties is strongly correlated to sleep disorders in PD patients (230).

Sleep disorders in sleep apnea have been associated with cognitive impairment in patients. Sleep apnea occurs in 5% of the population and is characterized by frequent episodes of interruption of air during sleep. Patients suffering from sleep apnea wake up several times at night because the muscle tone falling in the airway blocks the air from reaching the heart and ends up disturbing sleep patterns. The continuous blockage of the air in the oropharynx causes an increase in the levels of carbon dioxide and a decrease in oxygen saturation, which leads to activating the chemosensory system in the medulla. Consequently, the parabrachial nucleus is activated to increase muscle tone and release the airway from the pressure of obstruction. This process occurs in sleep apnea patients hundreds of times at night, which raises difficulty in managing cognitive tasks during the day and causes a defect in cognitive skills in the long term. According to some medical hypotheses, cognitive impairment in sleep apnea occurs due to repetitive episodes of hypoxia, as detected in EEG studies, which show a drop of oxygen saturation by 3% during sleep apnea episodes. Cognitive enhancement in patients with sleep apnea has been shown in many clinical studies when patients submit to continuous positive airway pressure (CPAP) devices during sleep (231; 232).

Patients of sleep apnea, who are exposed to hundreds of night arousals with severe sleep apnea (more than 30 episodes per hour) and those who are moderate (15-29 episodes per hour), have a tremendous risk for arrhythmia, hypertension, myocardial infarction, and stroke.

2.4.2 Sleep loss and cognitive errors in high-skilled professions

According to Bonnet and Arand 2003, sleep deprivation reduces the high cognitive functions of the brain and causes 71,000 fatal injuries, 100,000 auto crashes, and 1150 mortalities based on statistics provided by the National Sleep Foundation in 2002 (233; 234). One of the risks of

sleep deprivation is taking longer to react to a stimulus. Medical interns showed reduced abilities to make the right decisions, which caused fatal errors in their diagnosis after a shift of 24 hours or more (235). Cognitive factors such as biases were identified to be among the causes of clinical reasoning errors (236).

Sleep deprivation in residents has a severe impact on the patient's life. In one study that tended to measure sleep-deprived residents' performance of simulated laparoscopic surgical skills at Parkland Memorial Hospital, the results showed an increased number of technical errors and consumed time to fulfil surgical skills (237).

The effect of night rotations on sleep-wake patterns in internal medicine residents was measured to detect any medical errors over two months. Daily working memory capacity (WMC) is measured supported by activity watches worn during the night and sleep log recordings. Every 4 nights, a rotation of 30 hours has been called for the residents (call rotation). The same group of 39 residents was taken as a control group during the days off of shifts (no-call relation) to compare the results with the call relation. Surprisingly, the results showed that during the call rotation, the residents showed higher self-assessed sleepiness and poorer WMC. In the Ospan score variable (on-call mean of 54.11, SD 1.91, while the non-call mean was 56.71, SD 1.54). In letter performance (during the call, the resident got the standard of 65.47, SD 1.07, while during the non-call, the mean was 67.15, SD 0.75). In math errors, the residents got during the call rotation mean of 5.32, SD 0.40 vs. non-call rotation mean of 4.25, SD 0.33. In the speed errors task, residents show during the call-rotation mean of 1.24, SD 0.19, vs. the non-call mean of 0.76, SD 0.11. Concerning the accuracy error, task residents show high errors during call rotation with a standard of 4.07, SD 0.27, while in non-call rotation received a mean of 3.49, SD 0.29 (238).

In a meta-analysis of 476 studies about sleep deprivation, 21 studies reported that 760 deprived sleep subjects for (24 hours and 11 nights) equal to 72-992 hours have impairments in their cognitive modalities. The researchers reported visual distortion, hallucination, and the somatosensory system. In 90% of studies, visual perception has been affected. In 52% of studies, the somatosensory modality has been affected. In 33% of the studies, the auditory modalities have been impaired due to sleep deprivation. Within the first 24–48 hours of sleep deprivation, the subjects started developing certain symptoms of anxiety, petulance, and depersonalization. Within the next 48–90 hours of sleep deprivation, subjects started experiencing fuzzy thinking and hallucinations. Within 72 hours of sleep deprivation, delusions similar to psychosis or toxic delirium manifested in the subject's cognitive system. On the third day, all the studies with consensus reported hallucination of the three modalities, visual, auditory, and somatosensory.

2.5 Mechanisms underlying the effects of smoking on sleep quality and cognitive function

Smoking is a major variable leading to numerous physiological and psychological pathologies. Tobacco is the primary independent cause with sleep and mental difficulties being the most common side effects. This chapter discusses the basic mechanics of sleep patterns as well as the systems involved in cognition and how smoking affects these mechanisms.

2.5.1 The Relationship Between Sleep Regulation and Neuroendocrine Systems

The sleep system is intricately linked to various physiological systems, notably the neuroendocrine system. It interacts with the paracrine and endocrine systems in diverse ways via hormones and neurotransmitters. These interactions serve to control circadian rhythms and have a substantial impact on a variety of biological functions and activities.

2.5.1.1 Hormones Involved in Sleep Regulation

Different studies have been investigated about biological agents or biomarkers related to sleep disorders. Identifying the sleep segments may help clinicians and specialists control the sources of many smoking diseases.

In a meta-analysis study, a relevant correlation has been found between certain biomarkers such as growth hormone (GH) and growth hormone-releasing hormone (GHRH). Growth hormone-releasing factor (GRF), tumor necrosis factor α (TNF), and interleukin-1B (IL-1) as a reference for the elicitation of NREM, while nitric oxide and prostaglandin are linked to the REM sleep structure of patients (240).

2.5.1.1.1 Growth hormone (GH)

The first investigations into GH studies on sleep structure found a strong correlation between the increased slow-wave (SW) sleep and secretion of the GH during sleep, reciprocally the awakening and decrease of GH (Van Cauter et al., 1998).

According to Takahashi, Y., and colleagues, based on EEG recordings, the deep sleep stage matches the high secretion of growth hormone (13–72 mug/ml) for 1.5–3.5 in seven subjects. Interestingly, the subjects showed another peak of (14–46 mg/ml) after they woke up and returned to sleep again (242). Another study has shown a significant correlation between a higher GH peak in PM sleeping subjects and the GH peak of those AM subjects. The experiment was conducted on 15 male adults who had been sleeping from 8 AM to 10 AM compared to 14 subjects who slept from 4 PM to 6 PM (243).

Growth hormone is a critical segment in sleep physiology. Previous works have shown how the growth hormone is significantly related to sleep-wake patterns. The GH secretion has been documented in many research papers to be released during the first onset of sleep (244). The first onset of sleep is synchronized with slow-wave sleep (SWS), specifically stages III and IV. Animal studies have shown that intravenous injection of GHRH, the endogenous hormone released by the hypothalamus, suppresses the alertness and elevation of the SWS. Subjects in different scenarios witnessed a high release of GH after the first sleep onset. It has been found that 70% of GH is highly released during SW sleep, and secretion depends on the duration of SW. After persistent arouse from sleep for 3h, 5h, 8h, 12h, 16 and 28, the peak of GH has been raised (245). Interestingly, naps have been linked with high releases of GH correlated to SW sleep in the afternoon.

GH has been documented to have a link to cortisol release. In human studies, sleep has been identified to influence the release of GH and cortisol. In a review research study that was conducted on 149 adults to check the level of GH correlated to cortisol, the sleep quality decrease has been associated with the increase of cortisol at night. In the same study, the GH has decreased between early and late age during sleep SWS in correlation to GH with the rates (-372 microg per decade; P.001) and (-43 microg per decade, P 0.2), respectively (245).

The glucose level in the bloodstream is believed to suppress the GH level. Growth hormone leads to the secretion of insulin-like growth factor type I (IGF-I) hormone by the liver. IGF-I can be measured during the day, and it is considered an indicator of GH in the blood. IGFs inhibit the release of GH. GH secretion decreases gradually with age, specifically during the sixties of age. Automatic suppression has been observed in GH when sleep was suddenly interrupted (246). The same author reveals in another study about age changes in sleep segments related to GH and cortisol that slow wave sleep (SEM) decreases from 18.9% in ages between 16 and 25 to 3.4% in ages between 36 and 50. This decrease in the SEM has significantly been correlated to a decrease in GH secretion (-372 g per decade; P.001). Whereas an increase in cortisol secretion (+ 19.3 nmol/L per decade; P.001) has been correlated to the increase in age and decrease of REM sleep in subjects (245).

It is worth mentioning that delay in sleep does not affect the GH peak, as shown in the plasma of 8 young subjects whose sleep activity was recorded in different sleep scenarios during the night (242). This result has been confirmed by the study of Honda, Yutaka, et al. about the onset of human-grown hormone during sleep in ten subjects. The blood plasma was collected every 20 minutes from the subjects via venous catheter to measure the GH levels. The GH secretion in the subjects peaked immediately after sleep, followed gradually by reduced peaks during the five stages of this study (247). Growth hormone is influenced by the secretion of other neuroendocrine hormones, GH-releasing hormone (GHRH) and somatostatin (SS).

Growth hormone deficiency has been identified to lead to sleep disorders. Growth hormone deficiency has been correlated to a decrease in stage 3 and stage 4 slow-wave sleep (SWS) (248). This study was confirmed by another study about GH deficiency and decreased sleep quality in patients and the control group (249). Though GH has been observed to have a deep connection with sleep, it is worth mentioning that hypothalamic-pituitary-somatotropic axis hormones are also involved in sleep regulation. In subjects with GH deficiency identified with abnormal REM, submitting to six months of daily 2IU/m2 GH treatment increased the SW sleep (250).

2.5.1.1.2 Growth hormone releasing hormone (GHRH)

Growth hormone-releasing hormone (GHRH) is a neuropeptide that regulates growth hormone synthesis in the body. It is important for a variety of body activities, including sleep regulation, hunger management, and memory formation. GHRH, also known as somatostatin, is largely generated in the hypothalamus but can also be found in other organs. It is produced only in the arcuate and paraventricular nuclei of the brain. Its principal role is to stimulate the pituitary gland to produce growth hormone into the circulation, which aids in the regulation of hormones along the hypothalamic-pituitary-adrenal (HPA) axis. GHRH has also been proven in studies to facilitate REM and NREM sleep in animals (251).

2.5.1.1.3 Growth hormone-releasing factor (GRF)

In a rodent study, growth hormone-releasing factor (GRF) and corticotropin-releasing hormone (CRH) showed a noticeable effect on sleep patterns. Intracerebroventricular (ICV) injection of (2.0 nmol) of GRF enhances SWS (1-2 Hz) and reduces the high frequencies (32-64 Hz) (252).

2.5.1.2 Inflammatory and immune system regulators

2.5.1.2.1 C-Reactive protein (CRP)

High concentrations of C-reactive protein (CRP) in blood can be an earlier indicator of cardiovascular disorder due to sleep deprivation. In the Journal of the American College of Cardiology, Meier-Ewert, Hans K., et al. aimed to find out the effect of sleep deprivation on the level of C-reactive protein, which is used as a biomarker for cardiovascular disease. In this study, they have three groups of 10 subjects in each group. In the first study, they were deprived of sleep by 10 subjects for 3 days and 6 hours. The CRP was collected from their blood every 90 minutes for five days. In the second study, 10 participants were split into two groups: the control group, who slept for 8.2 hours, and the other group, who slept for 4.2 hours for 10 days. The blood CRP was collected on the first and last days of the study. The result showed elevation of CRP in both total and partial sleep-deprived groups, but not in the control group. Surprisingly, the systolic blood pressure increased in the first study-deprived group (253). The study reveals the association between sleep deprivation and the increase of the C-reactive protein as an inflammatory reaction.

It seems that an increase in CRP is not only an indicator of cardiovascular diseases but also is associated with obstructive sleep apnea. In a study that includes 22 patients, the increased CRP plasma has been linked to obstructive sleep apnea in 20 patients with 0.33 [0.09 to 2.73] versus 0.09 [0.02 to 0.9] mg/dL, P 0.0003, compared to the control group in this study (254).

2.5.1.2.2 Tumor necrosis factor α (TNF)

Kubota et al.‘s study has shown that infusion of tumour necrosis factor α is in the preoptic area and induces non-REM sleep in rats (255). This study has been in line with other studies concerned with seeing whether TNF is involved in the regulation of sleep physiology. The study aimed to inhibit TNF based on receptor fragments (TNFRF).

Autoimmune diseases have been correlated to the increase of tumour necrosis factor-C in smokers. This effect has been detected in blood lymphocytes and monocytes of all smoker types 8 (current and non-current smokers) compared to 8 healthy subjects by Ryder, M. I., et al. The study's purpose was to measure the effects of different concentrations of smoking on the levels of (TNF)-α in short and long exposure times. The study's findings demonstrated that 0 to 2 minutes of smoke exposure raised the mean TNF-α level. In contrast, both smoker's and non-smokers' TNF-α levels have dropped in response to two to five minutes of tobacco exposure. Nonsmokers have shown greater levels of TNF-α than smokers in both short- and long-term exposures (256).

An assessed serum of TNF-α of 43 heavy smokers and 19 healthy non-smokers to identify the body’s reaction to high levels of tobacco using ELISA has been investigated in a similar study. Smokers have been categorized based on the consumption of cigarettes into three groups: less, more, and one pack per day. The result showed a significant correlation between the level of TNF-α and the number of packs smoked in the serum of the heavy healthy smokers (P, 0.004) compared to non-smokers (257). An epidemiological study tried to decipher the underlying mechanisms of TNF- α in inducing inflammatory and connective tissue breakdown in COPD smokers; P55 and 75 TNF-α cell receptors turned out to be the mechanisms that cause an inflammatory response in COPD smokers (258).

2.5.1.2.3 Interleukin-1 (IL-1)

Despite the protective role of inflammatory and immune system interleukin-1 (IL-1) in sleep aetiology, it is considered an endogenous sleep promoter. Neuro-immune-endocrine studies have linked the sleep-wake patterns to some cytokines like Interleukin-1, which is believed to be involved in sleep pathology (259). An initial study has found that the neuroendocrine and the immune systems have reciprocal communication (260). The preliminary work in this field focused primarily on cytokines. Interleukin-2 revealed that the IL2 segment has an analgesic effect on the nervous system (261). In an animal study, interleukin-1 has been witnessed to be involved in sleep deprivation. In an animal study, interleukin-1 has been witnessed to be involved in sleep deprivation. In terms of studying the sleep behaviour in some animals, antibodies have been intracerebroventricularly injected to identify the direct effect of the interleukin 1β (anti-IL-1β). The result showed that a 100 μg dose of interleukin 1β affected only the non-rapid eye movements (NREM) sleep segment by 20 minutes in the first 4 hours. The same study has screened an increase in plasma concentration of IL-1β after sleep deprivation in the rabbit (262). Though the result is a novel approach to tracking the sleep agent pathways, the study fails to consider that the rabbits have a polyphasic sleep pattern, unlike the human, who has monophasic sleep patterns.

The sleep system is tremendously complex and has a couple of sleep promoters. These promoters include Factor S, muramyl peptides, interleukin II, alpha-interferon, tumour necrosis factor, prostaglandin D2, vasoactive intestinal peptide, and delta sleep-inducing peptide, to name but a few, which interfere with the neuroendocrine system and nervous system on many levels.

2.5.1.3 Neuropeptides involved in sleep modulation

2.5.1.3.1 Neuropeptide Y

Neuropeptide Y is involved in sleep aetiology. Research has shown that neuropeptide Y (NPY) is produced by numerous neurons of the sympathetic nervous system, specifically by the arcuate nucleus of the hypothalamus, and has different functions, among which decreasing pain and influencing the circadian rhythm (263). Neuropeptide Y (NPY) has the efficacy of inhibiting the corticotropin-releasing hormone (CRH) (264). In the same study, NPY was intravenously injected (100 μg) in young adults for four consecutive hours: 22 h, 23 h, 24 h, and 1 h in the morning. Adrenocorticotropin hormone (ACTH), cortisol, growth hormone (GH), prolactin, and leptin hormones have been screened during the night synchronized with EEG recordings. The findings of the study have shown a decrease in ACTH secretion during the first part of the night, while cortisol has been shown during the second part of the night due to NPY injection. Interestingly, the result showed the ability of NPY to maintain sleep patterns and regularity and reduce the fragmentation induced by the HPA hormones.

Neuropeptide Y has been associated with sleep disorders in smokers. Preliminary studies have shown that the increased level of CRH is considered one of the major factors in the pathophysiology of sleep disorders in smokers. A study suggested that nicotine reduces NPY secretion in the hypothalamus. Nicotine decreases NPYergic neurons in the ARC area of the brain as well as in the paraventricular nucleus PVN projection (265). These findings have been confirmed by another rodent study that used immunohistochemistry to screen the effect of nicotine on the synthesis of neuropeptide Y (NPY) in the hypothalamus. Surprisingly, the

synthesis of NYP in the arcuate nucleus (ARN) has been absent, while PVN has not stressed any result (266).

2.5.1.3.2 Prostaglandin D2

Mast cells, Th2 cells, basophils, and eosinophils synthesize the prostaglandin known as prostaglandin D2 (PGD2), which is present in several organs, including the brain, prostate, spleen, and human reproductive system. Multiple physiological processes appear to be related to PD2. A pioneering study found that PGD2 has a critical role in maintaining inflammatory responses, sleep patterns, and vascular dilation (267). Some sleep studies have identified PGD2 as the most robust sleep factor. In a Japanese study, the concentration of rat cerebrospinal fluid was correlated with a strong sleep tendency. The catalyzer enzyme, lipocalin-type prostaglandin (PG) D synthase (L-PGDS), which is localized in the human heart and central nervous system, has been documented to be involved with PGD2 within the ventricular systems and subarachnoid space of the brain to trigger the sleep sequence via activating the adenosine A2A receptor. Subsequently, it suppresses the tuberomammillary nucleus to release histamine in the brain (268). The intracerebroventricular injection of the prostaglandin D2 inhibitor, selenium tetrachloride (SeCl4), has a reverse effect on the amount of sleep in many animal studies. (SeCl4) appears to trigger insomnia in gene knockout (KO) mice of PGD2. While subarachnoid space injection of 200 pmol/min DP1R antagonist ONO-4127Na decreases the sleep REM by 30% in mice. Hence, the results show the importance of PGD2 and DP1R in sleep physiology (269).

2.5.1.3.3 Vasoactive intestinal polypeptide (VIP)

Vasoactive intestinal polypeptide plays a significant role as a sleep-promoting factor. In an animal study, cats have been implanted with a steel tube in the 3rd ventricular area of the brain. The 6 cats have been injected with 10ng /20 µl and the other 6 cats with 100 ng/20 µl a solution of Vasoactive intestinal polypeptide. The EEG sleep activity has been recorded in this group of cats as well as another baseline control group, post-VIP group and Ringer's solution group. The results have not shown any behavioural or motoric abnormalities in cats. Surprisingly, the REM sleep changes did not manifest in the group of cats injected with 10ng /20 µl but appeared in the group of cats injected with 100 ng/20 µl a solution of Vasoactive intestinal polypeptide. The vasoactive intestinal polypeptide is synthesized in the master gland of the brain suprachiasmatic nuclei (SCN). According to Aton and Herzog VIP is an important synchronizer of the circadian system within SCN (270). It is worth mentioning also the work of Harmar in 2002 about the essential role of VIP neurons in the control of the circadian system. His study shows how nonfunctional allele mice of VPAC2 receptor for VIP and pituitary adenylate cyclase-activating polypeptide (Vipr2-/-) mice fail to maintain the normal circadian system (271). Another study found that VIP helps regulate the prolactin secretion (272).

2.5.1.3.4 Angiotensin II

A significant component of the hormones that cause sleep, according to several endocrine studies, is angiotensin II (273). Diverse physiological systems are impacted by angiotensin II. The kidney, heart, brain, adrenal glands, and artery walls have all been demonstrated to benefit from angiotensin II. There is a vast amount of literature available about the intracrine,

autocrine, and endocrine effects of angiotensin II. By stimulating the brain's subfornical organ and the postrema, which are located in the medulla oblongata of the brainstem, angiotensin II contributes to the neurological processes that result in the sensation of thirst (274).

2.5.1.3.5 Bromine

Pharmacological studies have shown the presence of bromine, 1-methylheptyl gamma-bromoacetoacetate, in the human cerebrospinal fluid (275). According to Inoué Shojiro, MHBAA increases paradoxical sleep in cats (276). A qualitative determination of 1-methylheptyl gamma-bromoacetoacetate (MHBAA) substance has been done by a Japanese study to emphasize the previous study that the plasma of cerebrospinal fluid includes the range between 236 and 621 pmol/ml. The qualitative determination of bromine has been conducted based on combining the fluorometry and radio dilution techniques (277). The American Journal of Kidney Disease published a paper in December 2006 about the long-term hemodialysis of uremic patients and how bromine levels have been correlated to sleep decreased during hemodialysis (278).

2.5.1.3.6 Factor S

In a pioneer study has been done by Harvard Medical school about the sleep promoting factor extracted and purified from human urine has found that infusing factor S of 5 pmol / kg of body into the lateral ventricle area of the implanted EEG electrodes rabbits' brain increases the slow wave sleep by 50%. Interestingly, the same effect occurs in animals after sleep insufficiency (279).

2.5.1.3.7 Transforming growth factor β1

Transforming growth factor β1 is an anti-inflammatory cytokine involved in sleep regulation. Intracerebroventricular injection of transforming growth factor beta 1 or TGF-β1 in a dose of 200 ng during dark and light periods showed inhibition in the NREM during the light period. Surprisingly, the TGF-β1 did show the effect on the sleep physiology during the night but less than what has been seen during the light period (280).

2.5.2 Neurobiological Processes of sleep patterns

The sleep phenomenon has been since ages the interest of many researchers and clinicians. Due to its complex system, which interferes with other systems, sleep medicine has investigated sleep aetiology through many medical fields like neurology, immunology, endocrinology, psychiatry, and other fields to understand its complex system. This chapter concentrates on explaining the neuroendocrine mechanisms by which smoking influences sleep patterns in smokers.

2.5.2.1 Sleep disorders and comorbidity

According to clinical textbooks, comorbidity is considered the presence of more than one disease simultaneously in a patient. Smoking is a leading factor in either heavy or light smokers

to more than one condition such as COPD, lung diseases, diabetes, stroke, cancer, and heart disease, to mention but a few.

Sleep disorders in smokers can be triggered by a condition or more. It might also be induced due to all the conditions together. Therefore, it is hard for sleep scientists and clinicians to decipher the source of sleep disorders in the presence of many diseases.

Demystifying the interaction between physiological systems requires understanding the response of each system towards tobacco and its hazardous components. Investigating the effect of smoking on the endocrine system separately, for instance, without interaction of this system with other systems can be far beyond the reach of science for the time being. Human physiology interacts with tobacco agents differently and reacts up to levels of severity. These levels of severity toward tobacco exposure raise different forms of diseases simultaneously.

Diagnosing all the morbidities of tobacco is beyond the capability of clinicians. It may be even more difficult to recruit research teams to investigate the sources that trigger different types of sleep disorders in smokers. The reason for that goes back to the fact that these conditions are not static but dynamic from one patient to another.

The dynamicity of comorbidity increases the difficulty of investigation for clinicians. Smokers with sleep comorbidities may be affected by other factors in their daily lives. The psychological dimension, the environmental dimension, the socio-economic dimension, the genetic predisposition, the type of nutrition, as well as intelligence, may affect their level of comorbidities to a certain level.

2.5.2.2 Stress and arousal-related factors

2.5.2.2.1 Corticotropin-releasing factor (CRF)

Corticotropin-releasing factor (CRF) has been shown in EEG studies to increase brain activity and decrease the sleep period. In both rodent and human studies, CRF decreased slow-wave sleep. To confirm this result, the scientist reversed the effect of CRF by injecting R121919, the CRH-receptor antagonist, which resulted in decreased REM and increased N-REM in patients with depression (281a).

Some studies have reported the effect of sleep interruptions on increasing the level of catecholamine and aldosterone during the night. Catecholamines like dopamine, norepinephrine, and epinephrine are hormones released under physical or emotional stress. The mineralocorticoid steroid hormone aldosterone controls blood pressure, salt, potassium, and homeostasis.

2.5.2.3 Neurotrophic factors

2.5.2.3.1 Brain-Derived Neurotrophic Factor (BDNF)

Brain-Based Factor Neurotropic is a protein that plays a crucial role in the brain's sleep and waking cycles. BDNF has a significant role in higher-order cognitive functions and memory. It is located in the cortical, hippocampus, and basal forebrain areas. According to Kiyofumi and Toshitaka's research (281ba), increases in BDNF messenger RNA expression have been

linked to memory acquisition and have also been demonstrated to block learning and memory that are distributed according to BDNF. Saliva contains BDNF, which is necessary for the oral epithelium to recover, according to several study lines (282).

2.5.2.4 Sleep-inducing peptides

2.5.2.4.1 Delta sleep-inducing peptide (DSIP)

Delta sleep-inducing peptide (DSIP) has been suggested to be involved in sleep regulation. As a neuropeptide, DSIP in an animal study on rabbits evokes delta and spindle EEG activity. This neuropeptide, which consists of Trp-Ala-Gly-Asp-Ala-Ser-Gly-Glu amino acid compounds, was injected under a double-blind circumstance in the ventricular of 58 rabbits. The rabbit's neocortex was connected to a computer to analyze the EEG activity and prove the significant occurrence of spindle and delta patterns after they had been intraventricularly infused with the cerebrospinal fluid (CSF) of the synthesized DISP solution (283).

Several attempts have been made to detect the role of delta sleep peptides in various animals. The study of the DSIP on rabbits's sleep EEG has shown that delta sleep activity is induced between 30% and 50% by either intravenously, intracerebroventricularly, intraperitoneally, or subcutaneously administered ways in rabbits. Another study has confirmed the result of the previous study by injecting rabbits (30 nmol/kg) of a synthesized DSIP that increases SWS after 5 h (284).

An earlier baseline study has shown the minimum dose of Delta Sleep-Inducing Peptide (DSIP) that induces the SWS effect in rats is about 7 nmoles/kg intracerebroventricularly and about 30 nmoles/kg intravenously (285).

2.5.2.5 Neurotransmitter-related factors

2.5.2.5.1 Neurotensin

Neurotensin is a neuropeptide hormone and neurotransmitter that is involved in sleep-wake regulation and other physiological processes. This hormone is produced in the central system, specifically in the hypothalamus and gastrointestinal. One of the major functions of neurotensin is regulating the dopaminergic system, which is responsible for rewards and mood. Moreover, it controls the secretion of prolactin and luteinizing hormone. In a study that investigated the role of the neurotensin receptor 1 gene (NTSR1) in sleep behavior, the knockout gene in mice showed sleep patterns and mood changes in mice (286).

2.5.2.6 Growth factor

2.5.2.6.1 Transforming growth factor- β1

Transforming growth factor β1 is an anti-inflammatory cytokine involved in sleep regulation. Intracerebroventricular injection of transforming growth factor beta 1 or TGF-β1 in a dose of 200 ng during dark and light periods showed inhibition in the NREM during the light period.

Surprisingly, the TGF-β1 did show the effect on the sleep physiology during the night but less than what has been seen during the light period (287).

In summary, sleep disorders in sleep medicine have been considered a pathological enigma. The human body has complex systems that interfere synchronically with each other, and it is hard to figure out the trigger that influences the onset of sleep disturbance. Furthermore, sleep aetiology is characterized by comorbidity, and numerous biological factors may indicate sleep disorders in smokers. This chapter has covered a significant number of biomarkers and indicators linked to REM and NREM segments.

2.5.3 Neuropharmacological Effects of Nicotine on neurotransmitters

2.5.3.1 Effect of tobacco on Melatonin

There is a large volume of published studies describing the role of melatonin in regulating the circadian system (288; 289; 290). However, smoking has an impact on the levels of melatonin in the serum. Malondialdehyde (MDA) is a biomarker indicating the level of oxidative stress in many diseases like cardiovascular disease, COPD, cancer, and psychiatric diseases. Malondialdehyde has been detected in smokers of one packet a day for a minimum of three years. In a comparative study of 21 smoker female nurses to 21 non-smoker female nurses, the results of female smokers showed increased levels of the antioxidant enzymes glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD) and plasma levels of MDA, while melatonin levels have been decreased in smokers (291).

Human melatonin levels are affected by tobacco. Polycyclic aromatic hydrocarbons in cigarette smoke stimulate CYP1A2, which is involved in the hepatic metabolism of melatonin (MT). This shows that, as compared to a non-smoking time, chronic smokers may have lower serum MT levels when smoking. On two occasions, 8 cigarette addicts were tested. Before the first event, they had smoked, but before the second, they had abstained for a week. Every test consisted of two portions. The first part happened at night, specifically from 8:00 PM to 8:00 AM. Tests were obtained for endogenous serum MT measures every other hour throughout this period. The next day, the second portion was delivered. Oral administration of 25 mg MT began at 09:30 hours, and blood samples for exogenous serum MT assay were obtained every hour between 10:00 and 16:00 hours. The areas under the serum MT-time curve (MT-AUCs) were computed for both endogenous and exogenous substances. MT-AUCs in endogenous serum were comparable between the two times. A dose of MT taken orally caused serum levels to rise above physiological values (292).

2.5.3.2 Effects of nicotine on GABA inhibitory neurotransmitters

Gamma-aminobutyric acid, known as GABA, is a major inhibitory neurotransmitter in the nervous system. GABA is primarily involved in inhibiting the excitatory neurotransmitters of the central nervous system. GABA is subdivided into GABA subunits, GABA-A, GABA-B, and GABA-C (McKernan & Whiting, 1996). GABA-A is found with a high concentration in the brain cortex.

Neurotransmitter modulation by nicotine intake is well documented. Nicotine's impact on the GABA inhibitory neurotransmitters was found to determine the levels of effect on male and female smokers. Nuclear magnetic resonance spectroscopy was applied to measure the concentration of GABA in the brain cortex of 10 healthy male and 6 female smokers. The subjects were asked to abstain from nicotine intake for 48 hours pre-experiment and after the experiment for men. The same protocol was applied to the group of females during and after their ovulation phase. The group control included 7 males and 13 female non-smokers. The results reveal significant differences in cortical GABA levels between the male and female groups. The cortical GABA levels of smoking females have significantly dropped during the ovulation period, while male smokers and non-smokers have shown no changes in the cortical GABA concentration (294).

2.5.3.3 Effects of nicotine on acetylcholine receptors and acetylcholine neurotransmitters

The first investigations into the neuropharmacology of smoking found that nicotinic AChRs are the main targets of nicotine in the cholinergic system. The cholinergic system consists of basal forebrain nuclei, mesopontine nuclei, and striatal interneuron neurons. The striatum, basal forebrain, and brainstem have a significant number of cholinergic neurons, whereas the cerebral cortex, hypothalamus, and olfactory bulb contain a small number of AChRs. The two subunits of acetylcholine receptors are α4 and β2. Research has found that the Ach α4 and β2 receptors are involved in reward, cognition, mood, and many neurological disorders (295). The findings of a positron emission tomography (PET) study have revealed that a single drag of tobacco leads to the activation of α4β2-receptors for 3 hours in many brain regions. Another study reported that the brain switches off 90% of these receptors for 3,5 hours after each cigarette (79). A defect occurs in smokers who puff 20 cigarettes a day and leads to the destruction of α4β2-receptors.

2.5.3.4 Effects of tobacco on dopamine

Tobacco has low CSF dopamine metabolite. For any detectable abnormalities in the CFS and plasma concentration in smokers and PTSD patients, Geracioti Jr. et al. investigated the dopamine metabolite. Thirteen healthy volunteers and eleven patients with PTSD due to battle underwent continuous subarachnoid sampling to collect 37 serial CSF samples over the course of six hours. The study included 10 smokers and 14 non-smokers. For 11 to 17 hours, the tobacco-using individuals abstained. Smokers had significantly reduced HVA levels in their CSF but not in their plasma. Regardless of diagnosis, the average HVA content in their CSF was only 54% of that in nonsmokers (296). In a study where CSF and plasma concentrations of dopamine homovanillic acid were measured in cigarette smokers, PTSD, and HIV patients (21), smokers had significantly reduced HVA levels in their CSF but not in their plasma. Regardless of diagnosis, the average HVA content in their CSF was only 54% of that in nonsmokers (22). Moreover, a rodent study showed the effects of nicotine on the rat brain's ability to absorb dopamine.

Rodent's study showed the effects of nicotine on the rat brain's ability to absorb dopamine. The leading factor in avoidable deaths globally is cigarette smoking. Cigarettes include different pharmacological components than nicotine alone, which may be involved in addiction. Although studies in the literature are frequently inconclusive and little is known about the effects of non-nicotinic tobacco components on dopamine uptake, it is known that nicotine

affects the uptake of dopamine in the brains of laboratory animals. In an investigation examining the long-term effects of tobacco on dopamine and norepinephrine transporters in critical brain regions using rotating disk electrode voltammetry, nicotine (0.35 mg/kg) dramatically reduced DAT function in the nucleus accumbens (NAc) after 30 minutes while not affecting protein expression. Mecamylamine, DHβE, but not MLA were able to amplify this action, proving that nicotinic receptors with the α4 subunit are necessary for its function. In addition, TPM, but not nicotine, improved DAT activity in the dorsal striatum at 1 hour in a way that was independent of nicotinic receptors and did not alter the expression of the DAT protein. Both acute and chronic TPM treatments resulted in a reduction in the ventral tegmental area's mRNA at 1 h DAT (297).

There is a link between dopamine metabolic enzyme polymorphisms and tobacco usage among smokers. Nicotine activates cerebral dopaminergic reward circuits, which cause dependency.

Smokers' consumption may be influenced by allelic variations in genes implicated in dopamine metabolism. Utilizing the enzyme polymerase chain reaction and sequence-specific primers, researchers created tests for polymorphisms in the enzymes dopamine-hydroxylase (DBH), monoamine oxidase (MAO), and catechol O-methyltransferase (COMT) (PCR-SSP). To determine if genotype was associated with daily cigarette consumption, researchers next genotyped 225 smokers. DBH 1368 GG genotype smokers smoked fewer cigarettes on average than GA/AA smokers [mean difference 2.9 cigarettes, 95% confidence interval (CI) 5.5, 0.4; P = 0.022]. In females, the results showed 3.8; the effect was statistically significant. While in males 1.5, it was not. The total impact was higher than 3.8 when the study's exclusive emphasis was on Caucasians. Interestingly, the study proved that obesity is also a risk factor in the effects of the allele by a difference of 5.1. When compared to light smokers (10 cigarettes a day), more heavy smokers (> 20 cigarettes a day) possessed the DBH 1368A gene. (Relative Risk 2.3). When analysis was limited to Caucasians, there was a larger tendency for the DBH A allele to be more prevalent (relative risk = 3.2). In contrast, the MAO-A 1460C gene was shown to be less often carried by heavy smokers (relative risk 0.3). A person's degree of cigarette consumption and heavy smoking can be determined by examining their DBH and MAO changes. These results support the hypothesis that these enzymes determine a smoker's need for nicotine and might help explain why certain people are more likely to get addicted to nicotine and struggle to stop smoking. (298).

2.5.3.5 Effects of tobacco on insulin

Nicotine is well known for affecting insulin functions (299). Research regarding the relationship between tobacco and type 2 diabetes syndrome showed that nicotine reduces insulin sensitivity, which increases the risk of insulin resistance (404). In addition to insulin resistance, smokers have been shown to have elevated blood glucose levels, which can result in hyperglycemia. Remarkably, compared to non-diabetics, hyperglycemia has been associated with cognitive deficits, poor verbal acquisition, psychometric functions, and glycemic older adults without insulin dependency (405). However, motor skills remain unaffected. Smoking has been related to oxidative damage and inflammation, both of which exacerbate diabetes in smokers.

2.5.3.6 Tobacco compounds and Neuroprotection

Smoking consists of a potent exogenous pharmacological monoamine oxidize (MAO), an enzyme known for oxidative catabolism of neurotransmitters like dopamine, serotonin, and

norepinephrine. In a pharmacological study, smokers were screened by PET, and results showed that smokers have less than 30% MAO-A and 40% less MAO-B than non-smokers. β-carbolines are a natural compound of alkaloids that exist in the brain tissue and serve as neuroprotective, antioxidant, and cognitive enhancement. Norharman (β-carboline) and Harman (1-methyl-β-carboline) are potent inhibitors of monoamine oxidase (MAO). According to the findings of the same study, Harman is an inhibitor of MAO-A (Ki = 55.54 ± 5.3 nM), while Norharman is an inhibitor of MAO-A (Ki = 1.2 ± 0.18 μM) and of MAO-B (Ki = 1.12 ± 0.19 μM), (300). There is evidence from toxicokinetic studies that inhalation exposure to norharman and Harman results in a rapid increase in plasma levels and high bioavailability (301).

2.5.3.7 Smoking effects and oxidative stress

Several studies thus far have linked oxidative stress with smoking (302; 303; 304). In Ellegaard and Poulsen's meta-analysis study, oxidative stress has been reported to be triggered by smoking factors. In 36 cohort studies about the effect of smoking on DNA oxidation based on the excretion of urinary 8-oxo-7-hydroxydeoxyguanosine (8-oxodG), agreement of all studies that smoking has an impact of 15.7 % (95% CL 11.0:20.3, p50.0001) on DNA oxidation. In 22 studies which applied the chromatography method on 1709 subjects, 29.3% of studies reported (95% CL 17.3;41.3) increased oxidative stress effects on smokers. However, 14 studies that applied ELISA methodology on 3668 subjects reported a non-significant effect of 8.7% [95% CL1.2;18.6]. In this study of Ellegaard and Poulsen ELISA method tracing urinary 8-oxo-7-hydroxydeoxyguanosine is not suggested (305).

2.5.3.8 Epigenetic Effects of Smoking

According to the American Society of Cancer, more than 70 types of chemicals in tobacco lead to cancer. The carcinogenic agents of tobacco include arsenic, lead, hydrogen cyanide, a radioactive element like polonium-210 (306), carbon monoxide, and polycyclic aromatic hydrocarbons (PAHs), to name but a few (307). Epigenetic change is a risk factor for many serious diseases (308).

According to Egger et al. (2004), epigenetics involves meiotically and mitotically changes in gene expressions that are not part of the DNA sequence (310). DNA methylation and histone modification affect gene transcription and protein synthesis. Smoking can lead to severe epigenetic changes. In an epigenetic study, smokers turn out to have less DNA methylation than non-smokers in the AHRR part of their gene (311). Understanding epigenetic modification due to smoking can explain the link between some symptoms and signs of diseases shown in smokers, such as myeloid leukaemia, COPD, and peripheral vascular disease (312; 313; 314).

Epigenetic changes lead to the inactivation of some genes synthesizing tumour-suppressing proteins (315). Methylation is an essential biochemical reaction involving several molecular processes such as ageing, carcinogenesis, and X-chromosome inactivation required for body functions (316).

In eukaryotes, DNA methylation is the bonding of a methyl group cytosine's carbon 5 position (317). DNA methylation is responsible for alteration in the DNA, which leads to several disorders such as cardiovascular diseases, cancer, and nervous disorders (318). It is well documented in epigenetic changes that DNA process alteration, namely in nucleosome

remodelling, histone regulation, and cytosine methylation, is linked to silent cancer genes (319; 320).

2.5.4 Neurotransmitter Systems and Their Role in Cognitive Function.

Cognition is the brain's capability to acquire knowledge, process information, make decisions and reasoning, and process complex mental abilities such as attention, planning, language, social cognition and memory. Cognitive performance is measured by different neuropsychological methods, tools and batteries clinically reliable in detecting cognitive dysfunctions of the brain in many mental or behavioural disorders. Working memory is a parametric factor used to measure the proper functions of the dorsal region of the prefrontal cortex with conjunctions of cingulate and temporal cortices (321). Different domains of life require deep reasoning, decision-making, solid memory and highly selective attention. These cognitive abilities are impaired in many psychiatric diseases and neurodegenerative diseases. To identify the underlying mechanisms behind these impairments, the neuroanatomical substrates involved in Parkinson's disease, frontotemporal dementia, Huntington's disease and Alzheimer's disease should be understood. This study investigates numerous neurochemicals affecting visual processing, auditory processing, working memory, long-term memory, logic and reasoning, selective attention, and divided attention.

2.5.4.1 The Cholinergic System and Neurocognitive Process

The Cholinergic system affects behavior, learning, sleep-wake cycles, attention, and high-level cognitive processing. The forebrain is believed to be responsible for cholinergic neurons associated with memory and some cognitive dysfunctions. N-acetyl aspartate (NAA) is an endogenous amino acid site in brain neurons. Magnetic resonance spectroscopy showed that the decreased concentration of NAA in the frontal lobe and occipital lobe is linked to cognitive decline (322).

An electrophysiological study of nucleus basalis activity reveals that the cholinergic system of the forebrain activates the cortex and inhibits the rhythmic movement of the reticular thalamic-cortical circuits (323). The cholinergic system engaged in the reticular activating system theory, which was published by Moruzzi and Magoun in 1949 (324). This theory explains how stimulation of the brainstem activates the sleep EEG and attention. According to Richardson and his fellows, the nucleus basalis of Meynert (NBM) is the source of acetylcholine in the brain's cerebral cortex. NBM has a significant role in learning (325). Misalignment in the NBM is associated with Alzheimer’s disease, memory impairment, and interruption in cognitive functions (326). In an animal study, a lesion in the forebrain correlated to disturbance of memory, learning, and visual recognition (325). The basal forebrain has been found to be in charge of attention and object recognition (327).

Acetylcholine is the primary neurotransmitter involved in the autonomic nervous system. Ach works as a modulator in the brain's cholinergic areas such as the brainstem (laterodorsal, pedunculopontine tegmental nuclei), basal forebrain (basalis, medial septum, diagonal band of Broca). The acetylcholine projection in the forebrain, hippocampus, and cerebral cortex is linked to cognitive functions in the human brain. The cholinergic receptors consist of muscarinic or nicotinic types. The thalamus has a high concentration of nicotinic receptors.

Defects in cholinergic neurotransmitters were the reason behind many cognitive impairments in Alzheimer's disease (328). Preventing the work of cholinergic muscarinic receptors by an anticholinergic drug called scopolamine causes attention and learning impairment. According to the same author, injecting physostigmine, a reversible cholinesterase inhibitor, enhances the acetylcholine release and, therefore, the cognitive functions in Alzheimer's patients (329).

β-carbolines were found to increase the brain-derived neurotrophic factor (BDNF) in rat hippocampus by injecting (10 and 15 mg/kg) of harmine. Brain-derived neurotrophic factor (BDNF) is a protein synthesized in the brain and spinal cord. BDNF is found in the hippocampus, cortex, and basal forebrain and has a significant role in memory and higher thinking processes. The research of Yamada and his fellows has shown that the increase in BDNF mRNA expression is linked to long-term memory and learning. Activation of TrkB/phosphatidylinositol-3 kinase (PI3-K) in the hippocampus was associated with spatial memory (330). Several studies show that BDNF exists in saliva for recovery of the oral epithelium (331). Genetic knockdown of BDNF or its receptor known as tyrosine receptor kinase B (TrkB) causes the severity of memory and learning ability in mice, chicks, and rats (332).

2.5.4.2 The Glutamatergic System and Neurocognitive Processes

Glutamate belongs to the family of amino acids. Glutamate is a biomarker that traces the function and dysfunctions of the working memory. Some psychiatric diagnoses rely on glutamate as a biomarker in referring to working memory dysfunctions in the diagnosis of schizophrenia (333; 334). Glutamatergic neurotransmissions are essential systems for memory, learning, and cognition. Ketamine has been used as a glutamate blocker. It has been documented that abnormalities in glutamate lead to cognitive disorders in 1H-MRS research. Glutamate is one of the major neurotransmitters and amino acids required for the functions of the nervous system. Excessive release of glutamine leads to hyperexcitability of the nerves and ends up with excitotoxicity and cytotoxicity (335). Excitotoxicity of hypothalamus nerves linked with impairments of spatial learning. It appears to be that long-term potentiation requires the activity of glutamate receptors (336). NMDA receptors are necessary to trigger LTP functions, whereas AMPA receptors are required to induce LTP functions (337).

2.5.4.3 The GABAergic System and Neurocognitive Processes

GABA is well documented to be involved in perceptual and attentional functions. According to a magnetic reasoning imaging study, the concentration of GABA in the brain decreases with age and leads to the decline of cognitive functions. To prove the link between GABA concentration and normal mental processes, a study applied the Mescher-Garwood point-resolved spectroscopy (MEGA-PRESS) 1H-MRS approach on 94 healthy adults. Montreal Cognitive Assessment was used to measure the cognitive abilities of subjects. The results showed that a high concentration of GABA in the frontal and posterior midline is related to high cognitive performance in the subjects. This study confirms the importance of GABA neurotransmitters for normal cognitive functions and proves that the decline of GABA occurs due to the natural increase of age (338).

In a cross-sectional study done by the Johns Hopkins Medical Institution aimed to measure GABA concentration in attention deficit hyperactivity disorder ADHD children (8-12 years old), the study used magnetic resonance spectroscopy 3T in primary somatosensory and motor

cortices. To assess the IQ of kids, the assessment tool the Wechsler Intelligence Scale for Children III or IV has been applied. The study eliminated any score below 80 IQ score. The investigation included 13 children with ADHD and 19 typically developing (TD) children. Linear regression analysis results revealed that the mean (SD) of GABA concentration for ADHD males was 0.96 (0.23) and 1.05 (0.03) for ADHD females. While for TD females, the mean (SD) was 1.26 (0.47), and for TD males was 1.49 (0.43). The mean (SD) of GABA concentration in ADHD children was 0.98 (0.22), while the GABA concentration of TD children was 1.34 (0.47) (339).

Dysfunctions of the neurotransmitter pathways GABA and glutamine are associated with cognitive deficits in many neurological disorders. A decreased level of GABA concentration is correlated with cognitive dysfunctions in patients with neuromyelitis optica spectrum disorder (NMOSD).

2.5.4.4 The Serotonergic System and Neurocognitive Processes

Serotonin belongs to the family of monoamines. Serotonin (5-hydroxytryptamine; 5-HT) is a major neuromodulator of the nervous system. Tryptophan is the precursor of serotonin. According to Fitoussi and his fellows, the highest quantities of serotonin exist in the substantia nigra by normal production of (500–1000 pg/mg), ventral tegmental area, and raphe nuclei (340). However, another study showed that serotonin is present in all organs of the body, like the liver, lungs, kidneys, intestines, skin, and testicles. Moreover, the 5-HT exists in all species on Earth (341). The 5-HT is considered a critical signaling molecule in plants and animals, and it acts as a precursor in the synthesis of melatonin (342; 343). Several studies have revealed that serotonin is involved in multiple physiological functions in humans (344; 345).

The large volume of published studies has described the role of serotonin in the behaviors of many species. An animal study has revealed that aggressiveness is linked to lower tissue levels of 5-HT. The 5-HT1A and 5-HT1B receptors were identified in this study as the key players in the modulation of offensive aggression (346). Two different sets of healthy mice were given two dosages (25 g and 100 g) of an amino acid combination absent of tryptophan in another mouse investigation. The result showed that decreased plasma tryptophan levels correlated to a higher level of aggressiveness in the group of mice dosed with 100 g after six hours (347). Previous research has documented the connection between cognitive functioning and the serotonergic system. Administration of antagonists of the 5-hydroxytryptamine 2A, 5-hydroxytryptamine 2C, 5-the HT4, or 5-HT1A and the 5-HT3 receptors has alleviated cognitive impairment (348). Schmitt, J., and his fellows reported that reduction of 5-HT is linked to long-term memory dysfunction (349).

A study found that the gut-brain axis track has a bi-directional interaction between the brain and gastrointestinal tract while investigating the underlying mechanisms behind low levels of serotonin associated with depressed mood and poor memory. This gut-brain axis links cognitive and emotional centers in the central nervous system with the peripheral functioning of the digestive tract. The enterochromaffin cells of the gastrointestinal epithelium are known to produce 90% of all serotonin in the body. Despite the serotonin synthesis by endocrine cells, serotonin still behaves as a paracrine hormone in the gut. While depleted serotonin affects the cognitive system, verbal reasoning, episodic memory, and working memory, the intake of tryptophan improves attention and memory (350).

In Alzheimer's disease, neurotransmitter pathologies occur in the cholinergic, noradrenergic,

glutaminergic, and serotonergic systems. The serotonergic system has an influence on emotional processes and emotionally related tasks (351).

2.5.4.5 The Dopaminergic System and Neurocognitive Processes

Dopamine is member of catecholamine family. It is contributing to many functions, such as sleep, reward, and advanced mental processes. Abnormalities in dopamine secretion was documented in the pathologies of many behavioral or neurological dysfunctions. reduced dopaminergic neurons in the substantia nigra is a key pathogenic to a common cause of numerous neurodegenerative diseases. In PET study, dopaminergic regulation related to human cognition was examined in healthy patients with Parkinson's, Huntington's, and schizophrenia in pre-, intra-, and post-synaptic clefts.

Goldman-Rakic (1979) conducted preliminary research on the relationship between dopamine and working memory. Using 6-hydroxydopamine, a neurotoxin organic compound known as oxidopamine, to knock down the dopamine in the principal sulcus of the brain disturbed the function of working memory in monkeys. A delayed task is a working memory (WM) task. This task uses a shape-8 maze. The maze demands the animal to choose the right or left side to get a reward (353).

2.5.4.6 The Adrenergic System and Neurocognitive Processes

Epinephrine and norepinephrine, known as adrenaline and noradrenaline neurotransmitters, belong to the family of catecholamines. The adrenergic nervous system is the autonomous nervous system that requires adrenaline and noradrenaline neurotransmitters. The subdivision of the adrenergic system is 5-receptor subtypes, namely, α1, α2, β1, β 2, and β3. Noradrenaline has numerous functions, including but not limited to memory, learning (354), sleep activity, information processing, and the development of neurogenesis in the brain (355). Noradrenaline deficiency is reported to be involved in attention-deficit disorders and other neurological disorders in the brain (355). The α1-adrenergic receptor subtypes (α1A, α1B, α1D) play a significant role in synaptic plasticity and high cognitive functions. However, some animal studies reported that activation of the α1-adrenergic receptor inhibits the work of spatial and consolidation memory (356). These results were explained by a hypothesis that proves that high doses of noradrenaline lead to desensitization of the adrenergic receptors and induce negative feedback on memory. A knockout mouse α1B adrenergic receptor showed spatial learning impairments (357), and memory consolidation disorder (358). Knockout α1D adrenergic receptors did not show the same cognitive defects in mice (359).

2.5.4.7 The Histaminergic System and Neurocognitive Processes

When the brain is executing high-level cognitive processing, histamine is required as a key neurotransmitter. Pioneer studies by Almeida and Izquierdo prove the importance of histamine in the complex process of memory and learning (360; 361).

Histamine is reported as an essential aspect for cognitive function. Experimental studies showed how H1, a histamine receptor (H1Rs), contribute to cognitive functions and memory enhancement. Histaminergic neurons exist in the posterior hypothalamus. Histamine (H1) antagonist is a well-prescribed agent for sleep loss and mental disturbances. The system of histamines is linked to the cholinergic system which is important in recall of events and

education. A plethora of data proves the interconnection between the cholinergic and histaminergic systems in the cognitive deficits in many neurodegenerative diseases. Histamine induces the synthesis of acetylcholine (ACh) in the cortex and amygdala and modulates (ACh) neurons in the nucleus of the medial septal area and nucleus basalis magnocellularis (NBM). Pharmacological studies prove the essential use of H3 receptor antagonists to enhance histamine for better functions of memory disorders and learning (362).

2.5.4.8 Glucocorticoids and Neurocognitive Processes

Glucocorticoids influence attitude, behaviour, learning, and memory. Many studies have shown that glucocorticoid insufficiency is associated with sleep difficulties and cognitive functions. Cortisol overproduction is linked with hypercortisolemia, which is connected to cognitive dysfunctions in the medial temporal lobe of declarative memory. According to Jamieson and his colleagues, type 2 glucocorticoid receptors (GRs) are linked to memory dysfunctions due to their sensitivity to cortisol under stressful conditions (363). Another animal study found a link between high glucocorticoid levels and decreased hippocampal function in cognitive flexibility, evaluated via an anagram test. Sixteen subjects showed a 32% improvement in solving anagram puzzles when waking from REM sleep compared to non-REM sleep. The study emphasizes the connection between REM sleep, reasoning, and creativity in participants (364).

In a longitudinal ageing study that lasted between 3 and 6 years, the link between cortisol levels and cognitive decline was explored in 1,154 elderly people to determine whether this relationship was due to depression or ageing. The concentrations of total cortisol (CRT) and corticosteroid-binding globulin (CBG) were measured. The study aimed to assess information processing speed, verbal memory performance, and global cognitive functioning in individuals aged 65 to 88, taking lifestyle and environmental factors into account. The findings revealed a significant connection between increased cortisol levels and poor verbal learning ability in males and females ($\beta = -0.32$). Women had higher cortisol levels, which were associated with slower information processing times ($\beta = -0.85$). According to the overall findings of this longitudinal study, elevated cortisol levels in the elderly are linked with decreased memory function and information processing, rather than with full cognitive decline (365).

2.5.5 Brain Regions Involved in the Sleep-Wake System

2.5.5.1 Ascending Reticular Activating System ARAS: The Wake System

The ascending reticular activation system area is a group of regions that govern the body's wakefulness (366). This system encompasses multiple critical places, including the reticular formation. Locus coeruleus raphe, the thalamus, hypothalamus, pedunculopontine nucleus, and the laterodorsal tegmental nucleus. All these regions work together to orchestrate our ability to stay awake and conscious (367).

Ascending Reticular Activating System (ARAS) pathways

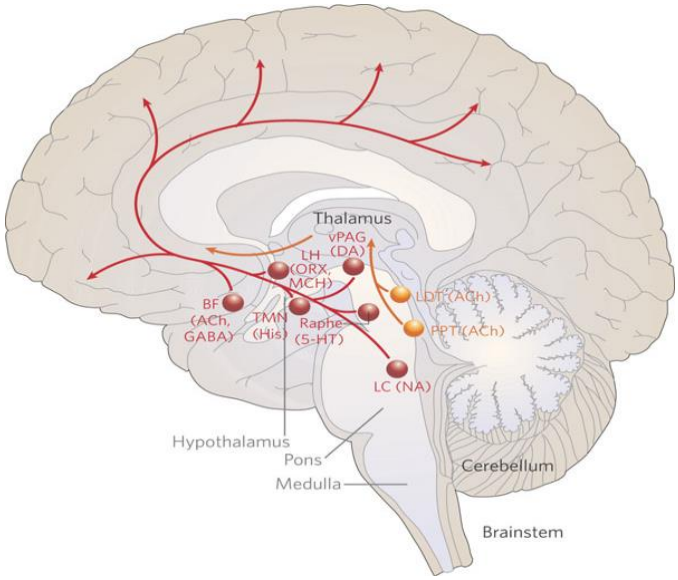


Figure 2:Saper et al., Nature In Sight, 2005

Researchers have discovered between the 1970s and 1980s the primary pathway involved in the wake system with its neurotransmitters. This pathway contains two main branches. One route takes an upward pathway to the thalamus, stimulating the thalamic relay neurons that are necessary for sending information to the cerebral cortex.

The two cell groups in Figure 2 that produce the neurotransmitter acetylcholine are the laterodorsal tegmental nuclei and pedunculopontine (LDT/PPT). These cell groups are thought to be the main source of upper brainstem input to the reticular nucleus of the thalamus and the thalamic-relay nuclei (367). Strecker, R.E. et al. have discovered that REM waves activate LDT/PPT neurons. Strecker has found different physiological changes during REM, like a decrease in muscle tone and brain activity, while decreased activities of these cells during NREM sleep (368). Moreover, the PPT/LDT neurons have major functions in linking between the thalamic relay nuclei and cerebral cortex to maintain consciousness.

The cerebral cortex is reached by the lateral hypothalamus and basal forebrain as part of the second route of the ascending reticular activating system (370). This neuropathway comprises many neurotransmitters, including monoaminergic cells situated in the upper brainstem and posterior hypothalamus. It also includes noradrenergic neurons from the locus coeruleus (LC), serotonin from dorsal (DR) nuclei and median raphe, dopamine from ventral periaqueductal grey matter, and histamine from the tuberomammillary region. Melanin-concentrating hormone (MCH) neuropeptides, as well as orexin, communicate with the cerebral cortex via GABA and acetylcholine. Any damage to this system, particularly the rostral midbrain and lateral hypothalamus, results in a coma or deep slumber. During wakefulness, monoamine neurotransmitters such as norepinephrine, dopamine, and serotonin are more active; during NREM sleep, they are less active, and during REM sleep, they are not active. Neurons concentrating on melatonin are active during REM sleep, whereas orexin neurons are active throughout waking. REM and NREM sleep are characterized by the activity of acetylcholinergic, GABAergic, and glutaminergic neurons.

2.5.5.2 The ventrolateral preoptic nucleus (VLPO): The Sleep-System

The ventrolateral preoptic nucleus is a set of sleep neurons in the brain found in the anterior part of the hypothalamus that regulate sleep and control the work of ARAS during sleep. Any dysfunction in VLPO neurons may lead to insomnia disorders. The VLPO triggers the work of non-rapid eye movement NREM sleep and includes neurons that induce galanin and GABA which behave in the brain as a wake-centre inhibitor and are involved in the shifting process from wake to sleep status. Animal investigation has reported that abnormalities in the VLPO are connected with a decline in the NREM sleep segment and an increase in arousal. Research has shown that VLPO is controlled by prostaglandin D2 and adenosine this system is shut down by neurotransmitters like acetylcholine and noradrenaline (371).

The Ventrolateral Preoptic Nucleus (VLPO) Pathways

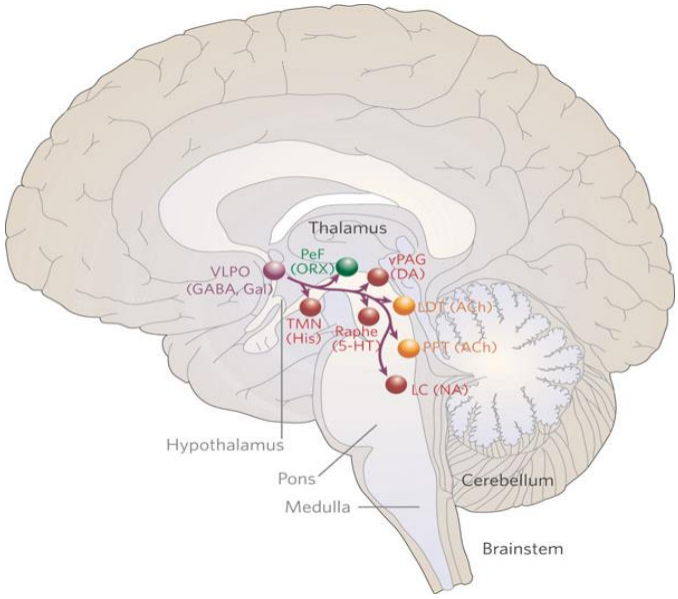


Figure 3:Saper et al., Nature InSight, 2005

In a pioneer study by J. E. Sherin in the Department of Neurology of Harvard Medical School, the role of VLPO and sleep generation related to the tuberomammillary nucleus (TMN) in the posterior hypothalamus has been investigated. This study has searched the FOS protein, a gene product expressed by neurons active during sleep state. This study applied two major techniques on rats: retrograde tracing techniques and immunocytochemistry.

Immunocytochemistry Photomicrographs of FOS Protein in the VLPO of Rats

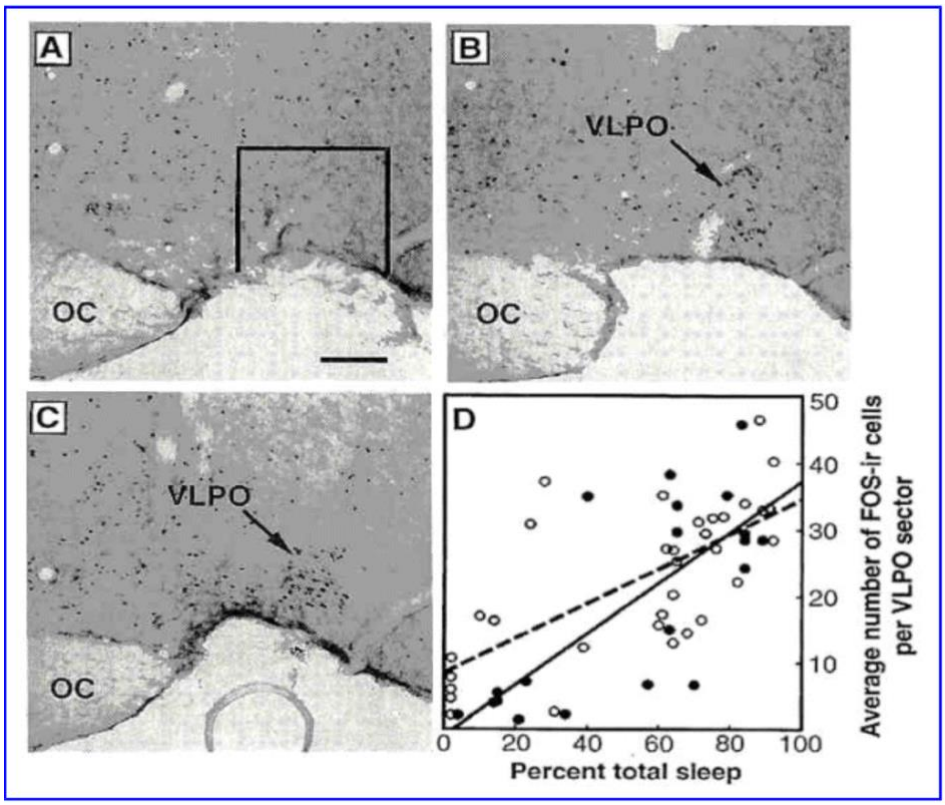


Figure 4: Ovid: Sherin: Science, Volume 271(5246). January 12, 1996.216-219

Figure 4: This figure includes photomicrographs (A to C) of FOS-immunostained coronal sections (slices) through the preoptic hypothalamus of rats. Photomicrograph-A shows a rat that slept only 15% of an hour before being killed. Photomicrograph B shows a rat that slept 63% before being killed, whereas Photomicrograph C shows a deprived rat that slept for 83% of the hour before being killed. The black nuclei represent in these photomicrographs the FS-ir cell expression in VLPO of the rats. B and especially C photomicrographs show the high significance of FOS-ir cell expression in rats who slept more than Photomicrograph A. The photomicrograph-D represents the correlation analyses between the increased level of FOS-ir cells in VLPO and the increased sleep hours. The black circles in the Photomicrograph-D show rats' behaviour with a solid black regression line, while the open circles with a dashed regression line stand for sleep-deprived rats. The correlation coefficient according to the study of J. E. Sherin et al. shows a significant correlation between FOS-ir cell expression and total sleep time for the two types of rats: behaving rats (R equals 0.743) and sleep-deprived rats (R equals 0.704).

The study findings revealed the activation of VLPO, showing increased levels of FOS-ir cells during long sleep hours. Interestingly, the study has shown a significant correlation between the increased levels of FOS-ir cells in VLPO and the increased hours of sleep. The results of the study have also shown that the decreased sleep hours lead to a decrease of FOS-ir cells in the VLPO in deprived rats. The FOS-ir cell level has increased again once rats have been allowed to recover from sleep deprivation.

The injection of retrograde tracer in the TMN area has shown that activated sleep neurons in VLPO build a connection with histamine-producing cells in TMN. The study has found that GABA released by the VLPO inhibits the functions of histaminergic neurons in the TMN to control sleep-wake patterns.

In another rodent study about the long-term effects of bilateral preoptic lesions on sleep patterns in rats, Lu, Jun, and his colleagues investigate the ventrolateral preoptic nucleus and its surrounding regions using ibotenic acid lesions to understand the significance of the VLPO

cluster and the ventromedial preoptic nucleus (VMPO) in sleep and thermoregulation in rats. The results have shown a decrease in NREM sleep in rats with bilateral lesions of VLPO cluster in the first week by 45%, during the second week by 63%, and in the third week by 57% compared to the controls. The loss of 80 to 90% of cells due to bilateral lesions leads to NREM sleep by 50% and delta power by 60%. Surprisingly, the bilateral lesions in the ventromedial preoptic nucleus did not lead to disorders in sleep time or circadian rhythm. The study revealed a linear association between the dropping number of clusters of cells of VLPO and NREM, delta power sleep (373). This study confirms the previous studies that prove the association between VLPO lesions and insomnia, emphasizing the significance of VLPO for sleep regulation (374; 375).

2.5.5.3 Other regions involve in Sleep-Wake patterns

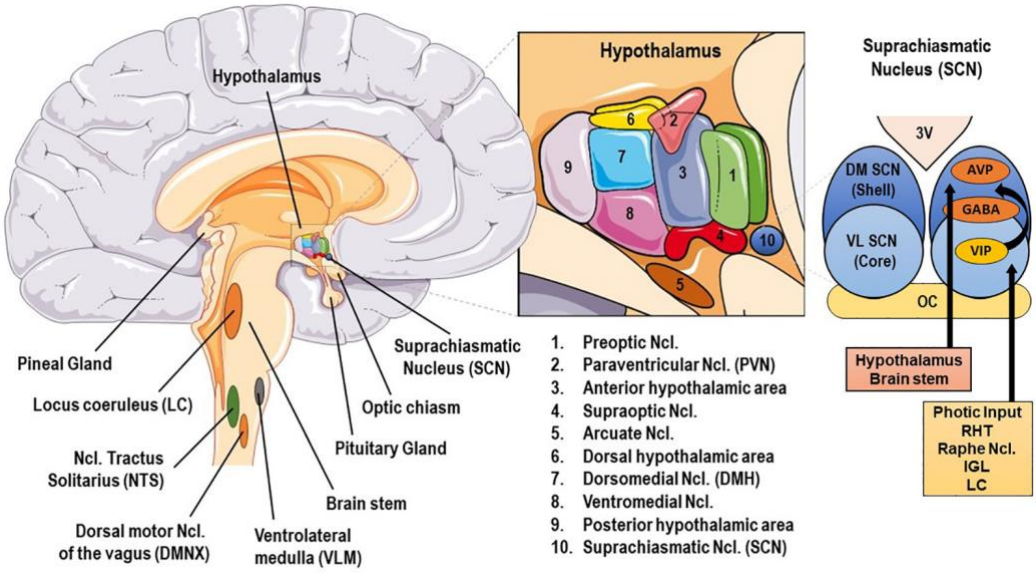
2.5.5.3.1 The hypothalamus

It is always necessary to be aware of the main brain glands that regulate sleep-wake patterns while discussing the sleep-wake system. For sleep physiology and other intricate bodily processes, the hypothalamus is a crucial component. Similar to the Greek meth of Pandora's box, any injuries in this region of the brain would cause many illnesses in the human body. This middle brain nucleus, which is located underneath the thalamus, is engaged in a number of circadian processes. Most medical textbooks refer to the hypophysis, or pituitary gland, as part of the hypothalamus, which is the stem that connects the neurological and endocrine systems.

The hypothalamus has multiple complicated roles, the most important of which is to orchestrate the network that connects the neurological and endocrine systems. It controls emotions, sleep-wake cycles, homeostasis, the autonomic nerve system, and metabolism. This area of the brain governs all hormonal body activities by the use of key hormones including gonadotropin-releasing hormone (GnRH), thyrotropin-releasing hormone (TRH), growth hormone-releasing hormone (GHRH), corticotropin-releasing hormone (CRH), somatostatin, and dopamine (376; 377). The pituitary gland is controlled by the hypothalamus via the hypothalamic hypophyseal tract and portal system. The endocrine system is connected to the hypothalamus through the pituitary gland. Homeostasis is controlled by this region of the brain. It governs behaviors, sex desire, eating, and pain perception. Three anatomical groupings comprise the hypothalamus. The anterior group consists of the following nuclei: anterior, suprachiasmatic, supraoptic, paraventricular, and preoptic. Dorsomedial, ventromedial, and arcuate nuclei make comprise the hypothalamus's middle group of neurons. The hypothalamus's posterior zone comprises both mammary and posterior nuclei (378). In this chapter, we shed light on certain nuclei associated with sleep-wake cycles, which may explain the pathophysiological functions of sleep disorders. The biological rhythm is influenced by the light-sensitive suprachiasmatic nucleus, which is connected to optic fibers. Sleep patterns include both the posterior and mammary nuclei (382).

2.5.5.3.2 Suprachiasmatic nucleus (SCN)

The Suprachiasmatic Nucleus (SCN) and sub-Anatomical Nucleus of the Circadian System



Jacobson S, Marcus EM, Pugsley S, Jacobson S, Marcus EM, Pugsley S DOIhttps://doi.org/10.1007/978-3-319-60187-8_1

Figure 5: This graph represents the anatomical structure of suprachiasmatic nucleus and sub anatomical nucleuses involved in the circadian system in the brain.

The suprachiasmatic nucleus, situated near the front of the hypothalamus, serves as the body's internal clock. It regulates our daily biological cycles depending on the solar cycle. The SCN regulates these rhythms, which include cellular activity and general body functioning, utilizing light and dark signals. These signals are detected by specific cells in the retina and sent to the SCN via the retinohypothalamic tract. The SCN engages complex transcriptional-translational feedback loops, leading to the spontaneous oscillations of gene and protein expression. Despite the use of GABA as a major neurotransmitter, SCN neurons express different neuropeptides like vasoactive intestinal polypeptide and gastrin-releasing peptide by a ventral core of SCN and arginine vasopressin by a dorsal shell, which involve in SCN function. Any changes in the secretion of VIP induce behavioural changes in the cellular rhythms and cause light response problems (379).

2.5.5.3.3 The pituitary gland

The pituitary gland forms one of the important parts of the endocrine system. As indicated in the Medical Textbooks, 380, the pituitary gland is composed of two glands, namely the anterior and posterior pituitary glands. Several studies have reflected on the number of hormones secreted by the pituitary gland, particularly the interior one. The anterior gland, conceived as a regulating organ of many functions via the signals received from the master gland hypothalamus, secretes six major hormones in the endocrine system through its different endocrine cells: growth hormone GH, adrenocorticotropic hormone-ACTH, prolactin-PRL, thyroid-stimulating hormone-TSH, luteinizing hormone-LH, and follicle-stimulating hormone-FSH. It is a small gland situated on the wall of the third cerebral ventricle. The pineal contains cells called pinealocytes; they are rich in the hormones melatonin, noradrenaline, and

serotonin, which the pineal organ employs as melatonin precursors thanks to the enzyme manipulated by the suprachiasmatic nucleus.

Unlike the anterior pituitary gland, which produces six hormones by itself, the posterior pituitary gland only uses hormones from the hypothalamus, like an antidiuretic hormone called vasopressin, which manages water in the kidney and controls blood pressure, as well as oxytocin, which is involved in many physiological and emotional body functions like during birth and breastfeeding, affection, but few to mention.

2.5.5.3.4 The Pineal gland

A little gland hunger located in the third ventricle is known as the pineal gland, or epiphysis cerebri. The pineal gland uses the hormones melatonin, noradrenaline, and serotonin found in the pinealocytes, the cells of the pineal gland, as precursors of melatonin through the action of an enzyme that is controlled by the suprachiasmatic nucleus (Jacobson, Marcus, & Pugsley, 2018). Melatonin is one of the peptides secreted by the human pineal gland, and it plays a significant role in regulating the circadian rhythm in response to photoperiodism. Many peptides, including pineal antigonadotripin, gonadotropin-releasing factor, arginine, oxytocin, vasopressin, vasotocin, and neurophysin I and II, have been identified by a groundbreaking research that demonstrates how the pineal gland interacts with these structures through the hypothalamus and brain stem (Erlich & Apuzzo, 1985).

2.6 Smoking and Chronic Disease-Related Cognitive Impairments

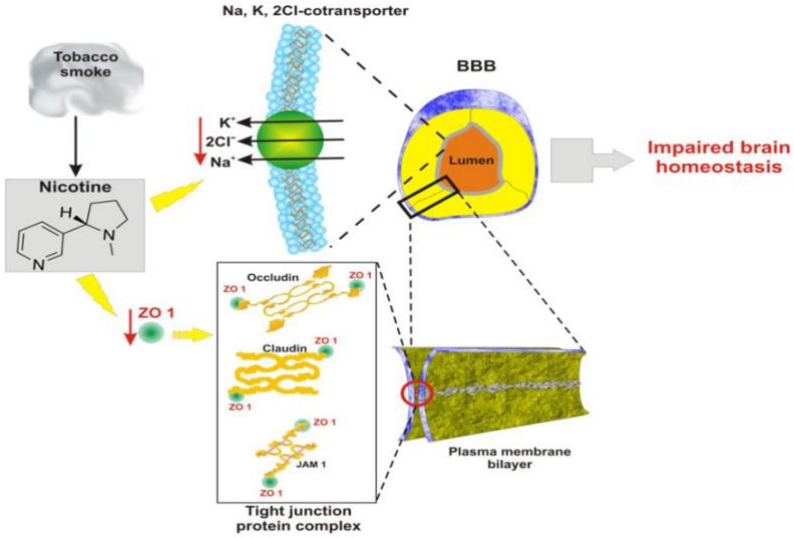
In the assessment of cognitive performance on nicotine intake, 20 smokers were subjected to a Questionnaire on Smoking Urges (QSU) and 2 cognitive tests before and after puffing two cigarettes during two sessions of 90 minutes each. In every session, the subjects had to be deprived of smoking for 18 hours after smoking two cigarettes. The findings of these tests did not show any significance in reasoning items, while the response was slow and the score of QSU increased. The result emphasizes that tobacco obstination enhances cognitive performance (383).

2.6.1 Impact of Smoking on Cerebrovascular Disease

Smoking is the second factor causing cerebrovascular disease. The cerebrovascular disease leads to cognitive impairments (385). A study examined the impact of smoking on cerebral hemodynamics. Using the transcranial Doppler ultrasound technique to measure the changes in flow velocity and cerebrovascular reactivity in the middle cerebral arteries of 24 smokers and 24 healthy smokers, scientists found that smoking reduces breath-holding index (BHI) after 20 minutes of smoking, which increases the risk of cerebrovascular diseases and stroke in smokers (384).

Another study by Peter Mazzone and his colleagues investigated the impact of smoking on the cerebrovascular system, particularly on the blood-brain barrier (BBB) and found that both active and passive smoking cause oxidative stress and inflammation, which lead to endothelial dysfunction. The endothelial dysfunction leads to disruption of BBB, which causes stroke and small vessel ischemic disease, and increases the pathogenesis of neurological diseases due to the inflammatory responses, as explained in the figure below (385).

Effects of Oxidative Stress and Inflammation on Blood Brain Barrier (BBB) of Smokers



Int. J. Environ. Res. Public Health **2010**, *7*(12), 4111-4126; **https://doi.org/10.3390/ijerph7124111**

The Figure 6: The figure above demonstrates the way tobacco damages the function of the blood-brain barrier (BBB). Nicotine reduces the production of ZO1 which is an essential protein involved in tight junctions. Tobacco also affects the functions of Na, K, 2C co-transporter. These defects impair the blood-brain barrier function and affect the brain homeostasis.

2.6.2 Smoking as a Risk Factor for Cardiovascular Diseases and Cognitive Impairment

Smoking is a significant risk factor for lung illness, cardiovascular disease, and dementia in the elderly. In 2000 participants, over 50 tobacco measures were measured in patients with subclinical atherosclerosis. A correlation between longer life span smoking and a decline in cognitive functions was detected in men but not women (386).

In an Australian cohort study of 188,167 subjects lasted for 7.4 years and tended to measure the impact of tobacco on 36 risk factors of cardiovascular disease (CVD), current smokers who were 8% of the population study had significantly higher risks of hospitalization and death from various CVD compared to past smokers who were 34% with adjusted relative risks (RRs) of 1.65 for ischemic heart disease, 2.45 for acute myocardial infarction, 2.16 for cerebrovascular disease, 2.23 for heart failure, and 5.06 for peripheral arterial disease (387).

Deckers et al. conducted a meta-analysis study of 6,132 abstracts and 24 papers about the link between coronary heart disease (CHD) and cognitive impairment and dementia. The meta-analysis of 10 cohort studies showed that there is a high risk of 45% of cognitive issues (OR = 1.45) to have cognitive impairment or dementia (388).

The risk of smoking on the cardiovascular system and cognitive system has been raised as an issue of investigation in the study of Okusaga, Olaoluwa, et al. and colleagues about smoking hypercholesterolaemia and hypertension as a risk factor for cognitive impairments in adults. Recruiting a cohort study of 2,312 subjects between 50 and 75 years old, Okusaga, Olaoluwa, et al. could assess the cognitive patterns of subjects throughout various standardized tests of cognition and intelligence. The analysis showed that higher diastolic blood pressure was negatively linked to a decrease in the auditory-verbal learning tests (AVLT). Interestingly, all

the cognitive tests have shown a negative association with smoking except the verbal fluency test. The study concluded that smoking causes high blood pressure and so cognitive deficits (389).

2.6.3 Smoking, Hypoxemia, and Cognitive Impairment

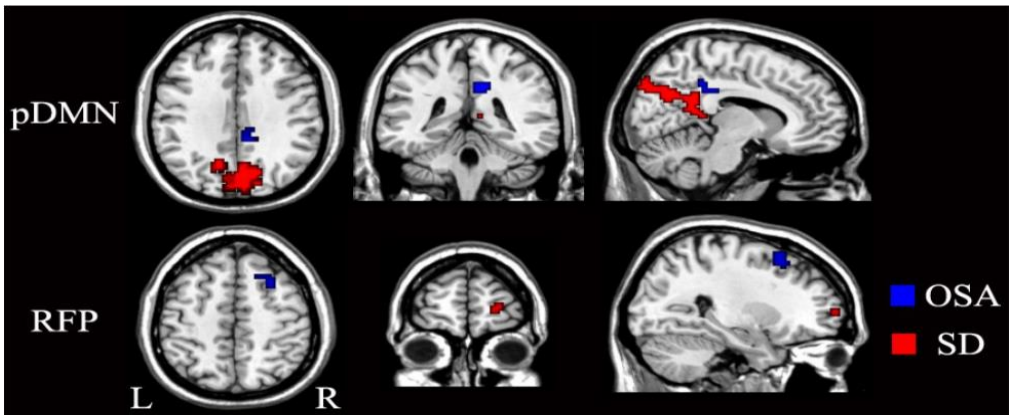
Smoking is a risk factor for hypoxemia (Nizet, Tessa AC, et al., 2005). Patients who face repeated hypoxemia are most likely exposed to episodes of sleep apnea. Intermittent hypoxemia indicates a pulmonary system disease associated with disorders in reasoning, problem-solving, physical movement, coordination, and impairment in motor skills (390).

There are a considerable number of MRI studies that have investigated the link between hypoxemia and sleep apnea (OSA) in the brain. Frequent airway blockages during sleep cause episodic hypoxemia called OSA, which has been involved in brain structure and function alterations. The MRI studies screened changes in gray and white matter volumes in areas involved in memory, executive function, and attention in the hippocampus, prefrontal cortex, and cingulum (391).

Resting-state studies are types of studies that provide insights on various cognitive functions in the absence of external stimuli to understand the brain function and identify any abnormalities or neurological disorders. In a resting state fMRI study, abnormal connectivity in various brain networks, like the default mode network (DMN), involved in cognitive and emotional impairments has been seen in OSA patients, as demonstrated in the figure below (392).

Numerous studies explain these changes in the brain functions due to underlying mechanisms including oxidative stress and sympathetic nervous system activation as results of repeated apneic events, which are beyond the scope of this study (393; 394).

Structure and Functional Deficits in Obstructive Sleep Apnea Patients



Sleep, Volume 36, Issue 5, 1 May 2013, Pages 651–659, https://doi.org/10.5665/sleep.2620

Figure 7: This figure demonstrates resting-state functional connectivity (rsFC) differs in two sites in the brain: the posterior default-mode network (pDMN) and the right frontoparietal network (RFP) between patients with obstructive sleep apnea (OSA) in blue and sleep-deprived subjects in red.

III. Methodology:

3.1 Research design: meta-analysis study and systematic review

1. **Methodological concepts:** Meta-analysis is an appropriate tool of investigating the effects of smoking on sleep quality and cognitive functioning, as this meta-analytical research combines results of 94 investigations, increasing study-population size and statistical power of detecting effects.

2. The methodology employed in this study to determine and assess how smoking affects sleep and cognitive abilities is supported by the systematic review. This systematic review can assist in detecting any gaps in the literature and guarantees that all pertinent studies are included in the meta-analysis.

   3. The meta-analysis and systematic review of this thesis make use of the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA) (395).

   The specific techniques used in this meta-analysis research and systematic review to look at how smoking affects sleep and cognitive abilities were determined by the following standards:

3.2 Literature search strategy

Literature search:

Literature search: a comprehensive literature search to identify all relevant studies on smoking, sleep, and cognitive functions has been conducted. The main source of this investigation is the database of Lesch typology and aetiology, which is summed up in the second version of the book “Alcohol and Tobacco,” written by Lesch.

The databases and search engines for academic and scholarly research papers of this investigation have been conducted using: PsycINFO, PubMed, Embase, Google Scholar, Scopus, Web of Science, MEDLINE, and Springer Link.

3.3 Inclusion and exclusion criteria

Inclusion criteria:

• Studies on the impact of smoking/tobacco/nicotine on sleep quality/sleep functions/ sleep patterns/ sleep disorders/obstructive sleep apnea and/or cognitive processes/cognitive performance/memory/attention/decision/reasoning/reaction time.
• Studies involving only human subjects.
• Studies that employ validated sleep quality and cognitive function measurements such as numbers (N) of participants (smokers/current smokers versus non-smokers/control group), mean (mean) value of smokers or current smokers, the mean value of non-smokers or control group, standard deviation (SD) of smokers or current smokers, the standard deviation of non-smokers or control group.
• Studies that provide clear statistical numbers about the differences in sleep quality and cognitive function between smokers and non-smokers groups.

• Studies involving current or nonsmokers but not past smokers/former smokers were not considered in data collection and analysis.
• Studies published in peer-reviewed journals.
• Studies published between 2000 and 2024.
• This study includes meta-analysis, cohort, cross-sectional, and randomized controlled trials.
• Only studies that have been published in English have been screened and included in this meta-analysis study.

Exclusion Criteria:

• Studies done on animals or insects
• Studies that include participants with a pre-existing sleep disorder (primary insomnia) or cognitive impairment before even smoking have been excluded.
• Studies that include the use of any substances like alcohol, narcotics, and medicaments that may cause drug interference and impact sleep quality and cognitive performance have been screened but not included in this meta-analysis.
• During the process of data collection, it appeared that many studies cover sleep quality as a part of their studies in combination with alcohol or certain types of drugs either for treatment or drug abuse. Such studies have been excluded during the data-entering process because sleep patterns can easily be affected by exogenous stimulants or any comorbidities or chronic diseases in smokers or non-smokers like diabetics, neurogenerative disorders, or hypertension.
• Some studies that provide the conclusion without reference to concrete numbers or include just the final result of the p-value have also been excluded from the study.
• Research that has not been published in journals with peer review has been excluded.
• Studies that test the effect of placebo compared to nicotine effects in smokers have been excluded from this instigation.
• Studies that test the effects of electronic cigarettes on smokers compared to non-smokers have been excluded from this instigation.

3.4 Study selection and quality assessment

Study selection: to guarantee the significance and credibility of the studies included in the meta-analysis, all papers were chosen based on predetermined inclusion and exclusion criteria with regard to the previously mentioned parameters.

Quality assessment: the quality of each study has been assessed separately without any assessment tools. Since this meta-analysis includes many randomized controlled studies, observational studies, cohort studies, and case studies, it was scientifically reasonable to evaluate the quality of each study based on the inclusion criteria of this thesis (396).

The Data Extraction Method: The data extraction procedure has involved systematically looking for research on the effects of smoking on sleep and cognitive processes in electronic sources including PubMed, Embase, Google Scholar, MEDLINE, and Springer Link. The terms used in this meta-analysis study were: smoking, tobacco, addiction, smokers, non-smokers, sleep, sleep disorders, insomnia, sleep problems, cognition, cognitive system, cognitive functions, cognitive processes, cognitive disorders, cognitive impairments, attention, learning, language, and concentration. The search yielded a total of 164.000 articles when the effects of smoking on sleep quality and cognitive functions terms were called in the search bar of Google Scholar. The researchers were assessed based on the inclusion and exclusion criteria mentioned in the 3.3 methods (397).

● **Study characteristics:** include the authors, publication year, study design, sample size, and population characteristics such as age, gender, smoking status, ethnicity, and study location.
● **Smoking measures:** smoking status (current smoker, non-smoker), smoking duration, frequency, and intensity, as well as any other smoking-related variables that were measured in the studies, have been considered but not analyzed.
● **Sleep quality measures:** cover subjective measures of sleep quality such as self-reported sleep quality, sleep duration, and insomnia symptoms) and objective measures (polysomnography and actigraphy, the Apnea/Hypopnea Index, the Epworth Sleepiness Scale (ESS), and the Pittsburgh Sleep Quality Index (PSQI).
● **Cognitive function measures:** include objective measures of cognitive function (neuropsychological tests, cognitive performance tasks) and subjective measures (self-reported cognitive function), as seen in the included tables below.
● **Effect sizes:** include the measures of association between smoking and sleep quality and cognitive function, such as mean differences, standard deviations (SD), odds ratios, risk ratios, and correlation coefficients.

Statistical methods: as mentioned earlier, the methods used to analyze the data of a meta-analysis of continuous data (mean difference (MD), standardized mean difference (SMD), weighted mean difference (WMD), fixed-effect model and random-effect model, publication bias analysis, heterogeneity assessment, and subgroup analysis), as well as the significance levels and confidence intervals associated with the effect sizes.

3.5 Data synthesis and statistical analysis

Data synthesis: To determine the overall impact of smoking on sleep quality and cognitive abilities, the obtained data was either statistically analyzed based on the random-effects model or random effects model. These models take into consideration the fact that the real effect size differs between studies by including both within-study and between-study variable components in the meta-analysis. Moreover, the fixed effect size model is used to measure studies with similar items of investigation, while the random effect model is used to measure various items in many studies. These options are selected in SPSS, as seen in this meta-analysis, while others in JASP merge these models in a default option.

Subgroup analyses: This method has been applied to determine the impact of smoking on sleep quality and cognitive function changes between different groups. It investigated the effect sizes across subgroups of studies, like the attention variable among the cognitive functions in current smokers vs. non-smokers, as will be seen in this analysis.

Effect size calculation: each research included in this meta-analysis has its effect sizes estimated in order to determine the strength of the relationship between smoking and cognitive function and sleep quality. I used standardized mean differences (Cohen's d) or Hedge’s g for continuous outcomes of cognitive function and sleep quality (398). It is worthwhile noting that Hedges' g is often preferred in meta-analyses due to its ability to correct for small sample bias and provide more accurate effect size estimates in the presence of heterogeneity rather than Cohen’s d or other effect measures.
Data Analysis: SPSS and JASP for statistics have been used in this study to examine the data that was gathered. To determine the total impact size of the intervention, it was specifically performing a meta-analysis with random effects and fixed-effect models up to the type of data I have. The assumptions and limitations of the data analysis were thoroughly addressed and

stated in the findings section. The implications for future clinical work and research have also been discussed (399).

3.6 Heterogeneity assessment

Heterogeneity assessment: Cochran's Q and I^2 statistic have been measured to assess heterogeneity among studies (400).

3.7 Potential limitations and ethical considerations

The degree to which the conclusions of the meta-analysis are impacted by selective reporting or publication of studies has been evaluated through the use of a funnel plot, Egger's regression, and the trim-and-fill approach. To ascertain if publication bias is present in this meta-analysis of the relationship between smoking and the quality of sleep and cognitive function of smokers, the Egger's regression test is employed. In this section of the analysis, publication bias in studies on how smoking affects sleep quality is evaluated. The intercept, standard error, t-value, p-value, and 95% confidence interval are among the statistical components of this instrument. The level of asymmetry in the meta-analysis'sfunnelplot is indicated by the intercept in Egger's regression.

A meta-analysis employs the trim-and-fill approach to reduce the extremely small studies in the funnel plot and fill it with imputed missing studies to achieve symmetry in the funnel plot, therefore assessing and correcting any potential publication bias (401).

Meta-Analysis: Continuous Data for Sleep Assessment Tests

IV. Results

The impact of smoking on overall health is one of the leading causes of death worldwide. The effects of smoking on physical and mental health have been a significant concern in various medical fields, including psychiatry, neurology, pulmonology, cardiology, and oncology, to name but a few. Each of these fields assesses the effects of smoking on specific health factors using different approaches and assessment tests. In this study some tests have high scores obtained by smokers indicate to high severity, while in other tests, high scores indicate high performance. I managed to include the tests having identical measures together.

Researchers often modify assessment tests to suit the type of problem addressed in their studies, which has increased the challenge of investigation. It is worth to mention that the exclusion of such modified assessment tests has been considered in this analysis for clarity and validity. However, data collection regarding smoking's effects on sleep quality and cognitive functions in smokers has been insufficient for the needs of this analysis due to the absence of such studies. Consequently, this meta-analysis categorizes the studies into two relevant groups based on their assessment measurements: studies with high scores indicate high severity and low scores indicate low severity, and studies with results where high scores indicate higher performance and low scores indicate lower performance.

1. Summary of Findings:

This meta-analysis examines the impact of smoking on sleep quality and cognitive functions in smokers by dividing the analysis into four sub-analyses. The first analysis includes studies from various medical fields that aim to measure the effects of smoking on sleep functions. This analysis includes 8667 smokers and 22436 non-smokers. All the sleep studies use the same standardized tests: the Epworth Sleepiness Scale (ESS), the apnea-hypopnea index (AHI), and the Pittsburgh Sleep Quality Index (PSQI), without any modifications.

To investigate the effects of smoking on sleep quality, the following collected data for meta-analysis was performed using SPSS version 29. The analysis was applied to continuous outcome data from various studies. The nature of the studies selected in this group of papers related to ESS, AHI, and PSQI require using Cohen's d for effect size measurement. Cohen's d measures the magnitude of the effect size by expressing the difference between the means of two groups, such as smokers and non-smokers, in terms of standard deviations. According to the statistical literature, the use of Cohen's d fits large sample sizes where bias is limited. In my studies what explains this choice is the larger sample sizes of some studies, like Cohrs, S. et al. in the PSQI test (1071 smokers vs. 1243 non-smokers) and Wang, W. et al. (1370 smokers, 3973 vs. non-smokers), or in the EES test by the Bielicki study (796 smokers vs. 2817 non-smokers), or Zhang in the AHI test by (779 smokers vs. 2916 non-smokers). This analysis applies a random-effects model to consider variances both within and between studies. This meta-analysis regarding the continuous data for sleep assessment tests" includes 16 studies. The data entries were 100% complete without any missing data.

2. Effect Size Estimates:

Effect Size Estimates							
					95% Confidence Interval		95% Prediction Interval[a]
	Effect Size	Std. Error	Z	Sig. (2-tailed)	Lower	Upper	Lower
Overall	.190	.0195	9.779	<.001	.152	.228	.063

Effect Size Estimates	
	95% Prediction Interval
	Upper
Overall	.318

a. Based on t-distribution.

The overall effect size of these studies reveals a small to moderate effect of smoking on the sleep functions of smokers with an estimation of 0.190 (Cohen's d) ($Z = 9.779$, $p < 0.001$) and a standard error of 0.0195. The effect size is highly significant ($p < .001$), suggesting a strong association between smoking and changes in the sleep quality of smokers.

Based on the estimation of the t-distribution, the prediction interval of this analysis is 95%. It indicates that the effect size is estimated to range from 0 to 0.318 with 95% probability in future studies.

The analysis covers 7 Epworth Sleepiness Scale (ESS) assessment tests, 7 Apnea-Hypopnea Index (AHI), 7, 6 Pittsburgh Sleep Quality Index (PSQI), and 2 (Chronic Insomnia and Arousal Index) assessment tests. Some authors run all assessment tests in the same study, as seen in the table of studies below.

Concerning the Epworth Sleepiness Scale (ESS), 7 studies investigated the ESS assessment tests to measure daytime sleepiness among smokers compared to non-smokers. The ESS test has been performed in this analysis by Bielicki, Conway, Esen, Hsu, Shao, Varol, and Yosunkaya. The effect sizes for ESS studies ranged from 0.083 to 0.336. Many studies showed significant differences between smokers and non-smokers, as demonstrated in the forest plot below.

To evaluate the severity of sleep apnea in smokers, Apnea-Hypopnea Index (AHI) tests have been performed by the same previous authors except Yosunkaya. This test was covered by Bielicki, Conway, Esen, Hsu, Quan, Shao, and Varol. The effect sizes ranged from 0.036 to 0.336, emphasizing the significant impact of smoking on sleep apnea.

The Pittsburgh Sleep Quality Index (PSQI) test was investigated by six studies to assess overall sleep quality. The authors who investigated the PSQI test have been Chehri, A. et al., Arbinaga, F. et al., Salah, A. B. et al., Cohrs, S. et al., Wang, W. et al., and Asghari, Alimohamad, et al. The PSQI assessment studies showed effect sizes from 0.170 to 0.394, indicating a significant degeneration in sleep functions among smokers compared to non-smokers, as the forest plot demonstrated.

Concerning other sleep assessment measures, only two relevant studies focused on different aspects of sleep quality utilizing chronic insomnia, like Wetter, David W., and Terry B. Young authors, while Conway, Silvia Goncalves, et al. analyzed the arousal index tests. These researchers provided additional proof of the smoking effects on sleep quality.

The analysis of sleep assessment produces data with effect sizes ranging between 0.036 as the minimum effect size value and 0.394 as the maximum effect size value, and several studies show statistically significant results, indicating poor sleep outcomes for smokers compared to non-smokers, while others do not show any significant effects.

Concerning the Epworth Sleepiness Scale (ESS) test, this study found a statistically significant difference in sleep quality between smokers and non-smokers, indicating worse sleep outcomes for smokers as reported by the following authors: Bielicki with (effect size = 0.127, $p = 0.002$), Hsu with (effect size = 0.223, $p = 0.015$), Shao with (effect size = 0.164, $p = 0.030$), Varol with (effect size = 0.182, $p = 0.001$), and Yosunkaya with (effect size = 0.336, $p = 0.002$). These studies have found a significant difference with relatively large effect sizes.

There were no significant differences between Conway (effect size = 0.093, $p = 0.188$) and Esen (effect size = 0.083, $p = 0.421$) in terms of the Epworth Sleepiness Scale (ESS) assessment test. In addition to ESS assessment test findings, the analysis also produces data about the Apnea Hypopnea Index (AHI), which measures sleep apnea severity among smokers and non-smokers. Similarly to ESS assessment test results, the same authors found a significant difference in sleep apnea severity between smokers and non-smokers, like Bielicki who published (effect size = 0.099, $p = 0.014$), Hsu (effect size = 0.336, $p < 0.001$), Quan reported

(effect size = 0.159, p = 0.030), and Varol who found (effect size = 0.259, p < 0.001). These authors reported a highly significant difference.

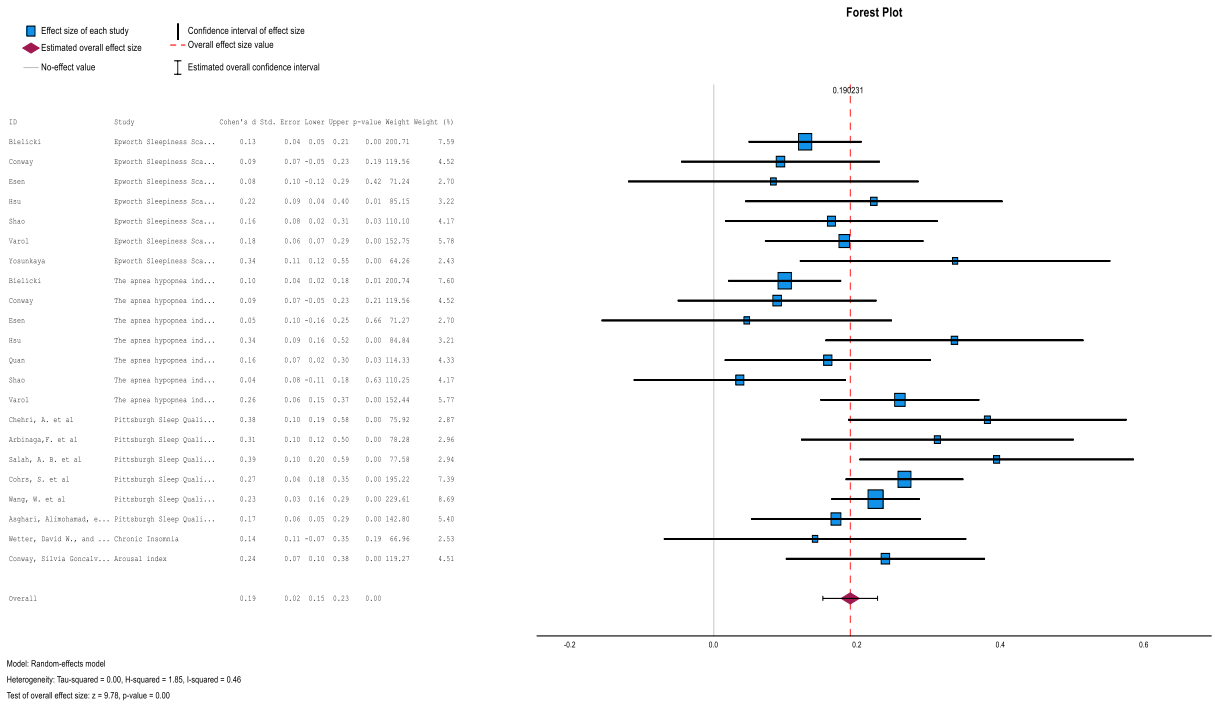
Unlike the ESS results, Shao in the AHI test has found no significant differences in smokers (effect size = 0.036, p = 0.631), but Conway and Esen, similarly to their previous tests, reported no association between sleep apnea and smoking (effect size = 0.088, p = 0.212) and (effect size = 0.046, p = 0.657) respectfully.

Investigating the effects of smoking using the Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality in smokers, surprisingly, shows that most studies, unlike the other tests, have found a strong association between smoking and sleep quality in smokers. Chehri, A. et al. found a significant difference in sleep quality (effect size = 0.381, p < 0.001). Arbinaga, F. et al. have also reported a significant effect (effect size = 0.312, p = 0.001), and Salah, A. B. et al. have found the highest significant effect among all the other studies with (effect size of 0.394, p = 0.001). The same has been found in the Cohrs, S. et al. study (effect size = 0.266, p < 0.001), Wang, W. et al. (effect size of 0.225, p < 0.001), and Asghari, Alimohamad, et al. (effect size of 0.170, p = 0.005), who reported significant differences.

To provide a more comprehensive view, other assessment measures have been investigated in this analysis, like the Chronic Insomnia assessment test by Wetter, David W., and Terry B. Young, who reported (effect size = 0.141, p = 0.189). This author did not find a significant difference in smokers, while the test of the arousal index by Conway, Silvia Goncalves, et al. found a significant difference (effect size = 0.239, p < 0.001).

Generally speaking, these studies range from 0.036 to 0.394, with statistically significant results in most of them, indicating poor sleep outcomes for smokers compared to non-smokers. The weights assigned to each study, ranging from 2.4% to 8.7%, reflect their relative influence on the overall meta-analysis, as will come to light in the forest plot interpretation details. Remarkably, the study by Wang, W. et al. using PSQI had the highest weight (8.7%), indicating a substantial contribution to the overall analysis. The analysis suggests a significant correlation between smoking and low sleep quality in smokers as obviously seen in the below Forrest plot.

Forrest Plot



ID	Study	Cohen's d	Std. Error	Lower	Upper	p-value	Weight	Weight (%)
Bielicki	Epworth Sleepiness Sca...	0.13	0.04	0.05	0.21	0.00	200.71	7.59
Conway	Epworth Sleepiness Sca...	0.09	0.07	-0.05	0.23	0.19	119.56	4.52
Esen	Epworth Sleepiness Sca...	0.08	0.10	-0.12	0.29	0.42	71.24	2.70
Hsu	Epworth Sleepiness Sca...	0.22	0.09	0.04	0.40	0.01	85.15	3.22
Shao	Epworth Sleepiness Sca...	0.16	0.08	0.02	0.31	0.03	110.10	4.17
Varol	Epworth Sleepiness Sca...	0.18	0.06	0.07	0.29	0.00	152.75	5.78
Yosunkaya	Epworth Sleepiness Sca...	0.34	0.11	0.12	0.55	0.00	64.26	2.43
Bielicki	The apnea hypopnea ind...	0.10	0.04	0.02	0.18	0.01	200.74	7.60
Conway	The apnea hypopnea ind...	0.09	0.07	-0.05	0.23	0.21	119.56	4.52
Esen	The apnea hypopnea ind...	0.05	0.10	-0.16	0.25	0.66	71.27	2.70
Hsu	The apnea hypopnea ind...	0.34	0.09	0.16	0.52	0.00	84.84	3.21
Quan	The apnea hypopnea ind...	0.16	0.07	0.02	0.30	0.03	114.33	4.33
Shao	The apnea hypopnea ind...	0.04	0.08	-0.11	0.18	0.63	110.25	4.17
Varol	The apnea hypopnea ind...	0.26	0.06	0.15	0.37	0.00	152.44	5.77
Chehri, A. et al	Pittsburgh Sleep Quali...	0.38	0.10	0.19	0.58	0.00	75.92	2.87
Arbinaga,F. et al	Pittsburgh Sleep Quali...	0.31	0.10	0.12	0.50	0.00	78.28	2.96
Salah, A. B. et al	Pittsburgh Sleep Quali...	0.39	0.10	0.20	0.59	0.00	77.58	2.94
Cohrs, S. et al	Pittsburgh Sleep Quali...	0.27	0.04	0.18	0.35	0.00	195.22	7.39
Wang, W. et al	Pittsburgh Sleep Quali...	0.23	0.03	0.16	0.29	0.00	229.61	8.69
Asghari, Alimohamad, e...	Pittsburgh Sleep Quali...	0.17	0.06	0.05	0.29	0.00	142.80	5.40
Wetter, David W., and ...	Chronic Insomnia	0.14	0.11	-0.07	0.35	0.19	66.96	2.53
Conway, Silvia Goncalv...	Arousal index	0.24	0.07	0.10	0.38	0.00	119.27	4.51
Overall		0.19	0.02	0.15	0.23	0.00		

Regarded as the primary visual representation of the analysis of the tract in the forest. The impact sizes of each study included in this analysis of how smoking impacts sleep quality based on the ESS AHI and PSQI assessment tests are displayed in the forest plot above. Each paper is represented by a blue square, the size of which indicates the study's significance. The red diamond at the bottom of the figure, with a value of 02, represents the 95 confidence interval ci estimate of the overall effect size across all studies. The horizontal line that extends beyond each square displays the effect size estimate from the study's 95-confidence interval CI.

Interpretation of Forrest Plot:

The present forest plot provides a visual representation of the effect sizes of 22 studies covering 7 EES, 7 AHI and 6 PSQI, 1 chronic insomnia and 1 Arousal Index sleep assessment battery test. According to the forest plot, none of the 22 studies report positive effect sizes to show the beneficial impact of smoking on sleep functions, instead all of them report negative effect sizes about assuring the impact of smoking on the health of smokers. The weight of some studies is higher than others. Due to this influence, the overall effect size estimate is influenced by these studies for instance the weight of the PSQI test by Wang, W. et al (8.69), ESS (7.59) and AHI (7.60) by Bielicki.

3. Homogeneity and Heterogeneity:

Test of Homogeneity			
	Chi-square (Q statistic)	df	Sig.
Overall	39.979	21	.007

Heterogeneity Measures

Overall	Tau-squared	.003
	H-squared	1.851
	I-squared (%)	46.0

Heterogeneity interpretation:

The test of heterogeneity reveals that the Chi-square (Q statistic) value is 39.979, with degrees of freedom (df) being 21, which corresponds to the number of studies minus one as demonstrated in the above statistical formula.

The p-value is 0.007, which is less than the typical alpha level of 0.05. Results show that the significant p-value (0.007) indicates that there is more variability in the effect sizes than would be expected by chance alone. These values suggest the presence of heterogeneity among the included studies for a reasonable choice will be discussed in the discussion part.

The tau-squared value is 0.003. Tau-squared is an estimate of the between-study variance in a random-effects model. A value of 0.003 indicates the amount of true variance between the effect sizes of the analyzed studies.

The H-squared value comes with 1.851. H-squared indicates how much the observed variance is larger than the expected variance. The H-squared value of 1.851 means the observed variance is 1.851 times larger than the variance expected if all studies were estimating the same effect.

According to the statistical literature, I-squared values in meta-analysis study with values from 0-25% indicate low heterogeneity, while 25-50% indicate moderate heterogeneity, 50-75% indicate substantial heterogeneity, and 75-100% indicate considerable heterogeneity. In this analysis, the I-squared value is 46.0%. I-squared measures the proportion of overall variation between studies that may be caused by heterogeneity as opposed to coincidence. Therefore, an I-squared value of 46% indicates moderate heterogeneity. This means that approximately 46% of the variability in effect sizes is because of differences among the studies rather than random sampling error.

The significant Q statistic indicates that the variability seen in the effect sizes of this analysis is probably not due to random chance which is confirmed by the I-squared value of 46%, showing that nearly half of the total variation in effect sizes is related to true differences between the studies. The tau-squared value estimates the magnitude of this variance between studies, while the H-squared value gives an additional measure of the degree of heterogeneity.

4. Publication Bias:

Egger's Regression-Based Test[a]						
					95% Confidence Interval	
Parameter	Coefficient	Std. Error	t	Sig. (2-tailed)	Lower	Upper
(Intercept)	.142	.0592	2.400	.026	.019	.266
SE[b]	.725	.8362	.866	.397	-1.020	2.469
a. Random-effects meta-regression						
b. Standard error of effect size						

The Egger's regression test is performed to see if there is any bias in this meta-analysis examining the influence of smoking on smokers' sleep quality and cognitive ability. Egger's regression-based test table has statistical components such as the intercept, 95% confidence interval, t-value, standard error, and p-value.

Publication bias is identified when investigation is limited to publications with favourable outcomes and excludes papers with negative outcomes or no published results. The meta-analysis's funnel plot's degree of asymmetry is indicated by Egger's regression intercept. The present study intercept has a statistical value of 0.142, with a standard error 0.0592. The t-statistic value of 2.400 and the p-value of 0.026 indicate that the intercept is statistically significant at the 0.05 level. This suggests that there is some asymmetry in the funnel plot, which might be an indication of publication bias. In statistics, publication bias is often shown by values less than 0.05.

The confidence interval is from (0.019 to 0.266), demonstrating statistical significance. The coefficient for the standard error of effect size is 0.725, with an error of 0.8362. The t-value is generated from the t-test, which measures the magnitude of the difference between means, in this example, smokers and non-smokers. The t-statistic in this study is 0.866, and the p-value is 0.397, suggesting that the coefficient is not statistically significant at the 0.05 level. The normal statistical significance is given by a confidence interval that does not include 0.

The results of this study show that the 95% confidence interval, which spans from -1.020 to 2.469, indicates that the genuine effect size is 95% likely to exist between these values, including zero. This suggests that there is no significant association between the effect size and the standard error.

In summary, the results of the meta-analysis remain unaffected by the standard error of the impact size, even in the presence of asymmetry in the funnel plot that suggests potential publication bias due to systematic differences between the size of studies.

Trim-and-Fill Analysis

Effect Size Estimates for Trim-and-Fill Analysis

	Number	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval
						Lower
Observed	22	.190	.0195	9.779	<.001	.152
Observed + Imputed[a]	23	.184	.0200	9.208	<.001	.145

Effect Size Estimates for Trim-and-Fill Analysis

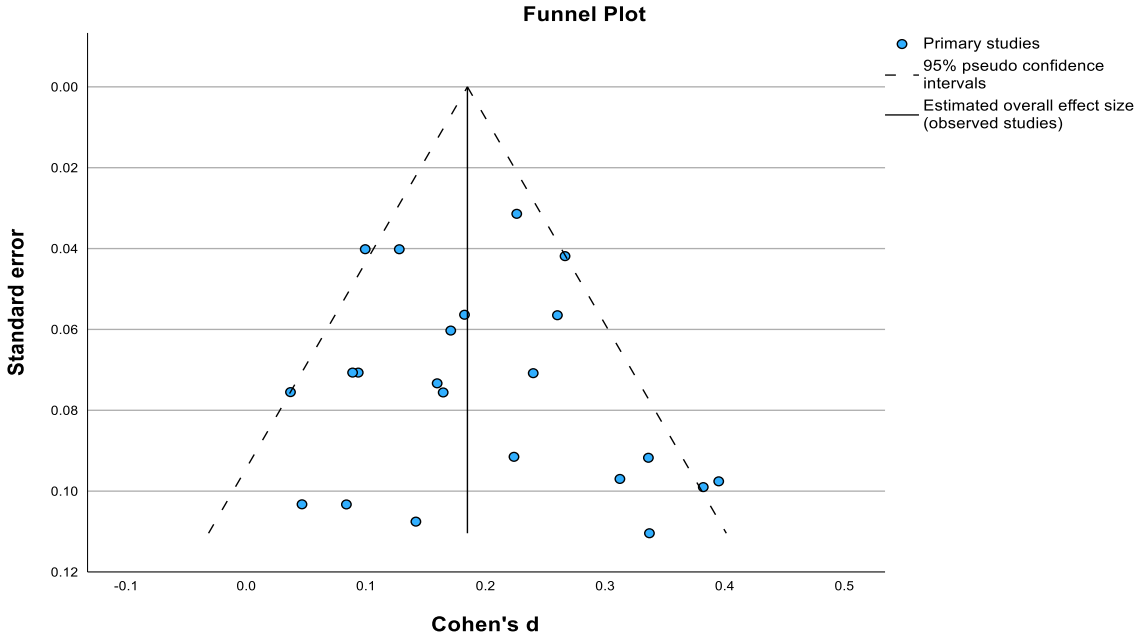
	95% Confidence Interval
	Upper
Observed	.228
Observed + Imputed[a]	.223

a. Number of imputed studies: 1

Statisticians assess and lessen publication bias in meta-analyses using techniques such as the trim-and-fill strategy. This approach "trimms" smaller, potentially biased studies to adjust for data asymmetry and "fills" the funnel plot with imputed, missing studies in order to attain symmetry. This modification provides for a more realistic assessment of the total effect size by taking into consideration the likelihood of unpublished research. In the current investigation of the effects of smoking on sleep quality, one imputed study was discovered using the trim-and-fill approach, bringing the total number of studies addressing the influence of smoking to 23.

As can be seen in the previous tables, the measured effect size was originally 0.190 with a 95% confidence interval (CI) extending from 0.152 to 0.228. Following the trim-and-fill correction, the effect size dropped to 0.184 with a 95% confidence interval extending from 0.145 to 0.223. Despite this little modification, the observed impact sizes continued to be comparable, within overlapping confidence ranges, and statistically significant ($p < 0.001$). This implies that the total effect size was not significantly impacted by publication bias, hence enhancing the validity of the results.

Funnel Plot



This funnel plot demonstrates the visual representation of the degree of asymmetry in the meta-analysis as previous analyzed in Egger's regression-based test section. The standard deviation of the mean difference between the smokers' and non-smokers' groups is represented by Cohen's d, a measure of effect magnitude. The Y-Axis (Standard Error) represents the precision of the sleep assessment studies. Smaller standard errors indicate more precise studies as appear at the top of this funnel plot. The solid vertical line represents the estimated overall effect size (observed studies), which appears to be slightly above 0.2. Every dot in this chart represents an individual study included in this meta-analysis. The dashed lines stand for the 95% pseudo confidence intervals.

Interpretation of funnel plot:

The funnel plot seen in this chart display clear symmetry around the line of Cohen’s d of 0 effect and suggests no publication bias. The studies are evenly distributed around the overall effect size (the vertical line). A few studies show larger positive effect sizes, which are scattered

towards the right. This implies that most studies indicate a detrimental effect of smoking on sleep quality, as positive effect sizes are associated with worse sleep outcomes in this category of studies.

V. Discussion:

1. Interpretation of Findings:

This first meta-analysis study tests the effects of smoking on sleep quality in smokers using continuous data from various selected studies using ESS, AHI, and PSQI sleep assessment tests. In this analysis I chose Cohen's d as the effect size measure within a random-effects model. This choice come due to the presence of different tests from different studies which requires random effect model but not fixed effect model. . Twenty-two studies include various sleep assessment measures. The overall effect size of this meta-analysis study was found 0.190, indicating a small but statistically significant positive effect on sleep quality among smokers. This suggests that smokers may experience poor sleep quality compared to non-smokers which confirms the results of previous studies in ESS, AHI, and PSQI as presented in the effect size estimate section.

These results highlight the significance of smoking cessation therapies for enhancing smokers' overall health and decreasing the negative impact on cognition and sleep quality. The heterogeneity throughout sleep tests emphasizes the necessity for an advanced understanding of the relationship between smoking and sleep quality.

2. Strengths and Limitations:

This part of the meta-analysis includes a large sample size of 8667 smokers and 22436 non-smokers which increases the statistical power of the analysis providing more precise estimates of effect sizes. The use of Cohen's d for effect size measurement selecting a random-effects model is considered a strong statistical approach. This statistical method concerns both within-study and between-study variance which gives this analysis a statistical advantage over any other research method. Unlike other research studies, the application of heterogeneity tests, such as the Q statistic and the calculation of I-squared, guarantees the examination of the differences among studies to determine the level of heterogeneity.

One of the strengths of this analysis is that widely recognized sleep assessment tools like the Epworth Sleepiness Scale, the Apnea-Hypopnea Index, and the Pittsburgh Sleep Quality Index have been investigated to allow this study consistency in measurement tools to enhance the comparability of results across different studies.

The quality of included studies is one of the main strengths of this analysis. For the sake of reliability of the overall results, the individual studies included in the meta-analysis were those with a high sample size. Studies with poor sample sizes or confounding variables that could have influenced the findings have been excluded during the process of analysis.

Despite the powerful statistical methods applied in this analysis, some limitations can still be dominating this meta-analysis study concerning potential biases. Most of the collected studies that have been included in this investigation were published in English but only with significant

results excluding non-significant results which may be regarded by some researchers as selection bias.

Variability between studies is another issue in this study. The heterogeneity assessment indicated by the I-squared statistic (46%) suggests that there are real differences among the studies. These differences may arise from variations in study populations, methodologies, also the type of medical specialty and other settings. According to some researchers, such variability can complicate the interpretation of the overall effect size and limit the generalizability of this finding.

This analysis has not covered any tobacco components except nicotine as the main agent of this investigation. Furthermore, the impact of smoking cessation on sleep quality has been beyond the scope of this analysis.

This analysis has some limitations represented in covering general assessment of sleep quality related to smoking without a specific focus on certain sleep items like sleep waves (delta, theta, alpha, beta and gamma) or N1, N2, N3, REM, NREM of sleep stages which may provide other key answers to explain the enigma of poor sleep quality in smokers.

3. Future Research Directions:

As mentioned earlier in the literature, tobacco includes thousands of pharmacological components estimated between 5000 and 9600 components based on 7000 references as documented in the book of Rodgman and Perfetti. Via the course of this investigation significant data has been collected that show the effects of other agents rather than nicotine on the nervous system of smokers. Further studies should be conducted to track the effects of harmful agents like Acetaldehyde which has strong neurotoxic effects on the nerves and neurotransmitter functions. Carbon Monoxide impacts the nervous system by reducing the oxygen-carrying capacity of the blood and any chronic exposure to CO leads to hypoxia and cognitive function impairment. Lead and cadmium cause oxidative stress and lead to neurological dysfunction and increase the risk of neurodegenerative diseases.

Future studies should address these issues and run meta-analysis subgroup analyses that allow researchers to determine the effect of each agent individually on sleep patterns. Moreover, longitudinal studies are preferred in such types of studies to establish causality and explore the bidirectional relationship between smoking and sleep quality.

Meta-Analysis: Continuous Data for Cognitive Functions and Sleep Quality Assessment Tests

IV. Results

1. Summary of Findings:

This analysis investigates the effects of smoking on sleep quality and cognitive functions in smokers. Unlike the previous two meta-analyses, which measure the impact of smoking on sleep quality with scores indicating high severity, the following analysis has different

measurements and scoring systems. According to this analysis, all the scores obtained from these studies with high scores indicate high performance, while a low score indicates low performance. In this analysis, the number of smokers is 6219, while the number of non-smokers is 19680.

2. Effect Size Estimates:

Fixed and Random Effects

Q	df	p
Omnibus test of Model Coefficients	87.291	1
Test of Residual Heterogeneity	1685.026	33
Note: p-values are approximate. The model was estimated using Hedges method		

This analysis covers 14 studies and includes 35 cognitive and sleep-related tests. Analyzing this data using the statistical software JASP produces the following data:

The Hedges g method was used to estimate the model. Hedges' method is normally used in meta-analyses for data with small sample sizes and corrects for biases in effect size estimation. Unlike the SPPS, which has the function of either fixed or random effect size models, JASP statistical software merges fixed and model effect size models in its statistics. The fixed and random effects analysis come out with a significant impact of smoking on cognitive functions and sleep quality in smokers. The analysis is based on the Omnibus Test of Model Coefficients. It determines whether there is a significance of the overall effect in the model of the study by testing the null hypothesis, assuming all regression coefficients in the model are equal to 0. In this study, the Q statistic for the model coefficients' omnibus test was 87.291 with one degree of freedom and a p-value less than 001. The result ($Q = 87.291$, $p < .001$) indicates that the overall effect of smoking on cognitive function and sleep quality is statistically significant.

Based on the overall model, this result emphasizes that smoking has a significant impact on sleep quality and cognitive functions in smokers. Additionally, the residual heterogeneity test in this analysis produced a Q statistic of 1685.026 with 33 degrees of freedom and a p-value below 001. Furthermore, this analysis's residual heterogeneity test produced a Q statistic of 1685.026 with 33 degrees of freedom and a p-value less than 001. This highlights significant heterogeneity among the group of studies included in the meta-analysis. The Q value of 1685.026 in the test of residual heterogeneity calculates the difference in variability of the effect sizes. The degrees of freedom (33) reflect significant heterogeneity among the effect sizes across the studies due to other factors that may influence the outcome. Since the significant results of heterogeneity require further studies to explore the source of differences between these studies, I have conducted subgroup analyses to understand the conditions under which smoking influences cognitive function and sleep quality in some tests.

Coefficients

	Estimate	Standard Error	z	p	95% Confidence Interval
Intercept	-1.491	0.160	-9.343	< .001	[-1.804, -1.178]
Note: Wald test.					

The intercept of this analysis has an estimate of -1.491 which indicates the average effect size across the studies included in the meta-analysis. This negative estimate means that smokers perform worse than non-smokers on the cognitive and sleep tests analyzed. The standard error of 0.160 shows the variability of the estimate. The z-value of -9.343 indicates that the effect size is significantly different from zero. The p-value shows less than .001, which means in statistics that the result is statistically significant. It suggests strong evidence against the null hypothesis which confirms that the observed effect size is not due to random chance but to a real effect of smoking on sleep quality and cognitive functions in smokers. The confidence interval ranges from -1.804 to -1.178 indicating that the interval is below zero supporting the conclusion that smokers have significantly worse performance than non-smokers in the tests.

3. Homogeneity and Heterogeneity:

	Estimate	95% Confidence Interval
τ^2	0.839	[0.538, 1.476]
τ	0.916	[0.733, 1.215]
I^2 (%)	98.704	[97.993, 99.259]
H^2	77.149	[49.828, 134.981]

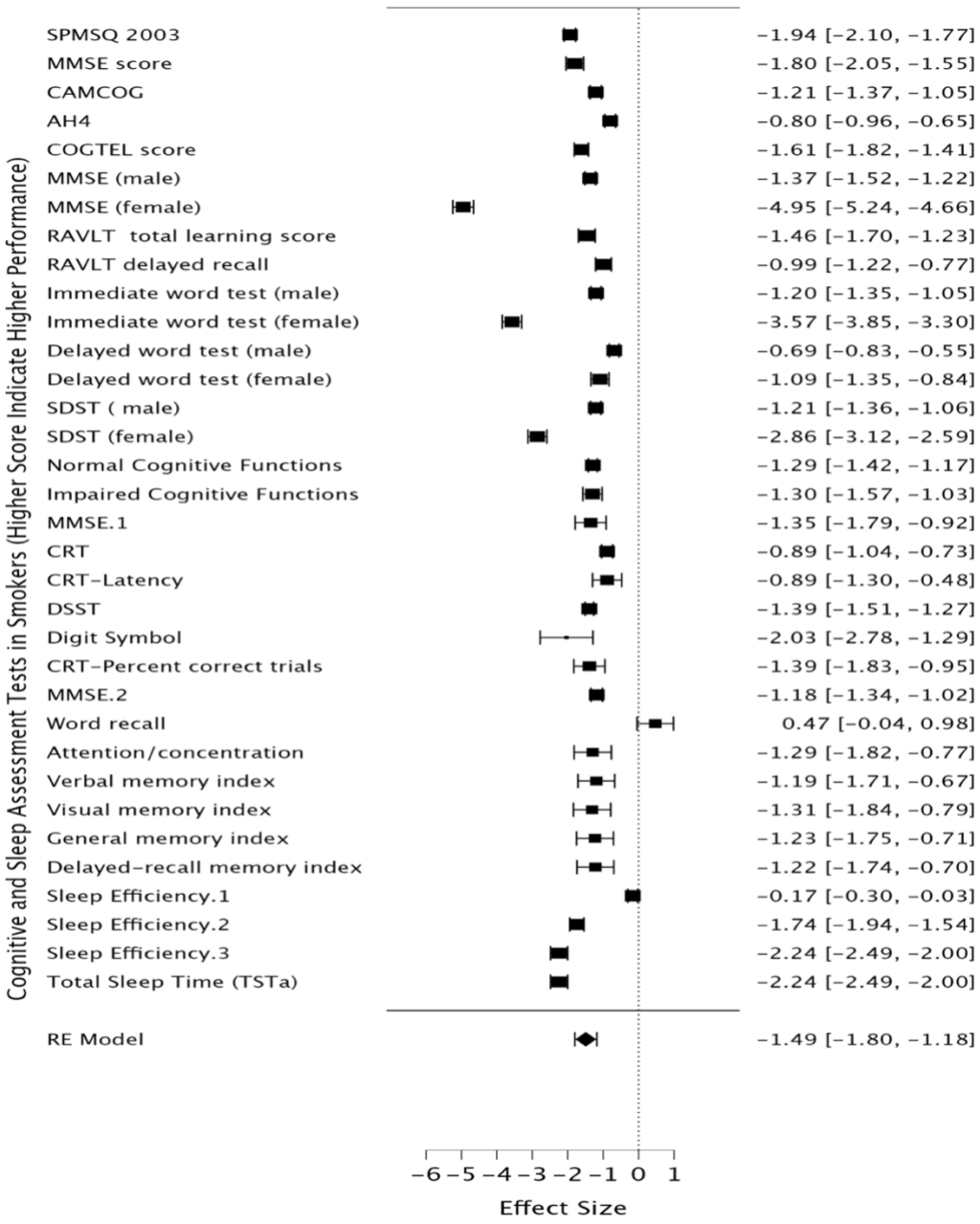
Residual Heterogeneity Estimates

The heterogeneity estimate analysis shows that τ^2 (Tau-squared) is 0.839, with a confidence interval from 0.538 to 1.476. Meta-analysis τ^2 reflects the degree of variability in the true effect sizes between different studies. Furthermore, the value of the non-zero tau-square, such as in this analysis ($\tau^2$0.839), suggests that there is variability in the effect sizes, indicating a certain degree of heterogeneity.

The tau estimate of this analysis is 0.916, with a confidence interval from 0.733 to 1.215. According to the analysis's tau value, the effects of smoking on sleep quality and cognitive abilities vary between studies because of differences in research designs, population demographics, methods for measuring, and other aspects that were not covered in this analysis.

This analysis produced an I^2 value of 98.704%, having a confidence interval from 97.993% to 99.259%. The I^2 value above 75%, which is high according to statistical literature, suggests that most of the variability in effect sizes is due to real differences across studies rather than sampling error, which will be explained during the process of this analysis and covered in the discussion part.

The H^2 value in the above table shows 77.149 with a confidence interval from 49.828 to 134.981, indicating that the observed variability in effect sizes is due to heterogeneity, while an H^2 value of 1 indicates no heterogeneity.



Forest plot Interpretation

The forest plot of this analysis was synthesized by JASP software to present the results of the effect sizes and confidence intervals obtained from various cognitive and sleep assessment tests. Unexpectedly, most of these tests show significant negative effect sizes, demonstrating poor performance of smokers compared to non-smokers except for word recall test by Phillips and Fox (1998).

V. Discussion:

1. Interpretation of Findings:

Cognitive Function Tests:

In Mini-Mental State Examination (MMSE) tests scores obtained by Wu, Peiliang, et al. (2020) the effect size is -1.800, Hotta, Ryo, et al. (2015), (male) the effect size is -1.366, Hotta, Ryo, et al. (2015) the effect size is -4.952, Riaz, Tuba, et al. (2021) the effect size is -1.354, and by Elwood, Peter Creighton, et al. (1999) the effect size is -1.182. The negative effect sizes of this common test of MMSE across these studies indicate that smoking is associated with poorer performance for cognitive function. Surprisingly, the larger effect size for females in Hotta, Ryo et al. with the value of (-4.952) in MMSE suggests a very pronounced harmful effect of smoking on cognitive function in female smokers. This may open a horizon in front of research to investigate whether women have any genetic predisposition or sensitivity underlying mechanisms affected by tobacco!?

Memory Tests:

In this analysis, many memory tests aimed to measure the effect of smoking on smokers compared to non-smokers, like the RAVLT, which was conducted by Wu, Peiliang, et al. (2020), scoring -1.462 in the effect size, while the Wu, Peiliang, et al. (2020) study shows a value of -0.993 in the score of the effect size. Concerning the immediate word test conducted by Hotta, Ryo et al. (2015) show an effect size of -1.201 by males and -3.574 effect size by females. In the Delayed Word test by the same author, in males, the effect size has a value of -0.687, and in females, it has -1.091. On the delayed-recall memory index test, Liu, Jui-Ting, et al. (2013) show an effect size value of -1.219, while in a similar test by Phillips and Fox (1998), the effect size has a 0.471 value in the word recall test.

Generally speaking, most of these memory tests show negative effect sizes, proving that smoking negatively influences both immediate and delayed memory recall. Unexpectedly, females again show high effect size values in Hotta, Ryo et al. with a value of (-3.574) in effect size, inspiring further studies regarding gender differences in how smoking impacts memory.

General Cognitive Tests:

Concerning other general cognitive tests like SPMSQ 2003, COGTEL, normal cognitive functions, and impaired cognitive functions Wang, Cheng-Ching, et al. (2010) findings show the effect size of -1.938 value in SPMSQ 2003, and Mons, Ute, et al. (2013) study shows the effect size of -1.615 value in COGTEL, while Johar, Hamimatunnisa, et al. (2016) show the effect size of -1.292 in normal cognitive functions and the effect size of -1.301 in impaired cognitive functions tests. These tests reveal that smoking hurts cognitive performance, as shown in various cognitive assessment tests applied to smokers compared to non-smokers.

Psychomotor and Attention Tests:

Regarding the psychomotor and reaction tests that aim to measure CRT (Choice Reaction Time) Related Tests, the results show that Elwood, Peter Creighton, et al. (1999) on CRT have an effect size of -0.888, while Riaz, Tuba, et al. (2021) on the same test have an effect size of -0.888, and in the CRT-Latency has the Effect Size of -0.888 value and in CRT-Percent correct trials test he has an effect size value of -1.390. These tests show that smoking impairs the reaction time and accuracy of smokers compared to non-smokers, as we saw in the literature previously. The negative effect sizes obtained in this meta-analysis indicate that smokers have slower and less accurate responses in tasks that require quick decision-making, which confirms

the results and conclusions of some previous studies mentioned earlier about the errors in the operations of some doctors.

DSST (Digit Symbol Substitution Test) and Similar Tests:

This analysis included studies done on brain damage, dementia, and age of the brain like the Digit Symbol Substitution Test and SDST (Symbol Digit Substitution Test). In DSST tests, the study of Zhang, Qiaoyang, et al. (2022) and Hill, Robert D. (1989) show effect size = -1.391 and effect size = -2.034, respectively, while the study of Hotta, Ryo, et al. (2015) on males shows the effect size of -1.209; on females, the effect size was -2.857, indicating significant negative effects of smoking on tasks requiring rapid symbol substitution and psychomotor speed, especially on females, as seen in other tests.

Sleep Quality Tests:

The rest of the tests covered Sleep Quality Tests like Sleep Efficiency done by Conway, Silvia Goncalves, et al. (2008), whose study shows an effect size value of -0.165, while Hsu, Wen-Yu, et al. (2019) have an effect size of -1.743, and Wetter, David W., and Terry B. Young (1994) show the highest effect size of -2.244. These results show that smoking significantly reduces sleep efficiency, as seen in the first analysis restricted to sleep assessment tests. The negative effect sizes indicate that smokers experience poorer sleep quality compared to non-smokers, showing larger effect sizes that reflect the level of impairments in smokers, which can also be seen in Wetter, David W., and Terry B. Young (1994) on the Total Sleep Time test with the effect size of -2.244.

Various mental Tests:

The Cambridge Cognition Examination, which aims to measure the cognitive ability to detect earlier onset of dementia, Elwood, Peter Creighton, et al.'s (1999) study reveals an effect size of -1.208 CAMCOG. On the AH4 test, which contains 130 items, with 65 items each measuring mental arithmetic and reasoning, the Elwood, Peter Creighton, et al. (1999) study has found a value of -0.803 in effect size. The test of attention and concentration done by Liu, Jui-Ting, et al. (2013) shows the effect size = -1.294. Concerning Liu, Jui-Ting, et al. (2013), the verbal memory index has reflected the effect size values of -1.193 and -1.314 on the visual memory index and effect size = -1.230 General memory index by the same author.

However, it is worth mentioning that the word recall test by Phillips and Fox (1998) This has been the only test that shows a positive benefit of smoking, getting an effect size of 0.471. This study is considered an outlier demonstrating the positive effect size, but still not statistically significant as the confidence interval includes zero falling in the interval between [-0.04, 0.98].

2. Strengths and Limitations:

Strengths:

This analysis includes numerous studies consisting of 14 studies and 35 cognitive and sleep-related tests. The total number of participants is 25899 which make this study unique. The number of smokers is 6219, and non-smokers are 19680. These large sample sizes increase the statistical power and precision of the effect size estimates. Unlike the previous analysis about the effects of smoking on sleep quality, which applied Cohen's for the effect size measure, this analysis about the effects of smoking on sleep quality and cognitive functions uses Hedge's d as the effect size measure and random-effects model, and for heterogeneity measures the Q statistic, I^2, and τ^2 which provides a precise analysis.

Limitations:

However, one has to admit the possible challenge of potential bias in this study. Bias in the selection of publication might be a part of the scientific process because the selection of studies is based on only English-published research papers with significant data and a large power size, as occurred in this study. Many research papers showed some positive effects of smoking on both sleep quality and cognitive functions but were excluded due to the restrictions followed by the PRISM guidelines, which focus on studies over 30 participants and also exclude any papers with less significant data, which was characteristic of most of the positive effects obtained during the selection process. The original studies that were excluded have either shown big effect sizes or very small effect sizes, which could affect the general meta-analysis results. Variability between studies is another limitation that characterizes this analysis. The high heterogeneity obtained in this analysis is ($I^2 = 98.704\%$) indicates substantial differences among the studies which can complicate the data interpretation and generalizability of the findings. The focus on specific cognitive and sleep assessment tests may not give a full picture about the effects of smoking-related cognitive and sleep issues.

3. Future Research Directions:

Future studies in measuring the effects of smoking on sleep quality and cognitive functions should consider many points discovered during the process of this meta-analysis. The interpretation of tools for assessment tests in cognitive functions and sleep quality are difficult to interpret and require much attention. Considerable efforts should be dedicated to categories of tests that indicate similar results. High scores in some tests may indicate high performance, while high scores in similar tests used for the same purpose may indicate high performance, like in the case of the sleep efficiency test used in the current meta-analysis and PSQI and EES (high scores indicate high severity) tests used in the previous analysis. Concerning the statistical methods used in a meta-analysis like this, it is preferred to use Hedge's over Cohen's d since Hedges' g includes by default the correction for small samples and also bias adjustment and is less biased in small sample sizes.

Subgroup Analysis: Continuous Data in Attention Assessment Tests

1- Summary of Findings:

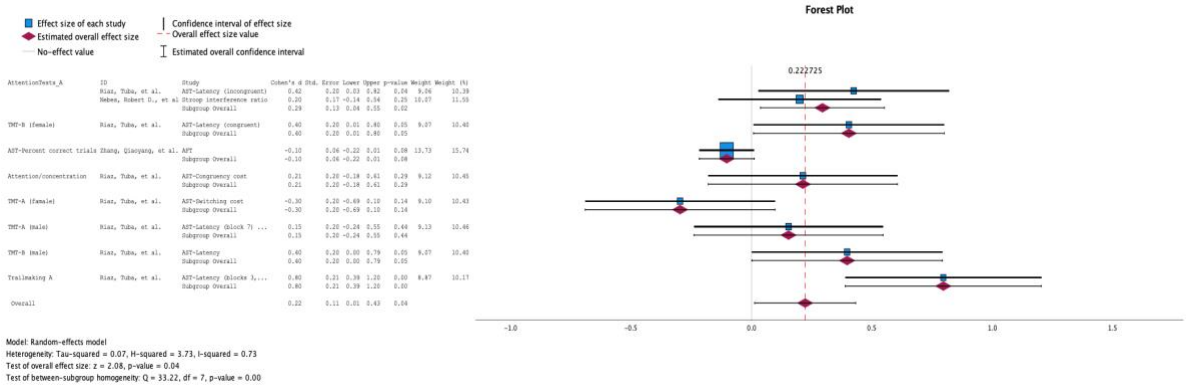
This chapter represents the subgroup analysis of attention tests using Cohen's d as the effect size measure and random-effects model with inverse-variance weighting to account for both within- and between-study variance. Out of 40 identified studies, only 9 (22.5%) were included in this subgroup analysis. The remaining 31 studies (77.5%) were excluded because they did not meet the purpose of this subgroup analysis. Furthermore, the attention assessment testing scoring system is different from the previous cognitive assessment scoring system, in which a high score indicates high performance, while in this attention subgroup analysis, high scores indicate high severity or slower attention.

2. Effect Size Estimates:

Effect Size Estimates for Subgroup Analysis							
	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval		95% Prediction Interval[a]
					Lower	Upper	Lower
	.295	.1313	2.243	.025	.037	.552	.
TMT-B (female)[b]	.404	.2021	2.001	.045	.008	.800	.
AST-Percent correct trials[b]	-.103	.0582	-1.772	.076	-.217	.011	.
Attention/concentration[b]	.213	.2006	1.063	.288	-.180	.606	.
TMT-A (famale)[b]	-.297	.2011	-1.476	.140	-.691	.097	.
TMT-A (male)[b]	.154	.2003	.767	.443	-.239	.546	.
TMT-B (male)[b]	.397	.2020	1.965	.049	.001	.793	.
Trailmaking A[b]	.797	.2079	3.832	.000	.389	1.204	.
Overall	.223	.1071	2.080	.038	.013	.433	-.450

Running data on SPSS version 29, the subgroup analysis of attention assessment tests produces an overall effect size of 0.223, indicating a small-to-moderate effect with a standard error of 0.1071 and statistical significance (p = 0.038). Various significant effect sizes were observed among the subgroup analysis of attention assessment tests, including Trailmaking A test with Cohen's d equal to 0.797, which considered a very large effect, while the TMT-B (female) test shows Cohen's d of 0.404 and TMT-B (male) shows Cohen's d of 0.397 (both with moderate effects).

Forrest Plot:



3. Homogeneity and Heterogeneity:

Test of Homogeneity			
	Chi-square (Q statistic)	df	Sig.
	.712	1	.399
TMT-B (female)[a]	.	.	.
AST-Percent correct trials[a]	.	.	.
Attention/concentration[a]	.	.	.
TMT-A (famale)[a]	.	.	.
TMT-A (male)[a]	.	.	.
TMT-B (male)[a]	.	.	.
Trailmaking A[a]	.	.	.
Overall	33.928	8	.000

The test of heterogeneity as seen above shows that the chi-squared (χ^2) value is 33.928, the chi-squared (χ^2) value is 33.928 and the degrees of freedom (df) is 8 and p-value is less than 0.001 ($p < .001$). The heterogeneity is obviously significant and it is very unlikely that the observed variability in effect sizes is due to chance alone.

4. Publication Bias:

In reference to the test for publication bias, Egger's regression-based analysis reveals no evidence of publication bias that is statistically significant (intercept = -0.288, p). Furthermore, no missing studies were imputed by the trim-and-fill analysis, indicating the validity of the observed impact size estimate, proving no possible bias as seen on the table below.

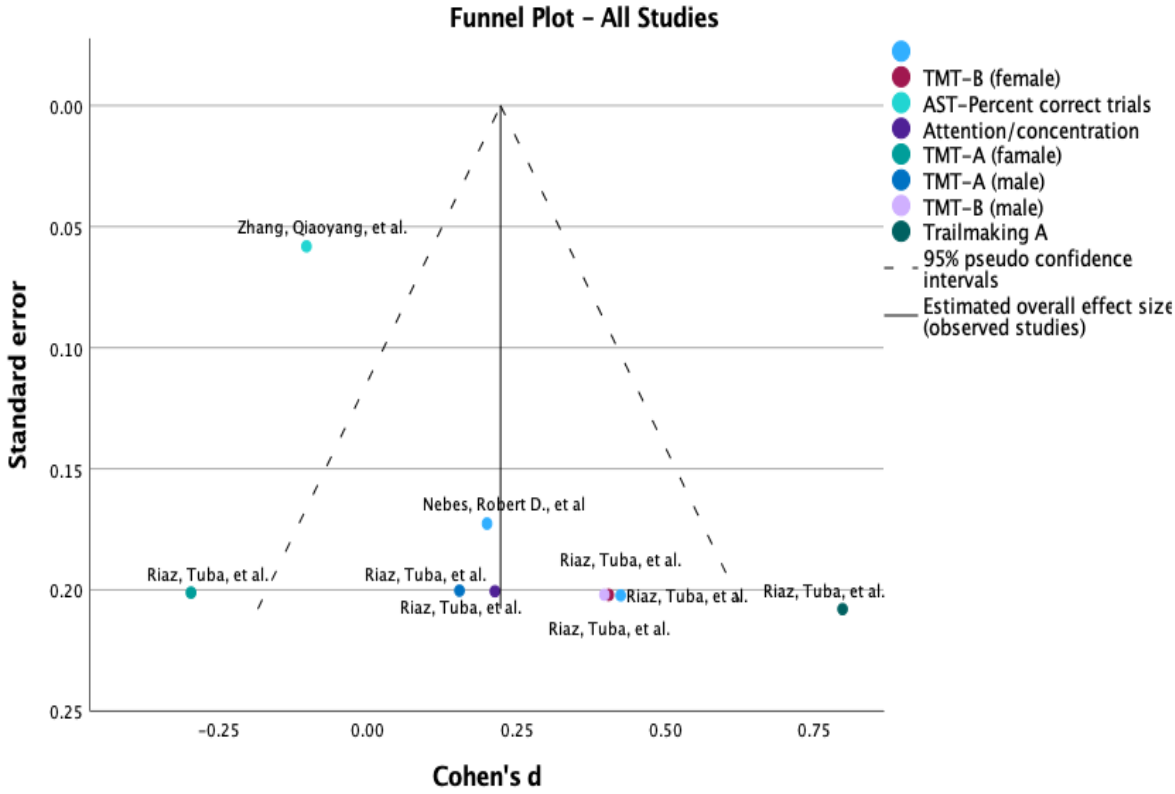
Egger's Regression-Based Test[a,b]							
						95% Confidence Interval	
	Parameter	Coefficient	Std. Error	t	Sig. (2-tailed)	Lower	Upper
	(Intercept)	-.288	.3208	-.899	.398	-1.047	.470

Over all	SE[c]	2.901	1.7636	1.645	.144	-1.269	7.072

a). Random effects meta-regression analysis

b). The regression-based test cannot be performed for the subgroups Attention Tests, TMT-B (female), AST-Percent correct trials, Attention/concentration, TMT-A (female), TMT-A (male), TMT-B (male), and Trailmaking A.

c). Standard error of the effect measurement



Funnel Plot:

In order to identify publication bias, meta-analyses employ scatter plots, which are displayed in this funnel plot graph. A standard error is plotted on the y-axis, and it gets less as sample size grows. Higher scores reflect slower response times or more cognitive impairment. The x-axis displays Cohen's d-effect magnitude. Each dot on this funnel diagram represents one study of this evaluation. This funnel plot in the meta-analysis differs from the previous one in that it has color coding for several test kinds, such as the attention and concentration tests, AST, and the TMT-A and B for males and females. The meta-analysis'stotaleffect size is shown by the vertical solid line above Cohen's d 0.25 value axis, while the dashed lines form a pyramid that shows the 95% pseudo-confidence intervals.

Notwithstanding a little amount of asymmetry, the plot appears to be largely symmetric around the overall effect size line. In the funnel's base Research with lower sample sizes and bigger

standard errors are more dispersed, whereas research with larger sample sizes and smaller standard errors are concentrated nearer the total effect size. Studies were conducted on both sides of the funnel plot. Although some studies show variation in effect sizes on both sides of the line, the majority of research are clustered close to the overall effect size line. However, the study by Zhang, Qiaoyang, et al. is viewed as an outlier on the left side with a very modest effect size. On the left side, nevertheless, the Zhang, Qiaoyang, et al. research is considered an outlier due to its extremely slight impact size. Effect sizes of around 0.25 and larger standard errors have been reported in many investigations on TMT-A and concentration tests by Riaz, Tuba, et al.

Interpretation of Funnel Plot:

The funnel plot above shows clear symmetry regarding publication bias assessment. The relative symmetry suggests the absence of significant publication bias. However, there is slight asymmetry, particularly outlier on the left top of the funnel plot by Zhang, Qiaoyang, et al., which indicates some variability that could be due to other factors rather than smoking effect, such as study quality or differences in methodologies. However, the Zhang, Qiaoyang, et al. study does not significantly affect the overall effect size.

In terms of effect size consistency, the clustering of studies around the overall effect size line proves that most studies found similar effect sizes, which supports the conclusion that smoking is associated with slower reaction times or greater cognitive impairment as discussed in the previous literature.

Generally speaking, the funnel plot in combination with trim-and-fill analysis, which did not show any imputation in studies, supports the lack of significant publication bias. All these facts support the overall effect size result of 0.22 that smoking has a small but statistically significant increase in reaction times or cognitive impairment among smokers. The statistical significance of the p-value of 0.038 shows that this effect is not due to random variation alone, furthermore, the relative symmetry of the funnel plot and the results of the trim-and-fill analysis indicate minimal publication bias, supporting the reliability of the findings.

To sum up briefly, this subgroup analysis shows that smoking is associated with a slight but significant negative impact on the cognitive functions of smokers compared to non-smokers, as proved by slower reaction times or greater cognitive impairment.

V. Discussion:

1. Interpretation of Findings:

This subgroup analysis focuses on attention assessment tests, employing Cohen's d as the effect size measure within a random-effects model based on 9 studies which is 22.5% of the dataset of all this study. The overall effect size across attention tests such as Trailmaking A test and TMT-B for male and female was 0.223, indicating a small-to-moderate effect. Heterogeneity was pronounced across studies, emphasizing variability in effect sizes.

2. Strengths and Limitations:

Since attention is one of the most essential cognitive abilities which is required in many sensitive tasks this subgroup analysis was conducted on 9 attention tests from different studies which meets the inclusion requirements to measure the effect of smoking on the time smokers take to react in different tasks.

The main challenge confronted this subgroup analysis was the limited studies including attention assessment test in smoking behaviors. This limitation includes heterogeneity across samples and future research should consider these limitations by conducting larger-scale studies but from different research papers with standardized protocols. Additionally, exploring attentional functions in diverse populations not limited to male and female smokers and utilizing longitudinal designs can provide deeper insights into the development and trajectory of attention-related disorders.

3. Future Research Directions:

These findings emphasize the importance of attention assessment tests in clinical and research settings, especially that nowadays our attention is easily distracted by many factors in our environment like mass media and digital devices.

The differences in effect sizes among studies of this analysis stress the necessity for structure assessment protocols. Moreover, increasing sample sizes to enhance reliability and generalizability since the tests used in the assessment of this sub-group analysis were derived from various clinical investigations with different purposes. Furthermore, significant effect sizes in specific subgroups suggest variations in attentional functions across different populations and test formats can provide deeper insights into attention-related disorders and cognitive functioning, preferably in various cultures and health conditions.

VI. Conclusion:

6.1 Recap of the Research Problem and Questions

This meta-analysis classifies data into four types. Type 1 research papers about the effects of smoking on sleep functions cover 29 studies. Type 2 research papers on the impacts of smoking on cognitive tasks cover 47 studies. Only 2 studies regarding type 3 research papers about the effects of smoking on cognitive functions and sleep quality have been found. Type 4 research papers related to the link between mental functions and sleep quality, which cover 16 studies.

6.2 Summary of the Findings

Among 94 studies processed in this research, only 34 studies met the requirement of this study. The first meta-analysis covers 16 studies about the effects of smoking on sleep quality, including a total of 31103 participants, 8667 smokers and 22436 non-smokers. The number of participants in the second meta-analysis about the effects of smoking on cognitive functions was 25899, based on 14 studies. The number of smokers in this analysis is 6219, while non-smokers are 19680. The subgroup analysis of the attention tests assessment covers 4 studies and includes 63,233 participants, 15802 smokers, and 47431 non-smokers.

The findings of two meta-analyses and one subgroup analysis study examining the effects of smoking on sleep quality and cognitive functions in smokers. The analyses focus on distinct but related aspects, namely sleep quality, overall cognitive function and sleep quality, and specific attention assessment tests as a subgroup analysis. Each study employed specific statistical method that meets the purpose of the analysis, including Cohen's d or Hedge's g as the effect size measure and random-effects models to adjust for variance within and between studies.

The first meta-analysis of this investigation on the effects of smoking on sleep quality shows a significant negative impact of smoking on sleep quality, and smokers experience poorer sleep quality compared to non-smokers. Moreover, increased difficulties in sleep onset and overall sleep satisfaction were revealed by different types of sleep assessment tests. The overall effect size (Cohen's d) indicated a moderate negative effect. This suggests that smoking decreases sleep quality. As explained previously, significant heterogeneity was observed across studies, indicating variability in the impact of smoking on different aspects of sleep.

The second meta-analysis study measured the effects of smoking on cognitive functions and sleep quality. It proves that smoking was found to affect cognitive functions and smokers show deficits in various cognitive domains, including memory, executive function, and processing speed. The Hedges' g method was used to measure the overall effect size for cognitive function and sleep quality analysis, producing a small to moderate negative effect suggesting that smoking leads to remarkable deficiency in cognitive abilities and sleep qualities. The homogeneity test shows considerable heterogeneity among the studies and reflects differences in the assessed cognitive domains and the methodologies used.

The third meta-analysis is a subgroup analysis measuring the effects of smoking on attention using assessment tests and the overall impact measured in the attention assessment tests of smokers demonstrated slower reaction times and higher severity of attention-related impairments compared to non-smokers.

The effect sizes for individual attention tests varied, with some tests showing moderate to large effects, like Trailmaking A and TMT-B, indicating significant effects, with Cohen's d values up to 0.797 for certain tests, suggesting substantial impairment in attentional functions due to smoking. High heterogeneity was observed with considerable variability in how smoking affects different types of attention tasks.

All these types of analyses, including tests for publication bias, such as Egger's regression test and funnel plot asymmetry assessments, indicate minimal publication bias. The trim-and-fill analyses further supported the validity of the findings. However, significant heterogeneity was noticed in several analyses, highlighting the variability in study designs, populations, and assessment tools used as discussed earlier.

6.3 Future Directions

Any future research in this term is advised to consider a few points that were grasped from this meta-analysis. Future studies should standardize assessment protocols. Developing and employing standardized cognitive and sleep assessment tools may strongly enhance

comparability across studies. Since smoking is a behavior adopted by smokers, it makes scientifically plausible sense to conduct longitudinal studies on this behavior. Conducting long-term studies helps researchers control all the factors and variables that influence the habit of smoking and may negatively interfere with and confuse the data. Diverse populations from different fields of study may have strong validity over one specific source of data. Including diverse demographic and clinical populations to understand the broader applicability of findings may be of great importance in future studies. Since smoking has a tremendous effect on sleep patterns and cognitive qualities, intervention studies are highly prioritized to limit the risk of smoking. Investigating the effectiveness of smoking cessation programs and other interventions in improving cognitive functions and sleep quality may enhance the life quality of many smokers and limit the risks of a considerable number of evitable chronic diseases.

6.4 Final Thoughts and Conclusion

This work has led us to conclude that the findings across all three meta-analyses and subgroup analyses are that smoking has a detrimental effect on both sleep quality and cognitive functions, including attention. This thesis has given a considerable amount of statistical methods and analysis explained by mathematical formulas in the index about the effects of smoking on sleep quality and many cognitive faculties. The negative effects of smoking on sleep and cognition could happen due to various mechanisms, such as the neurotoxic effects of nicotine, disruption of neurotransmitter systems, and vascular damage, as it was explained in the literature of this thesis.

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ABSTRACT

Human errors due to lack of sleep pose a serious threat to the public's safety. On September 25, 1978, US Flight 182 crashed in San Diego, and 135 people died, besides 9 civilians on the ground. Later investigations by the National Transportation Safety Board referred to “human errors" and sleep deprivation as contributing factors to the crash of PSA Flight 182 and other 85% of similar accidents. In 2017 only in the US, the National Highway Traffic Safety Administration reported 91,000 crash accidents leading to 800 deaths and 50,000 injuries due to drowsy driving. In a medical study that tended to measure sleep-deprived residents' performance of simulated laparoscopic surgical skills at Parkland Memorial Hospital, the results showed an increased number of technical errors and a longer time to fulfil surgical skills. In a similar study on medical interns, the results show that the decrease in cognitive abilities to make the right decisions caused fatal errors in the intern diagnosis after a shift of 24 hours or more. Several studies prove the effects of smoking on sleep quality as a contributing factor. Other studies demonstrate either positive or negative effects of smoking on cognitive functions. However, sleep disorders related to cognitive dysfunction in smokers have been given less attention in the medical literature. Through demystifying the underlying complex mechanisms behind smoking effects on sleep and cognitive functions we, therefore, hypothesize that smoking may have negative effects on the sleep quality and cognitive functions of smokers more than non-smokers. To test this hypothesis, a meta-analysis study has been conducted on the effects of smoking on sleep quality and cognitive functions in smokers. Among 94 studies, 34 met the requirement of this study and were classified into three meta-analysis studies based on the differences in measuring systems. The total number of participants was 120,235 (smokers: 30,688) and (non-smokers: 89,547). The first meta-analysis about sleep assessment covers 16 studies and includes 8667 smokers and 22436 non-smokers using ESS, AHI, and PSQI tests. The overall effect size of these studies reveals a small to moderate effect of smoking on the sleep functions of smokers with an estimation of 0.190 (Cohen's d) ($Z = 9.779$, $p < 0.001$). The test of heterogeneity reveals that the Chi-square (Q statistic) has a value of (39.979, $p = 0.007$) and I-squared (46%) indicates moderate heterogeneity. Egger's regression test indicates publication bias, however, the funnel plot visually shows no significant bias. The second meta-analysis investigated 14 studies covering 35 tests about cognitive and sleep assessment in 6219 smokers and 19680 non-smokers. The analysis was conducted using the JASP statistical software. The statistical methods applied in this analysis was the Hedges g method and fixed and model effect size models. The intercept of this analysis has an estimate of -1.491, indicating that smokers perform worse than non-smokers on the cognitive and sleep tests. The residual heterogeneity test produced a Q statistic of 1685.026 with 33 degrees of freedom and a p-value less than 001. The third meta-analysis was a subgroup analysis of the attention tests assessment covering 4 studies and including 63,233 participants, 15802 smokers, and 47431 non-smokers. Using SPSS version 29, and applied Cohen's d as the effect size measure and random-effects model produces an overall effect size of 0.223, indicating a small-to-moderate effect with a standard error of 0.1071 and statistical significance (p 0.038). The test of heterogeneity shows that the chi-squared (χ^2) value is 33.928, the degrees of freedom (df) is 8, and the p-value is less than 0.001 ($p < .001$) which means that the heterogeneity is highly significant and it is very unlikely that the observed variability in effect sizes is due to chance alone. Concerning the test for publication bias, Egger's regression-based analysis reveals no evidence of publication bias (intercept was -0.288, p). Thus, the three meta-analyses confirm that smoking has negative small-to-moderate effects on sleep quality and cognitive functions in smokers compared to non-smokers.

ABSTRAKT

Menschliche Fehler aufgrund von Schlafmangel stellen eine ernsthafte Bedrohung für die öffentliche Sicherheit dar. Am 25. September 1978 stürzte US-Flug 182 in San Diego ab, wobei 135 Menschen starben, zusätzlich zu 9 Zivilisten am Boden. Spätere Untersuchungen durch das National Transportation Safety Board verwiesen auf „menschliche Fehler“ und Schlafmangel als beitragende Faktoren für den Absturz von PSA-Flug 182 und anderen 85 % ähnlicher Unfälle. Im Jahr 2017 wurden allein in den USA von der National Highway Traffic Safety Administration 91.000 Unfälle mit 800 Todesfällen und 50.000 Verletzungen aufgrund von schläfrigem Fahren gemeldet. In einer medizinischen Studie, die die Leistung schlafloser Assistenzärzte bei simulierten laparoskopischen chirurgischen Fähigkeiten im Parkland Memorial Hospital untersuchte, zeigten die Ergebnisse eine erhöhte Anzahl technischer Fehler und eine längere Zeit zur Erfüllung der chirurgischen Fähigkeiten. In einer ähnlichen Studie an Assistenzärzten im Praktikum zeigten die Ergebnisse, dass die Abnahme der kognitiven Fähigkeiten zur richtigen Entscheidungsfindung nach einer Schicht von 24 Stunden oder mehr zu fatalen Fehlern in der Diagnose der Assistenzärzte führte. Mehrere Studien belegen die Auswirkungen des Rauchens auf die Schlafqualität als beitragenden Faktor. Andere Studien zeigen entweder positive oder negative Auswirkungen des Rauchens auf die kognitiven Funktionen. Schlafstörungen im Zusammenhang mit kognitiven Beeinträchtigungen bei Rauchern wurden jedoch in der medizinischen Literatur weniger beachtet. Durch die Entschlüsselung der zugrunde liegenden komplexen Mechanismen, die den Auswirkungen des Rauchens auf Schlaf und kognitive Funktionen zugrunde liegen, stellen wir daher die Hypothese auf, dass Rauchen die Schlafqualität und die kognitiven Funktionen von Rauchern stärker negativ beeinflussen könnte als die von Nichtrauchern. Um diese Hypothese zu testen, wurde eine Metaanalyse zu den Auswirkungen des Rauchens auf die Schlafqualität und kognitiven Funktionen bei Rauchern durchgeführt. Von 94 Studien erfüllten 34 die Anforderungen dieser Studie und wurden in drei Metaanalysen basierend auf den unterschiedlichen Messsystemen klassifiziert. Die Gesamtzahl der Teilnehmer betrug 120.235 (Raucher: 30.688) und (Nichtraucher: 89.547). Die erste Metaanalyse zur Schlafbewertung umfasst 16 Studien und beinhaltet 8667 Raucher und 22436 Nichtraucher unter Verwendung von ESS-, AHI- und PSQI-Tests. Die Gesamteffektgröße dieser Studien zeigt einen kleinen bis moderaten Effekt des Rauchens auf die Schlaffunktionen von Rauchern mit einer Schätzung von 0,190 (Cohen's d) ($Z = 9,779$, $p < 0,001$). Der Test auf Heterogenität zeigt, dass der Chi-Quadrat-Wert (Q-Statistik) 39,979 ($p = 0,007$) beträgt und I-Quadrat (46 %) auf eine moderate Heterogenität hinweist. Der Egger-Test zeigt eine Publikationsverzerrung, aber die Trim-and-Fill-Analyse zeigt einen minimalen Effekt, und das Trichterdiagramm zeigt grafisch keine signifikante Verzerrung. Die zweite Metaanalyse untersuchte 14 Studien mit 35 Tests zur kognitiven und Schlafbewertung bei 6219 Rauchern und 19680 Nichtrauchern. Die Analyse wurde mit der JASP-Statistiksoftware durchgeführt und wendete die Hedges-g-Methode sowie Modelle der festen und zufälligen Effektgrößen an. Der Interzept dieser Analyse hat eine Schätzung von -1,491, was darauf hindeutet, dass Raucher bei den kognitiven und Schlaftests schlechter abschneiden als Nichtraucher. Der Restheterogenitätstest ergab eine Q-Statistik von 1685,026 mit 33 Freiheitsgraden und einem p-Wert von weniger als 0,001. Die dritte Metaanalyse war eine Untergruppenanalyse der Aufmerksamkeitstests, die 4 Studien mit 63.233 Teilnehmern, 15802 Rauchern und 47431 Nichtrauchern umfasste. Die Verwendung von SPSS Version 29 und die Anwendung von Cohen's d als Maß für die Effektgröße und das Zufallseffekte-Modell ergaben eine Gesamteffektgröße von 0,223, was auf einen kleinen bis moderaten Effekt mit einem Standardfehler von 0,1071 und statistischer Signifikanz ($p = 0,038$) hinweist. Der Test auf Heterogenität zeigt, dass der Chi-Quadrat-Wert (χ^2) 33,928 beträgt, die Freiheitsgrade (df) 8 betragen und der p-Wert weniger als 0,001 ($p < 0,001$) beträgt,

was bedeutet, dass die Heterogenität hoch signifikant ist und es sehr unwahrscheinlich ist, dass die beobachtete Variabilität der Effektgrößen nur zufällig ist. In Bezug auf den Test auf Publikationsverzerrung zeigt die Egger-Regressionsanalyse keine Hinweise auf eine Publikationsverzerrung (Interzept = -0,288, p). Die drei Metaanalysen bestätigen, dass das Rauchen im Vergleich zu Nichtrauchern negative kleine bis mittelschwere Auswirkungen auf die Schlafqualität und die kognitiven Funktionen bei Rauchern hat.

LIST OF TABLES

Meta-Analysis: Continuous Data for Sleep Assessment Tests (SPSS 29)

Effect Size Estimates for Individual Studies									
ID	Study	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval		Weight	Weight (%)
						Lower	Upper		
Bielicki	Epworth Sleepiness Scale (ESS)	.127	.0402	3.168	.002	.049	.206	200.707	7.6
Conway	Epworth Sleepiness Scale (ESS)	.093	.0707	1.315	.188	-.046	.231	119.555	4.5
Esen	Epworth Sleepiness Scale (ESS)	.083	.1033	.804	.421	-.119	.286	71.236	2.7
Hsu	Epworth Sleepiness Scale (ESS)	.223	.0915	2.438	.015	.044	.403	85.152	3.2
Shao	Epworth Sleepiness Scale (ESS)	.164	.0756	2.169	.030	.016	.312	110.098	4.2
Varol	Epworth Sleepiness Scale (ESS)	.182	.0564	3.225	.001	.071	.292	152.753	5.8
Yosunkaya	Epworth Sleepiness Scale (ESS)	.336	.1104	3.047	.002	.120	.553	64.265	2.4
Bielicki	The apnea hypopnea index (AHI)	.099	.0402	2.460	.014	.020	.177	200.743	7.6
Conway	The apnea hypopnea index (AHI)	.088	.0707	1.248	.212	-.050	.227	119.560	4.5
Esen	The apnea hypopnea index (AHI)	.046	.1033	.445	.657	-.156	.248	71.268	2.7
Hsu	The apnea hypopnea index (AHI)	.336	.0917	3.657	<.001	.156	.515	84.842	3.2
Quan	The apnea hypopnea index (AHI)	.159	.0733	2.167	.030	.015	.303	114.330	4.3
Shao	The apnea hypopnea index (AHI)	.036	.0755	.481	.631	-.112	.184	110.251	4.2
Varol	The apnea hypopnea index (AHI)	.259	.0565	4.593	<.001	.149	.370	152.436	5.8
Chehri, A. et al	Pittsburgh Sleep Quality Index	.381	.0990	3.852	<.001	.187	.575	75.924	2.9

Arbinaga ,F. et al	Pittsburgh Sleep Quality Index	.312	.0970	3.214	.001	.122	.502	78.280	3.0
Salah, A. B. et al	Pittsburgh Sleep Quality Index	.394	.0976	4.041	<.001	.203	.586	77.580	2.9
Cohrs, S. et al	Pittsburgh Sleep Quality Index	.266	.0419	6.348	<.001	.184	.348	195.222	7.4
Wang, W. et al	Pittsburgh Sleep Quality Index	.225	.0314	7.178	<.001	.164	.287	229.607	8.7
Asghari, Alimoha mad, et al.	Pittsburgh Sleep Quality Index	.170	.0603	2.825	.005	.052	.288	142.796	5.4
Wetter, David W., and Terry B. Young.	Chronic Insomnia	.141	.1075	1.312	.189	-.070	.352	66.961	2.5
Conway, Silvia Goncalv es, et al.	Arousal index	.239	.0708	3.378	<.001	.100	.378	119.266	4.5

Meta-Analysis: Continuous Data for Cognitive Assessment Tests (SPSS 29)

Author(s)	Year	Tests	Effect Size	Std. Error	z	Lower CI	Upper CI
Wang, Cheng-Ching, et al.	2010	SPMSQ 2003	-1.938	0.0836	-23.173	-2.102	-1.774
Wu, Peiliang, et al.	2020	MMSE score	-1.800	0.1254	-14.353	-2.046	-1.554
Elwood, Peter Creighton, et al.	1999	CAMCOG	-1.208	0.0822	-14.703	-1.369	-1.047
Elwood, Peter Creighton, et al.	1999	AH4	-0.803	0.0787	-10.205	-0.957	-0.649
Mons, Ute, et al.	2013	COGTEL score	-1.615	0.1028	-15.716	-1.817	-1.413
Hotta, Ryo, et al.	2015	MMSE (male)	-1.366	0.0764	-17.893	-1.516	-1.216
Hotta, Ryo, et al.	2015	MMSE (female)	-4.952	0.1493	-33.169	-5.245	-4.659
Wu, Peiliang, et al.	2020	RAVLT total learning score	-1.462	0.1199	-12.188	-1.697	-1.227
Wu, Peiliang, et al.	2020	RAVLT delayed recall	-0.993	0.1139	-8.719	-1.217	-0.769
Hotta, Ryo, et al.	2015	Immediate word test (male)	-1.201	0.0747	-16.074	-1.347	-1.055
Hotta, Ryo, et al.	2015	Immediate word test (female)	-3.574	0.1399	-25.551	-3.849	-3.299
Hotta, Ryo, et al.	2015	Delayed word test (male)	-0.687	0.0708	-9.694	-0.826	-0.548
Hotta, Ryo, et al.	2015	Delayed word test (female)	-1.091	0.1299	-8.394	-1.346	-0.836

Hotta, Ryo, et al.	2015	SDST (male)	-1.209	0.0748	-16.160	-1.356	-1.062
Hotta, Ryo, et al.	2015	SDST (female)	-2.857	0.1360	-21.010	-3.123	-2.591
Johar, Hamimatunnisa, et al.	2016	Normal Cognitive Functions	-1.292	0.0628	-20.565	-1.415	-1.169
Johar, Hamimatunnisa, et al.	2016	Impaired Cognitive Functions	-1.301	0.1383	-9.408	-1.572	-1.030
Riaz, Tuba, et al.	2021	MMSE	-1.354	0.2226	-6.083	-1.790	-0.918
Elwood, Peter Creighton, et al.	1999	CRT	-0.888	0.0793	-11.197	-1.044	-0.732
Riaz, Tuba, et al.	2021	CRT-Latency	-0.888	0.2100	-4.229	-1.300	-0.476
Zhang, Qiaoyang, et al.	2022	DSST	-1.391	0.0626	-22.230	-1.514	-1.268
Hill, Robert D.	1989	Digit Symbol	-2.034	0.3798	-5.357	-2.779	-1.289
Riaz, Tuba, et al.	2021	CRT-Percent correct trials	-1.390	0.2237	-6.212	-1.829	-0.951
Elwood, Peter Creighton, et al.	1999	MMSE	-1.182	0.0819	-14.435	-1.342	-1.022
Phillips and Fox	1998	Word recall	0.471	0.2620	1.796	-0.042	0.984
Liu, Jui-Ting, et al.	2013	Attention/concentration	-1.294	0.2681	-4.826	-1.819	-0.769
Liu, Jui-Ting, et al.	2013	Verbal memory index	-1.193	0.2645	-4.512	-1.711	-0.675
Liu, Jui-Ting, et al.	2013	Visual memory index	-1.314	0.2689	-4.886	-1.842	-0.786
Liu, Jui-Ting, et al.	2013	General memory index	-1.230	0.2658	-4.627	-1.751	-0.709
Liu, Jui-Ting, et al.	2013	Delayed-recall memory index	-1.219	0.2654	-4.594	-1.741	-0.697
Conway, Silvia Goncalves, et al.	2008	Sleep Efficiency	-0.165	0.0707	-2.335	-0.303	-0.027
Hsu, Wen-Yu, et al.	2019	Sleep Efficiency	-1.743	0.1021	-17.071	-1.943	-1.543
Wetter, David W., and Terry B. Young	1994	Sleep Efficiency	-2.244	0.1230	-18.239	-2.485	-2.003
Wetter, David W., and Terry B. Young	1994	Total Sleep Time (TSTa)	-2.244	0.1230	-18.239	-2.485	-2.003

LIST OF TESTS DEFINITIONS

Assessment Tests for Cognitive and Sleep Functions

Test Name	Description	Year(s)	Purpose	Population	Cognitive Domains Assessed
SPMSQ 2003	The Short Portable Mental Status Questionnaire is a screening instrument aimed at evaluating cognitive decline in older adults.	2010	Screening for cognitive impairment	Elderly	Memory, attention, orientation
MMSE score	Mini-Mental State Examination score, a widely used test to measure cognitive impairment and dementia.	2020	Cognitive impairment assessment	Adults, elderly	Memory, attention, language, orientation
CAMCOG	Cambridge Cognitive Examination, a cognitive test assessing various cognitive domains such as memory, language, and attention.	1999	Comprehensive cognitive assessment	Adults, elderly	Memory, language, attention
AH4	A test used to assess cognitive functioning and intellectual ability.	1999	Intellectual ability assessment	Adults, elderly	General cognitive functioning
COGTEL score	A cognitive test used to assess cognitive function, often related to the use of technology or digital media.	2013	Cognitive function related to technology use	Adults, elderly	Technology-related cognitive function
RAVLT total learning score	Rey Auditory Verbal Learning Test, a measure of verbal learning and memory.	2015	Verbal learning and memory assessment	Adults, elderly	Verbal memory
RAVLT delayed recall	A measure of delayed recall in the Rey Auditory Verbal Learning Test.	2020	Delayed recall assessment	Adults, elderly	Verbal memory
Immediate word test (male/female)	A test of immediate recall of words, often used in cognitive assessments.	2015	Immediate verbal memory recall assessment	Adults	Verbal memory
Delayed word test (male/female)	A test of delayed recall of words, typically administered after a delay period following initial presentation.	2015	Delayed verbal memory recall assessment	Adults	Verbal memory
SDST (male/female)	Symbol Digit Substitution Test, a measure of cognitive processing speed and attention.	2015	Cognitive processing speed and attention assessment	Adults	Processing speed, attention
Normal Cognitive Functions	Assessment of cognitive functions within the normal range.	2016	Normal cognitive function assessment	Adults, elderly	General cognitive function

Test Name	Description	Year(s)	Purpose	Population	Cognitive Domains Assessed
Impaired Cognitive Functions	Assessment of cognitive functions indicating impairment or dysfunction.	2016	Cognitive impairment assessment	Adults, elderly	General cognitive function
CRT	Choice Reaction Time test, a measure of reaction time and processing speed.	2012	Reaction time and processing speed assessment	Adults	Processing speed, attention
CRT-Latency	Measure of the latency period in a Choice Reaction Time test.	2012	Latency measurement in reaction time task	Adults	Processing speed, attention
DSST	Digit Symbol Substitution Test, a measure of processing speed, attention, and executive function.	2022	Processing speed, attention, and executive function	Adults	Processing speed, attention, EF
Digit Symbol	A test assessing the ability to match symbols to numbers within a given time frame.	1989	Cognitive processing speed assessment	Adults, elderly	Processing speed
Word recall	A test of verbal memory, typically involving the recall of previously presented words or phrases.	2003	Verbal memory assessment	Adults, elderly	Verbal memory
Attention/concentration	Assessment of attentional focus and concentration abilities.	2013	Attention and concentration assessment	Adults	Attention, concentration
Verbal memory index	Measure of verbal memory performance.	2013	Verbal memory performance assessment	Adults, elderly	Verbal memory
General memory index	Composite measure of memory performance across different domains.	2013	General memory performance assessment	Adults, elderly	Memory
Delayed-recall memory index	Measure of memory recall performance after a delay period.	2013	Delayed recall memory assessment	Adults, elderly	Memory
Sleep Efficiency	Assessment of the efficiency of sleep, often measured as the percentage of time spent asleep while in bed.	2019	Sleep quality assessment	Adults, elderly	Sleep quality
Total Sleep Time (TSTa)	Total amount of time spent asleep during a sleep period.	1994	Sleep duration assessment	Adults, elderly	Sleep duration
Index of Visual Memory	an evaluation of visual memory performance.	2013	Evaluation of visual memory function	Adults, elderly	Visual memory

Test Name	Description	Year(s)	Purpose	Population	Cognitive Domains Assessed
MMSE (Mini-Mental State Examination)	A widely used test to measure cognitive impairment and dementia.	1975	Cognitive impairment assessment	Adults, elderly	Memory, attention, language, orientation
The Pittsburgh Sleep Quality Index (PSQI)	assessment tool for sleep quality	1989	Sleep quality assessment	Adults, elderly	Sleep quality
Apnoe-Hypopnoe-Index (AHI)	quantifies the number of episodes per sleeping hour.	1987	Evaluation of sleep apnea severity	Adults, elderly	Sleep disordered breathing
Epworth Sleepiness Scale(ESS)	A self-administered questionnaire measuring daytime sleepiness.	1991	Daytime sleepiness assessment	Adults, elderly	Sleepiness

LIST OF STATISTICAL FORMULAS

Cohen's d equation:

$$d = \frac{M_1 - M_2}{SD_{\text{pooled}}}$$

Where:

M1 = stands for mean of the smokers
M2 = stands for mean of the non-smoker
SD pooled, which may be computed as follows, is the total standard deviation of smokers and non-smokers.

$$SD_{\text{pooled}} = \sqrt{\frac{(n_1 - 1)SD_1^2 + (n_2 - 1)SD_2^2}{n_1 + n_2 - 2}}$$

The Key of Cohen's d equation:

- SD1 is the standard deviation of smokers group
- SD 2 is the standard deviation of non-smokers group
- n 1 is the sample size of smokers group
- n 2 is the sample size of non-smokers group

Egger's Regression Based-Test Equation:

$$\frac{\text{Effect Size}_i}{\text{SE}_i} = \beta_0 + \beta_1 \times \text{SE}_i + \epsilon_i$$

where:

- $\frac{\text{Effect Size}_i}{\text{SE}_i}$ is the standardized effect size for study i.
- β_0: The intercept
- β_1: The coefficient of the standard error
- SE_i: The coefficient of the standard error
- ϵ_i: The error term for study *i*

Homogeneity Equation:
Chi-square (Q Statistic):

$$Q = \sum_{i=1}^{k} w_i (Y_i - \bar{Y})^2$$

Where:

- k is the number of studies
- w_i is the weight given to the i-th study; it often refers to the variance of the study inverted.
- Y_i is the effect size of the *i*-th study
- $\bar{Y}$ is the weighted average effect size

Degrees of Freedom:

df = *k - 1*

If the null hypothesis of homogeneity is true, the Q statistic has a the chi-square probability with k - 1 degrees of freedom.

Heterogeneity Equation:

Tau-squared (τ^2):

This is the between-study variance.

$$\tau^2 = \frac{Q - (k-1)}{C}$$

Where:

$$C = \sum_{i=1}^{k} w_i - \frac{\left(\sum_{i=1}^{k} w_i^2\right)}{\sum_{i=1}^{k} w_i}$$

H-squared (H^2):

This measures the relative increase in the Q statistic due to heterogeneity.

$$H^2 = \frac{Q}{k-1}$$

I-squared (I^2):

This indicates the proportion of overall variance between studies that may be attributed to heterogeneity as opposed to random variation.

$$I^2 = \frac{Q - (k-1)}{Q} \times 100\%$$

Where:

- Q is Cochran's Q statistic
- k is the number of studies

Fixed-Effect Model Formula:

In a fixed-effect meta-analysis all studies estimate the same underlying effect size. This model was merged with the random effect model in the meta-analysis data for cognitive and sleep assessment tests.

Weighted Mean Effect Size (Fixed-Effect Model):

$$\bar{Y}_{\text{fixed}} = \frac{\sum_{i=1}^{k} w_i Y_i}{\sum_{i=1}^{k} w_i}$$

Where:

- w_i = Weight of the i -th study
- Y_i = Effect size of the i -th study

Random-Effects Model Formula:

In a random-effects meta-analysis assumes that the effect sizes vary between studies. The random effect size model was used in the three meta-analysis studies of this thesis.

Weighted Mean Effect Size (Random-Effects Model):

$$\bar{Y}_{\text{random}} = \frac{\sum_{i=1}^{k} w_i^* Y_i}{\sum_{i=1}^{k} w_i^*}$$

Where:

- $w_i^* = \frac{1}{v_i + \tau^2}$

- vi = Variance of the i-th study
- τ^2 = Between-study variance (heterogeneity)